# MOTOR ADAPTATIONS TO MOVEMENT-EVOKED LOW BACK PAIN

by

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# Abstract

Low back pain (LBP) is a main cause of disability worldwide, resulting in a significant socio-economic burden on society. In some people with LBP, the main mechanism of pain is nociceptive, and symptoms are increased by mechanical stimuli. By changing mechanical stresses applied to lumbar structures, movement and physical activity can exacerbate LBP, a phenomenon known as movement-evoked pain (MEP). Given the relationship between LBP and movement for many people, research has focused on how they influence each other with evidence supporting that people with LBP move differently. However, findings are often contradictory due to clinical heterogeneity. For this reason, experimental pain models have been used to better understand the effects of pain in the lumbar region on movement. Despite being clinically relevant, the investigation of MEP and its effect on motor adaptations remains underexplored in both experimental and clinical LBP. Understanding how movement-evoked LBP affects movement is essential as it could help to partially explain the clinical heterogeneity and mechanisms underpinning motor adaptations to pain, ultimately facilitating more personalised interventions for people with LBP. The primary aim of this thesis was to investigate how movement-evoked LBP affects how people move. Additionally, this thesis aimed to determine if such motor adaptations are specific to the direction of the pain provocative movement, and if they represent a purposeful strategy to reduce pain in accordance with contemporary theory on motor adaptation to pain. The first study within this thesis was a systematic review which supported the causal effect of pain experimentally induced in the lumbar region on motor adaptations, specifically

revealing a reduction of the range of motion of the lumbar spine, reduced activation of deep trunk muscles, and task-dependent increased or decreased activation of superficial lumbar muscles. The systematic review revealed that the investigation of the effects of MEP was limited, as one study out of twenty-six used an experimental model where pain was modulated by movement. The second study of this thesis investigated the effects of MEP experimentally induced in the lumbar region in association to either lumbar flexion or extension. This revealed that MEP is a main determinant of motor adaptations to experimental pain since a reduction of lumbar movement was only observed in the pain-provoking direction. Also, participants who showed larger reductions of lumbar range of motion also reported lower pain intensity, supporting the notion that motor adaptations to experimental pain represent a purposeful strategy to reduce pain. The third study investigated motor adaptations to movement-evoked LBP in people with clinical LBP. Kinematic differences were specific to what trunk movement was pain provocative, with larger lumbar flexion and smaller knee and hip flexion seen for people reporting higher pain intensity during forward bending. Overall, this thesis showed that clinical and experimental pain in the lumbar region changes movement, and that the pain provocative direction is a main determinant of the observed motor adaptations. These results also confirm that motor adaptations are purposeful strategies to reduce pain. Pain directionality may explain some of that heterogeneity of motor adaptations observed in people with clinical and experimental LBP, and it may offer new insights for the development of personalised and more effective interventions for people with clinical LBP.

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# List of Papers and Conference Abstracts

The following papers directly related to this thesis have either been published or presented at conferences during the candidate's PhD course. A summary of each paper and its use within this thesis will be provided at the start of each relevant chapter. Therefore, sections of this thesis incorporate verbatim text from published work and will resemble this work in terms of structure and content, with additional modifications as required to build the argument of the overall thesis.

## Published Articles directly related to the Thesis

- **Devecchi V,** Falla D, Cabral HV, Gallina A. Neuromuscular adaptations to experimentally induced pain in the lumbar region: protocol for a systematic review and meta-analysis. Syst Rev. 2021 Oct 15;10(1):270.
- **Devecchi V**, Falla D, Cabral HV, Gallina A. Neuromuscular adaptations to experimentally induced pain in the lumbar region: systematic review and meta-analysis. Pain. 2023 Jun 1;164(6):1159-1180.

## Published Articles with similar methodology

- **Devecchi V**, Saunders M, Galaiya S, Shaw M, Gallina A. Remote assessment of pelvic kinematics during single leg squat using smartphone sensors: Between-day reliability and identification of acute changes in motor performance. PLoS One. 2023 Nov 22;18(11):e0288760.

- Cabral HV, **Devecchi V**, Oxendale C, Jenkinson N, Falla D, Gallina A. Effect of movement-evoked and tonic experimental pain on muscle force production. Scand J Med Sci Sports. 2024 Jan;34(1):e14509.

## Conference Presentations

- **Devecchi V**, Falla D, Cabral HV, Gallina A. Neuromuscular adaptations to experimentally induced pain in the lumbar region: systematic review and meta-analysis. The 12th Congress of the European Pain Federation (EFIC). Dublin, Ireland, April 27 – 30 2022.
- **Devecchi V**, Falla D, Cabral H, Abboud J, Hodges PW, Gallina A. Kinematics adaptations to movement-evoked pain experimentally induced in the lumbar region. Pain Science in Motion Congress. Maastricht, The Netherlands. May 19-20, 2022
- **Devecchi V**, Falla D, Cabral H, Abboud J, Hodges PW, Gallina A. Motor adaptation to movement-evoked pain induced during lumbar flexion. International Society of Electrophysiology and Kinesiology (ISEK). Québec City, Canada, June 22-25, 2022.
- **Devecchi V**, Falla D, Cabral H, Abboud J, Hodges PW, Gallina A. Movement-evoked pain experimentally induced in the lumbar region increases motor variability. The International BNA 2023 Festival of Neuroscience. Brighton, UK, April 23 – 26, 2023

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# List of abbreviations

| Acronym | Definition |
|---|---|
| ANOVA | Analysis Of Variance |
| CI | Confidence Interval |
| CNS | Central Nervous System |
| CoP | Centre of Pressure |
| CTR | Control |
| DOMS | Delayed Onset Muscle Soreness |
| HSI | Hypertonic Saline Injection |
| ICC | Intraclass Correlation Coefficient |
| IMU | Inertial Measurement Unit |
| LBP | Low Back Pain |
| MD | Mean Difference |
| MEP | Movement-Evoked Pain |
| MSI | Movement System Impairment syndromes |
| NGF | Nerve Growth Factor |
| NRS | Numeric Rating Scale |
| NScLBP | Non-Specific chronic Low Back Pain |
| OCS | O'Sullivan Classification System |
| ODI | Oswestry Disability Index |
| PCS | Pain Catastrophising Scale |
| RoB | Risk of Bias |
| ROM | Range Of Motion |
| SMD | Standardised Mean Difference |
| TSK | Tampa Scale for Kinesiophobia |
| VAS | Visual Analogue Scale |

# CHAPTER 1 – GENERAL INTRODUCTION

## 1.1 Overview of chronic low back pain

Low back pain (LBP) is a common condition that results from different known or unknown causes, and it represents the leading cause of years lived with disability (1,2). LBP is typically defined as a pain occurring in the anatomical region localised between the 12th rib and the inferior gluteal fold, with or without radiating pain to the lower limb (3). Up to 40% of individuals experience LBP at some point in their life (4). The mean point prevalence estimated in a systematic review collecting data from 156 studies was 18.3%, with a 1-year prevalence of 38.0% (4). Data on the incidence on LBP differs across studies with a one-year incidence of new LBP episodes ranging from 1.5% to 36% (5). This heterogeneity is due to the recurrent nature of LBP, characterised by new episodes within the same year, which may contribute to the variability in incidence estimation across studies (5). Evidence shows that LBP is more frequent in women across all age groups, with the highest incidence reported between 40 and 69 years old (4).

LBP is a social and economic burden. Over the last 20 years, LBP has consistently been the primary cause of disability worldwide (2). In 2017, it accounted for 64.9 million years lived with disability, with higher rates observed among females (2). In 2016, LBP and neck pain led to the highest healthcare costs in the USA, with a total estimate of $134.5 billion (6). Low back pain has a significant impact on healthcare costs, with direct expenses (e.g., medical consultations, physical therapy, and surgery) constituting just a fraction of the indirect costs (e.g., lost workdays, decreased productivity, and

disability payments). For instance, in Australia, direct costs amounted to 1 billion $AUD, while indirect costs were nine times higher (7). Comparable findings were observed in the UK in 1998, with direct healthcare costs estimated at £1.6 billion, while the cost of informal care and production losses amounted to £10.7 billion (8). More recent data reveal a consistent pattern in the UK, showing an increase in direct costs to £2.8 billion (9).

Low back pain can be specific or non-specific (1). Specific LBP is caused by identifiable pathophysiological and anatomical conditions, either originating from the spine or elsewhere (10). Spinal causes encompass conditions like herniated disc, spinal stenosis, fracture, tumour, infection, and axial spondyloarthritis (10). Non-spinal causes for specific LBP include hip-related issues, pelvic organ diseases (e.g., prostatitis and endometriosis), and vascular or systemic conditions such as aortic aneurysm (10). Lumbar disorders that cause radicular pain, usually due to nerve-root involvement, are more common (with a prevalence of 5 to 10%) than other spinal causes, with herniated disc and spinal stenosis being the most common (11). In contrast, nonspecific LBP refers to LBP, which may or may not include leg pain, but lacks a specific pathophysiological and anatomical cause (1). This category represents around 80 to 90% of all LBP cases (3). Several lumbar structures could potentially be the source of pain (1). However, clinical tests cannot identify which structure is the cause of pain (1). Moreover, people with LBP often present other physical or psychological issues. Altogether, these elements suggest that nonspecific LBP represents a complex condition resulting from the interaction of biological, psychological and social factors (1).

The natural course of nonspecific LBP is highly heterogeneous across patients. While most experience spontaneous recovery after an acute episode, approximately 10-20% are at risk of developing non-specific chronic LBP (NScLBP), defined as pain persisting for more than 12 weeks (9). Overall, three pain-trajectories are identified after an acute episode of LBP; (i) a recovery trajectory, where patients experience rapid or gradual improvement towards minimal or no pain; (ii) an ongoing trajectory, characterised by fluctuation in pain intensity and remission periods (i.e., recurrent LBP); and (iii) a persistent trajectory, characterised by constant and moderate pain (i.e., NScLBP) (10). Given the nonspecific nature of LBP, it is not clear which mechanism might contribute to the transition from acute to chronic pain. However, several prognostic factors associated with poor outcomes have been identified, primarily related to pain characteristics, physical, and psychological factors, all within the context of the biopsychosocial model (12).

Since NScLBP is a multifactorial condition, one-size-fits all treatments are not effective in the management of people with NScLBP and multi-modal treatments able to address the clinical heterogeneity of LBP are required (13). Biological factors are commonly the targets of such multi-modal treatments in the management of people with NScLBP (13). Indeed, supervised exercise represent the first-line therapeutic options, targeting the physical components of LBP (14). A recent network meta-analysis highlights the effectiveness of exercises in reducing pain and functional limitations, especially those like Pilates (mean difference of pain intensity = -21.8, 95% CI −29.6 to −14.1, and mean difference of functional limitation = −13.1, 95% CI −18.6 to −7.7) and McKenzie therapy (mean difference of pain intensity = −14.1, 95% CI −27.7 to −0.4, and

mean difference of functional limitation = −16.1, 95% CI −19.5 to −12.8) which focus on the interplay between pain and movement (15). Also, recent randomised controlled trials support the effectiveness of movement-based interventions in the management of NScLBP (16,17). These interventions were more effective compared to usual care because they are tailored to the clinical presentation of patients, considering factors such as pain provocative movements and activities (16,17). Therefore, identifying those factors that differ across participants can be crucial for tailoring exercise prescription in the management of NScLBP. Also, an understanding of the biomechanics and neurophysiological control of the spine is fundamental for comprehending the role of movement in NScLBP and to develop effective assessment and treatment strategies.

## 1.2 Anatomy, biomechanics and neuromuscular control of the lumbar spine

The lumbar region is essential to transfer the biomechanical load from the torso and upper body to the lower extremities (18). This function is key both during static posture and movements. The lumbar area is a sophisticated system characterised by the interplay between bone, ligament, and muscle structures. These elements provide to this region its passive and active stability. In addition, optimal control of the lumbar region is achieved by a precise regulation of muscle activity through multilevel components of the nervous system (19).

The main passive components of lumbar spine comprise five vertebrae (L1-L5), the intervertebral discs, and a dense network of ligaments and connective tissues (20). Each lumbar vertebra is composed by a vertebral body anteriorly with a weight-bearing

function, and the laminae, pedicles, articular, transverse and spinous processes posteriorly which serve as attachment for several muscles acting on the spine and for protecting the vertebral canal (20). Consecutive vertebrae are connected to each other through three intervertebral joints composed by an intervertebral disc anteriorly, and two zygapophysial joints posteriorly. The intervertebral disc is responsible for resisting axial compression during weight-bearing activities and contraction of back muscles, in addition to limiting movements in other directions between two adjacent vertebrae (20). While minimal, the zygapophysial joints also contribute to supporting a portion of the vertical load, particularly in the lower segments of the lumbar spine during trunk extension movements or postures that result in increased lumbar lordosis (20).

Due to the different structure of vertebrae along the spine, the lumbar region is mainly responsible for the movements of the spine occurring in the sagittal plane (i.e., flexion and extension), which also present the larger range of motion (ROM) (20). During forward and backward movements, the load on the structures of the lumbar spine is modified with higher axial compression on the anterior portion of the intervertebral disc during forward bending and on the posterior portion of the intervertebral disc and zygapophysial joints during backward bending (20). Furthermore, the action of back muscles result in an increase of compressive forces, especially during lumbar extension. The ligaments present on the posterior portion of the intervertebral joints (i.e., supraspinous and interspinous ligaments) provide a passive resistance to lumbar flexion. Similarly, the anterior longitudinal ligament is tensioned during lumbar extension (20).

When providing passive stability, ligaments and other connective tissues demonstrate a distinct mechanical behaviour known as stiffness. This characteristic refers to the tissue's resistance to deformation, quantified by the amount of force needed to elongate and deform it (21). Structures with greater stiffness offer higher resistance to deformation. In the context of spinal ligaments, performing repetitive movements or maintaining sustained postures can cause tissue deformation and failure, leading to harmful consequences and reduced passive stability (20). This might occur even without a major traumatic event, due to fatigue failure since the tissue does not fully recover between successive biomechanical stresses (20). The principle of resistance to deformation is also relevant in the context of the spine, especially when considering how passive structures collectively contribute to spinal stiffness. Research indicates that degeneration at a single spinal level can affect the stability and control of the spine because of to the variability in spinal stiffness across different levels (19).

Spinal stiffness is also achieved by muscle force, and through a coordinated and rapid recruitment of spinal muscles which allow to resist to mechanical perturbations by acting on osteoligamentous structures (19). The active component of the lumbar spine consists of a complex arrangement of muscles which can be divided into four main groups: (i) psoas major and quadratus lumborum on the anterolateral and lateral portions of the lumbar spine, respectively; (ii) intersegmental lumbar muscles connecting consecutive vertebrae laterally and posteriorly; (iii) polysegmental muscles which span multiple levels of the lumbar region posteriorly, with or without attachment to the lumbar vertebrae; and (iv) abdominal muscles which form the anterolateral abdominal wall (20). These muscles work together synergistically, either as movers of

the spine or to enhance spinal stiffness. They achieve the latter by increasing axial compression and stability through a complex network of fascial and ligamentous connections, such as the thoracolumbar fascia and abdominal fascia (18).

Due to their closeness to the centre of rotation and small lever arm, intersegmental muscles are mainly responsible to 'fine tune' the movement and provide intersegmental stability to the spine (20). Instead, the polysegmental muscles are the prime movers of the lumbar spine, these include the multifidus and erector spinae which is constituted by the longissimus thoracic and the iliocostalis lumborum (20). These muscles are further divided, with specific portions of the muscles originating from the lumbar or thoracic regions, identified by the suffixes -pars lumborum and -pars thoracis, respectively (20).

The multifidus consists of multiple fascicles that span two or more lumbar levels from the spinous process to the laminae with an oblique caudolateral orientation (20). The primary action of the multifidus is exerted on the spinous process, and because of its vertical vector of action, it produces a posterior sagittal rotation resulting in the extension movement of the lumbar spine (20). It also stabilises the flexion component of movement produced by the external oblique in order to achieve a pure axial rotation. Since it is polysegmental, the multifidus increases the spinal lordosis and the compressive load in the intersegmental spaces that it spans (20). Importantly, the multifidus is composed of superficial and deep fascicles (18). The former have longer fibres spanning multiple vertebrae and are involved in global spine stabilisation and gross movements (18). The latter, span fewer vertebrae and are located closer to the

spine (18). The deep multifidus contributes to segmental stability and fine motor control (19).

The pars lumborum of the longissimus thoracis and iliocostalis originate from the transverse processes of the lumbar vertebrae and attach to the posterosuperior iliac spine and iliac crest with a dorsoventral and rostrocaudal orientation (20). Because of such orientation both muscles have a vertical and horizontal component of the vector defining their line of action. Thus, a bilateral contraction of this muscles results in a similar action described for the multifidus, or lateral flexion when acting unilaterally (20). Instead, the pars thoracic of these muscles originates from the ribs and transverse processes of the thoracic vertebrae and attach to the sacrum and ilium through the erector spinae aponeurosis (20). Although these muscles do not attach to the lumbar spine, they have an indirect role on the biomechanics of the lumbar spine by producing the so called “bowstring effect” on the vertebral column resulting in an increase of lumbar lordosis (20).

The abdominal wall is composed by four muscles, each arising from different osteoligamentous structures such as the thoracolumbar fascia, iliac crest, and costal cartilages (18). Based on their anatomical location and biomechanical function, two deep and two superficial abdominal muscles are identified. To the first category belong the transversus abdominis and internal oblique, and to the second category belong the external oblique and rectus abdominis (20). With the exception of the rectus abdominis, all other muscles mainly have a horizontal or inferomedial orientation of their fibres (20). Only the internal oblique has a superomedial orientation on the upper region of the

abdominal wall. The orientation of abdominal muscle fibres supports their biomechanical role for flexion and rotation of the trunk, and stabilisation of the lumbopelvic region thanks to the horizontal fibres located in the lower abdominal wall region (18,20). Additionally, the abdominal muscles play a crucial role in controlling mechanical perturbations to the body. This is achieved through their ability to quickly activate and generate force in response to unexpected forces or changes in balance, thereby maintaining posture and protecting the spine (19).

Beside the presence of passive and active components, sensorimotor control regulated by the nervous system is essential to guarantee the stability of the lumbar spine (19). Sensory information is obtained from different types of receptors and integrated by the central nervous system (CNS) to regulate and fine-tune motor actions and balance through muscle activity (19). At the same time, a coordinated recruitment of back muscle and movements during the execution of functional activities is essential for optimal spinal loading. Sensorimotor control is achieved through a dynamic interplay of feedback and feedforward mechanisms (19). Feedback control consists in a reactive process which allows the system to respond to events as they happen (22). By using sensory information, feedback control allows to monitor and adjust movements in real-time based on the position of the body and external forces acting on it (22). In the lumbar region, the reaction time between the external perturbation and the contraction of back and abdominal muscle needs to be as small as possible to guarantee spine stability (23). On the other hand, feedforward mechanisms are anticipatory since they rely on prior experience and learning to predict the sensory consequences of a movement and prepare the body before the next action is performed (22). In any action,

the CNS processes and integrates the available information to choose the most efficient motor solution in order to achieve the task goal. In the lumbar region, deep fascicles of the multifidus, transversus abdominis, and internal oblique have shown anticipatory activity to postural perturbation generated by the voluntary movement of the upper limbs (24–26). Thus, impairments in either the sensory or motor components of the sensorimotor system can significantly compromise spine stability and the optimal execution of movements (19,25).

Overall, three types of movement and muscle action can be distinguished at the lumbar region; (i) minor active movements to shift the centre of mass in the direction of the desired movement before gravity will provide the necessary force (e.g., backward or side bending while standing); (ii) postural control, especially to internal and external perturbations and activities requiring asymmetrical weight-bearing; (iii) major active movements like bending and lifting (20). During the flexion phase of bending, the anterior sagittal rotation and translation movement of the vertebrae is controlled eccentrically by the multifidus and erector spinae acting on the lumbar and thoracic spine (20). At about 90% of the total range of flexion movement, the activity of spinal muscle drastically reduces (i.e., flexion-relaxation phenomenon) and the stability of the spine is guaranteed by the tension of posterior ligaments and the locking of zygapophysial joints (27,28). Higher activity of spinal muscles is then observed during the extension movement, with a joint action of the iliocostalis and longissimus to lift the thorax by backward rotating it (20). A similar action is executed by the multifidus which rotates the lumbar vertebrae backward providing intersegmental control (20). During the extension movement from a standing position, the movement is initially produced by

the erector spinae to rotate the thorax backward on the lumbar spine, and, after that, it is controlled eccentrically by the abdominal muscles (20).

The biomechanics of lifting is more complex than simple trunk bending due to the multiple degrees of freedom involved. This complexity has significant implications for changes in spinal loading and, especially when lifting heavy loads, spinal stability might be compromised. During lifting, the spine is subject to high shear and compression forces acting on intervertebral discs and zygapophysial joints (29,30). Given their line of action, back muscles generate an extension moment resulting in an increase of the spinal load, as measured at the intervertebral discs, especially when the lumbar spine is flexed (31,32). At the same time, thoracolumbar fascia and non-contractile tissues of back muscles can also contribute to the extension moment of lifting while reducing the metabolic cost because they can store 'strain energy' during the forward bending phase of the task and use it while returning to an erect position (18). Indeed, different amounts of curvature of the lumbar spine during lifting can result in different distributions of pressure within the intervertebral discs because of changes in the position of vertebrae and tension on the ligaments (18). For example, during lumbar flexion close to physiological limits, the posterior portion of the intervertebral disc is stretched and thinner with an increased risk of posterior prolapse if it also subjected to axial compression (18,33). This understanding highlights the importance of avoiding lifting heavy weights while fully flexing the lumbar spine (34). The use of a lordotic lumbar posture has also been discouraged because of concentrated axial compression and shear force on the posterior portion of the intervertebral discs and zygapophysial joints (18,20,35). Beside the role of lumbar posture, increased knee flexion during lifting has

been shown to reduce the peak bending moments acting on the spine even when picking up a pen from the floor (32). However, such a strategy has shown to increase axial compression on the intervertebral disc and the metabolic cost required during the task (36). Additionally, the regional interdependence between the lumbar spine and hip can play a crucial role during lifting to ensure safe and efficient movement mechanics. Proper coordination between these areas distributes the load more evenly across the musculoskeletal system, reducing the strain on any single structure, and thus mitigating the risk of pain or injury (18). Finally, it is noteworthy to mention that experimental data and biomechanical models support that the main determinant of the pressure exerted on the intervertebral discs is represented by the distance of the lifted load from the body (37).

Although the precise source of pain remains unclear in individuals with NScLBP, it is essential to identify which spinal structures have the potential to be sources of pain, and to understand how movement can influence these structures.

## 1.3 Mechanism-based categories of pain and nociception in the lumbar spine

Pain is defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” (38). Pain differs from nociception, which is the “neural process encoding noxious stimuli” (38). Consequently, the presence of pain cannot be determined only from the activity in sensory neurons. For this reason, different pain mechanism categories have been suggested based on the

main driver that contribute and maintain the experience of pain (39). Specifically, LBP can be characterised by a dominant nociceptive, neuropathic, or nociplastic mechanism, or a combination of them (40). Key characteristics and features are identified for each pain mechanism (39). In people with nociceptive LBP, the main drivers of pain are noxious thermal, mechanical, or chemical stimuli which activate specific sensory receptors, called nociceptors (40). There are three main classes of nociceptors: thermal, mechanical, and polymodal (41). Thermal and mechanical nociceptors consist of both myelinated A-fibres and unmyelinated C-fibres, while polymodal nociceptors exclusively include unmyelinated axons (41). The type of nerve is critical in determining the conduction velocity of the nociceptive stimulus and its spatial discrimination, as unmyelinated axons are responsible for transmitting nociceptive signals at a slower rate and poorly localised (42). When driven by a nociceptive mechanism, the experience of LBP is proportional to the nociceptive input, and it is well localised (40). This includes pain that can originate from several musculoskeletal tissues able of eliciting nociception. Instead, a lesion or disease of the somatosensory nervous system is responsible for neuropathic pain (40). When a nerve in the lumbar region is compromised, shooting pain, altered sensory perception, and muscle weakness within dermatomal distribution are signs and symptoms suggesting for the presence of neuropathic LBP (40). Finally, nociplastic pain mechanisms lead to LBP characterised by a disproportionate and unpredictable pain response compared to the nociceptive stimulus, along with widespread hypersensitivity, even to non-musculoskeletal stimuli (40). Rather than mechanical factors, nociplastic pain is highly influenced by fatigue, cognitive and psychological issues, and sleep problems. Such

mechanism-based classification of pain has been proposed because better responses to treatments are expected when treatments are delivered according to the underlying pain mechanism (39,40).

In people with nociceptive LBP, pain can result from two primary sources: injury or damage of a musculoskeletal component of the lumbar spine, leading to somatic pain, or the noxious stimulation of an internal organ, resulting in visceral pain (20). This thesis will specifically focus on somatic pain because of its relationship with movement and mechanical loading. In the lumbar region, several musculoskeletal structures are considered potential sources of LBP because innervated by A- and C-fibres, and painful when stimulated by changes in mechanical loading (20). Specifically, intervertebral disc, laminae, zygapophysial joint, vertebral endplates (i.e., Modic changes) and vertebral body, muscles, thoracolumbar fascia and ligaments have been shown to have both A- and C-fibre nociceptors, making all of them potential candidates for generating LBP (1,43,44). Diagnostic tests have been proposed for the identification of the source of LBP based on the pain response to mechanical stress, but with inconsistent findings (45). Notwithstanding the inconclusive findings on the use of diagnostic tests, there is evidence to support how different movement and activities can exacerbate or relieve symptoms based on the mechanical stress applied to lumbar structures (46). For example, repeated movements in lumbar extension or sustained lumbar lordosis have been suggested as potential mechanisms irritating nociceptors in the laminae and interspinous ligaments resulting in clinical LBP (46,47). Movement in hyperextension and other activities requiring lumbar extension have also been advocated as provoking activities for facet joint syndrome and lumbar spine stenosis (i.e., narrowing of the

central spinal canal and lateral foramens) (46,48). Pain provoked by all these structures is often relieved by sitting, lying down, and trunk flexion (46). In addition to an improvement in symptoms, the repetition of specific movements can have an effect on the distribution of symptoms which become more localised in the lumbar region and result in the so called “centralisation phenomenon” (49). This clinical phenomenon has been reported for discogenic pain when postures and movements in lumbar extension are performed (49). Collectively, there is evidence to support the presence of different sources of pain in the lumbar region, and the strong impact that movement and posture can have on mechanical loading and nociception. A recognised characteristic in people with NScLBP is the occurrence of pain in response to movement and physical activity, a phenomenon known as movement-evoked pain (MEP) (50,51). Specifically, MEP has been defined as pain acutely provoked and experienced in response to active or passive movement of the involved tissue (52). Unlike resting or recalled pain, MEP is intrinsically related to the physical activities and movements that provokes it, thereby offering relevant insights into the functional limitations imposed by LBP (52,53). Interestingly, MEP is more related to pain sensitivity compared with resting or recalled pain, and potentially also more responsive to interventions, all elements that offer important implications for the assessment and management of people with LBP (53–55).

## 1.4 Interaction between movement and pain in low back pain

Clinical observations have shown that specific movements or postures can either worsen or alleviate symptoms in people with LBP (46,49). Based on these observations which support the impact of movement on pain, various movement-based classification

systems have been proposed (56). The identification of patient subgroups has represented a clinical and research priority over the last three decades since better outcomes are expected when treatments are personalised and targeted to the underlying cause of pain (57,58). Furthermore, personalised treatments not only address the specific pathology but also take into account individual motor strategies, lifestyle, and daily activities, ensuring a comprehensive approach to patient treatment and management. Given that in people with NScLBP the cause of pain cannot be clearly identified, movement-based classification systems have been proposed, especially for those patients with nociceptive pain as main driver of their condition (59). Movement-based classifications categorise patients based on their pain response to mechanical loading and standardised movements (56,59). When the pain response is assessed after specific movements or postures, different approaches are used to identify subgroups, including (i) clinical observations; (ii) physiological and psychological models derived from experimental observations; and (iii) data-driven subgroups obtained from statistical analyses (57). The first approach includes the McKenzie subgrouping system, or mechanical diagnosis and treatment scheme, which focuses on determining whether symptoms of LBP can be improved through direction-specific, repeated lumbar movements or sustained postures (57,60). Different categories are identified within this scheme, with treatments focusing on the redistribution of mechanical loads on musculoskeletal lumbar structures (56,60). The Movement System Impairment Syndromes (MSI) scheme and the O'Sullivan Classification System (OCS) are based on physiological and psychological models (61,62). The MSI aims to identify the direction of spinal movements and loading that increase symptoms (62).

The underlying rationale for this classification is that repeated movements and sustained postures can disrupt joint movement precision, leading to microtrauma and, in some instances, macrotrauma (56,62). Treatments following the MSI scheme focus on adjusting spine alignment and limiting movements in both the affected lumbar region and in the direction that induces pain, while also distributing movement to other joints (16,62). In contrast, the OCS distinguishes two primary categories of movement impairment, "pain avoidance" and "pain provocation" (61). Within these categories, individuals with LBP may exhibit either adaptive or maladaptive pain responses (61). Adaptive responses include protective behaviours against actions that reproduce symptoms, while maladaptive responses involve movements and cognitive processes that exacerbate the painful condition by affecting the musculoskeletal system (61). Regardless of the specific category identified by the OCS, treatments include motor control and graded exercises, complemented by cognitive behavioural interventions that address altered beliefs on the relationship between pain and movement (17,61). Differently from other classifications, the OCS has been the first to also consider psychological factors in the assessment and treatment of NScLBP (61). Finally, data-driven classification systems are based on a comprehensive analysis of multidimensional data, both patient-reported and clinician-measured (57,63). These systems let the data to "speak for itself", without relying on clinical opinions or theoretical models (57,64). In recent years, several studies have aimed to subgroup individuals with NScLBP across various domains, aligning with the biopsychosocial framework (65,66). The shift towards developing data-driven subgroups, as opposed to those based on clinical opinions or theoretical models, comes from the observation

that traditional methods can be overly reductionist, typically focusing only on spinal movements and postures (67,68). Additionally, traditional classifications are more susceptible to clinical biases since they are dependent on subjective assessments (68). Movement-based classifications have also demonstrated heterogenous interrater reliability, leading to doubts on their consistency and applicability (63,69). Data-driven approaches, in contrast, are better equipped to manage the complexity and heterogeneity typical of clinical populations, ensuring that patients with LBP can be classified without the risk of leaving some unclassifiable. For instance, some studies using traditional classification systems made belonging to a specific subgroup a criterion for inclusion, which limits the applicability of their findings to only a subset of the clinical population, thereby reducing their external validity (68). Despite these limitations highlighted by a recent systematic review with meta-analysis (68,69), it is important to mention that recent randomised controlled trials have demonstrated a clinically significant reduction in pain and disability when treatments were delivered in accordance with movement-based subgroup classifications compared to strength and flexibility exercises or usual care (i.e., any of those treatments offered by the health-care professionals, like massage, chiropractic care, or injections) (16,17). A way to integrate traditional approaches with newer ones involves examining the interplay between movement and pain, including the response to pain provocative movement, within a multidimensional framework (50). Recent studies adopted this approach, and they have summarised multidomain data from a cohort of 300 patients with NScLBP, underscoring the relevance of MEP in this clinical population (64,70). Specifically, these studies found that pain experienced during repetitive spinal bending is associated with

increased pain sensitivity and psychological distress (64). Recent findings also showed that MEP has a predictive role on patient outcomes. For instance, a longitudinal analysis of older adults suffering from chronic LBP revealed that MEP reported at baseline was associated to higher disability and lower self-efficacy after 12 months (71). Similarly, another study of patients with LBP showed that those who reported their pain as unchanged, improved, or absent during a battery of physical tests experienced a larger improvement in pain at a 3-month follow-up compared to participants who indicated their pain worsened during the same physical tests (72). Taken together, these data support the impact of MEP in people with NScLBP and the importance of its assessment.

Although existing classification systems consider movement and pain in their assessment and treatment strategies, they mainly focus on the unidirectional relationship between movement and pain. This means they primarily investigate how movement affects pain and how changing movement can reduce pain. However, new conceptual frameworks are highlighting the importance of understanding the bidirectional relationship between the two, specifically examining pain associated with movement, and its effects on movement and physical activity (50,51). In the context of a bidirectional relationship, while it is recognised that movement can provoke pain, observations from people with clinical pain also suggests that pain affects how people move. For this reason, different theories have been proposed to describe how and why pain changes how people move (reviewed below).

Collectively, these findings not only underscore the critical role of MEP on patient outcomes but could also be interpreted with those neurophysiological and motor differences observed in people with movement-evoked LBP. Specifically, people reporting LBP while performing a reaching task showed longer reaction time, delayed peak velocity, greater movement variability, and altered cortical activity compared to an asymptomatic control group (73). It is plausible that motor differences present during the performance of the painful movement could play a role in the worsening of symptoms in this population. However, the relationship between motor differences and pain provocative movements remains unclear, including whether these motor differences are specific to the movement that causes pain. Addressing these questions within the clinical population presents significant challenges, primarily due to the influence of psychological factors on MEP and its heterogeneous presentation in people with NScLBP. Understanding why pain leads to changes in movement strategies is key for developing targeted and effective treatments.

## 1.5 Theories on motor adaptation to pain

Based on the observed motor strategies in people with musculoskeletal pain, several theories have been developed to describe how pain affects movement, with new experimental and clinical data supporting or challenging them. Originally, two main theories were proposed to explain motor adaptation to pain. The vicious cycle theory predicts that muscle activity consistently increases in response to pain, regardless of the performed task (74). This sustained activity results in reduced blood flow and accumulation of algesic substances, which in turns leads to more pain (74). Instead of a

stereotypical increase in muscle activity, the pain adaptation theory hypothesises the presence of different types of muscle activity changes (75). Specifically, this theory predicts a reduction of the activity of those muscles that are painful or produce the painful movement, whereas the antagonist muscles increase their activity (75). Although some experimental data support these theories (76–79), several findings on motor adaptations in people with clinical and experimentally induced pain are not in accordance with them, suggesting the presence of more complex and heterogeneous mechanisms. Also, these theories consider nociception and pain interchangeably, despite the multidimensional nature of the latter. A more comprehensive theory has been proposed accounting for the multilevel and heterogeneous changes observed in how people change the way they move while in pain (80,81). The proposed theory describes five key elements based on the core principle that adaptations to pain aim at minimising pain and protecting the painful body region from further pain and/or injury (80). For this reason, pain is considered a motivational stimulus that induces changes in how people move. The five key elements of the proposed theory are presented in Figure 1.1.

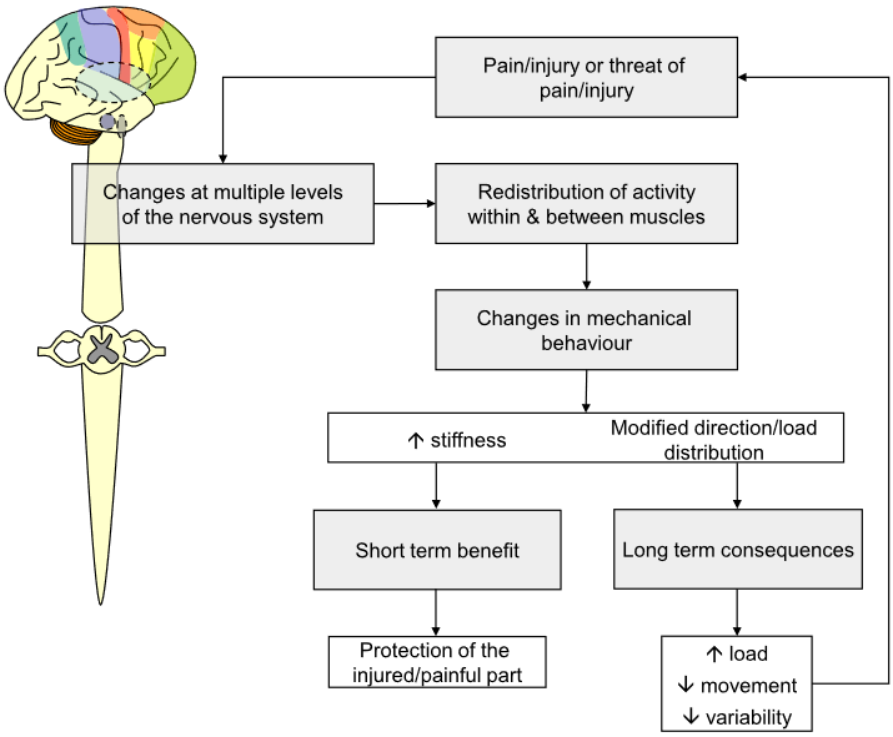


**Figure 1.1** *Contemporary theory on motor adaptation to pain.*
*From: Hodges PW. Pain and motor control: From the laboratory to rehabilitation. J Electromyogr Kinesiol. 2011 Apr;21(2):220-8, with permission.*

This theory finds support and it has been confirmed by several findings obtained from clinical and experimentally induced pain studies. Evidence using high-density electromyography supports the redistribution of muscle activity within muscle (82), as well as between muscles as demonstrated by changes in muscle synergies (83). By changing muscles activation and their coordination acting on the joint, the CNS leads to changes in movement and kinetics that redistribute the biomechanical load with the aim of protecting the painful region from further pain and/or injury(84–86).

Considered within the context of MEP, the proposed theory would predict that people change their movement to experience less pain and protect the painful region.

Thus, whether pain is provoked by movement, individuals should change the movement to experience less pain. Such changes have been hypothesised to occur along a spectrum of potential adaptations, extending from activity redistribution to movement avoidance (87). Indeed, the most straightforward solution would be avoiding the movement that is painful, which can have implications in both physical and psychosocial domains. For example, deconditioning is commonly observed in people with NScLBP, with alterations in muscle structure and composition (88). Also, movement avoidance could lead to activity limitations and affect the psychosocial domain of people with LBP (89). Indeed, MEP and its consequent movement avoidance can affect activity engagement and interfere with daily life activities (53). The recently proposed "Pain-Movement interface" framework underscores this interaction, highlighting how MEP, pain interference, and activity engagement collectively influence disability and patient outcomes (53). Therefore, investigating the impact of MEP on movement is fundamental due to its impact on people's lives.

Several other theories have been proposed to describe the impact of pain on movement and sensorimotor control. However, most of them focused on other factors related to the psychological and social domains. For example, the Fear-Avoidance Model of Pain hypothesis that movement avoidance results from a threatening interpretation of pain due to catastrophising thoughts and fear of pain (89). While such response might temporarily minimise pain, it can ultimately result in disuse, disability, and, paradoxically, increased pain over the long-term (89). Other similar theories also focusing on the psychological components are the Avoidance-Endurance Model (90), and the Integrated Pain Adaptation Model (91). The latter is similar to the theory on

motor adaptation to pain, but it also considers the sensory-discriminative, motivational-affective, and cognitive-evaluative components of pain and their influence on sensorimotor control. The theory of motor adaptation to pain, instead, primarily focuses on the physical component and the direct impact of pain on movement, and, for these reasons, it will represent the foundational framework for this thesis. This theory has been extensively validated, with substantial evidence supporting its claims regarding the general effects of pain on movement. However, findings from this thesis will provide further insights on the effects of pain on movement, specifically when movement is also pain provocative.

A long-debated question is whether motor differences observed in the clinical population are the cause or the effect of LBP. From a methodological point of view, to investigate whether pain changes how people move requires testing a causal relationship. This relationship can be evaluated at three distinct levels (92). The first and most common approach is a cross-sectional design to assess differences in people with and without LBP (i.e., seeing). However, such approach can only show if an identified change is associated to LBP, but not if it is specifically caused by LBP. The second level involves the ‘do’ action, or intervention, which disrupts the homeostatic state of a system through an external manipulation. In this context, the alteration is achieved by inducing pain. This methodology suggests a temporal relationship between the onset of pain and the observation of motor adaptation, as determined by assessment of movement before and during the experience of pain. Finally, the third level for establishing causality is described by counterfactual reasoning, framed as 'what if' scenarios. Specifically, if it is hypothesised that pain alters movement in a

specific way, the manipulation of how pain is induced should result in changes of movement as anticipated. This suggests, for instance, that the adaptation might be proportional to the intensity of pain or change depending on the location of pain and/or the specific movements that provoke it. In other words, the third level considers what would have happened in different circumstances of pain. This thesis will explore all levels of causal relationship between pain and motor strategies, with a specific focus on the effects of MEP on movement.

## 1.6 Motor strategies in clinical low back pain

To investigate if motor strategies differ between people with and without NScLBP, researchers have extensively analysed both movement and muscle activity during a range of tasks. Data collected from people with NScLBP were then compared to those from individuals without LBP to identify potential differences suggesting whether motor differences were related to the presence of LBP or not. Several changes have been identified over the last five decades of research, and findings have been summarised in systematic reviews and meta-analyses (93–96). Trunk kinematics, including ROM, has been one of the main physical outcomes investigated. Data from several studies and pooled in meta-analysis revealed that people with NScLBP show a restricted ROM during lumbar movements across all planes of motion (i.e., forward and backward bending, lateral flexion and axial rotation) (94). However, despite the large effect size of meta-analyses, findings were always affected by a large statistical heterogeneity as demonstrated by the $I^2$ being higher than 80%, with the source of such heterogeneity not explained (94). Similarly, qualitative summary revealed that in many functional activities

like sit-to-stand, pick up an object, lifting, stair climbing and sport activities, people with NScLBP exhibit reduced ROM in the sagittal plane (94). Also in this case, findings were not consistent across studies with some showing no differences with control groups or in some studies an increase of ROM was observed in people with NScLBP (94). Findings from another recent systematic review with meta-analysis revealed no differences in the ROM of the lumbar region in people with NScLBP during walking (97). However, altered coordination was observed, with more in-phase movement between the thoracic and lumbar spine (97). Collectively, findings from studies investigating kinematics in people with NScLBP highlight the presence of differences in how people move and the importance of identifying factors that could explain the observed clinical heterogeneity in order to inform assessments and treatments (94,97).

Beside kinematics, the electromyographic activity of trunk muscles in people with NScLBP has been investigated during tasks in which trunk muscles act as primary movers or with a postural control role based on feedforward or feedback mechanisms. Evidence from meta-analyses revealed alterations in the activity of the erector spinae with increased activity during walking and forward bending (93,97). In forward bending, about half the people with NScLBP do not present the flexion-relaxation phenomenon, which means that the erector spinae remains active resulting in a higher electromyographic activity compared to that observed in people without NScLBP (93,98). During other functional activities, like lifting, findings in people with NScLBP are more heterogeneous with some studies showing an increase, no changes or decrease of erector spinae activity, which were also phase dependent (99). This is in accordance with another systematic review highlighting task-dependent changes in muscle activity

(100). Regardless of the direction of change, both an increase and decrease of muscle activity could have negative biomechanical implications on the lumbar region. For example, a sustained activity of the erector spinae during low level activities like walking could increase the compressive load on the intervertebral disc (100,101). Similarly, higher activation of the erector spinae during forward bending increases the moment acting on L5/S1 (102). A reduction of activity of the erector spinae, instead, could impair the control of movement between spinal segments, making the system relying more on passive spinal structures (19). Differently from superficial muscles, changes in the recruitment of deep trunk muscles, including transversus abdominis, internal oblique and deep multifidus, consistently showed a delayed activation (96). Results pooled from different studies present low to moderate heterogeneity supporting a larger delay of the transversus abdominis to both expected and unexpected perturbations in people with NScLBP (96). Similar findings have been observed for the internal oblique and deep multifidus, but with smaller effect size (96). Altogether, these data reveal impairments in both feedforward and feedback control which make the system more unstable to biomechanical perturbations.

The importance of kinematics and muscle activity differences in people with NScLBP is supported by a systematic review highlighting the presence of movement and muscle activity biomarkers to discriminate people with NScLBP from asymptomatic populations (103). Two groups of movement biomarkers were identified, one focusing on spine kinematics during forward and backward bending, and the other one on lumbar-hip coordination during functional activities (103). Additionally, the authors also identified two groups of muscle activity biomarkers focusing on the temporal

recruitment of trunk muscles after postural perturbations, and the erector spinae activity during full forward flexion (103). Within a biopsychosocial framework, the proposed biomarkers refer to mechanical components, hence the biological domain of LBP. Taken together, clinical data supports the theory of motor adaptation to pain, with movement and muscle activity biomarkers consistent with this theoretical framework. Specifically, the reduction of spinal movements and changes in the lumbar-hip coordination represent alterations in the mechanical behaviour of the trunk, intended to protect the lumbar region. A similar interpretation is proposed for changes in muscle activity since the absence of the flexion relaxation phenomenon during spinal bending can represent potential strategies to protect the lumbar region. Although the identified motor adaptations serve a protective role for the painful region in the short term and are thus considered beneficial, maintaining these adaptations in the long term can be detrimental (80). Alterations in the biomechanical load could have consequences since an increase of muscle activity and axial compression can result in disc degeneration (80,100). Also, the avoidance of movement, altered motor variability and reduced ROM could lead to deconditioning of muscles and sensorimotor restriction in the long-term (80,87).

Although kinematics and muscle activity data show that people with NScLBP present with altered motor control compared to asymptomatic populations, these differences are characterised by a large heterogeneity. This is not surprising, given the comparison of two distinct populations, which provides limited insights into the causal relationship between pain and movement. To obtain stronger evidence on the causal effect of pain on movement, it is necessary to apply an intervention (i.e., induce pain by

'doing') to allow for the assessment of the same subject under different conditions, while also controlling for changes in the pain experience over time. For this reason, experimental pain models have been extensively used to investigate the effect of pain induced in the lumbar region on movement. Since the intervention is applied within the same subject, the use of experimental pain models also removes the effect of potential confounders that are present when data from different populations are compared. Thus, a comprehensive overview of experimental models to investigate motor adaptations to pain are summarised in the next section.

## 1.7 Motor adaptations in experimentally induced pain

Over the last five decades, motor adaptations to pain have been investigated using different pain models and targeting different body locations. Experimental pain models allow to assess how someone moves before, during and after pain is experienced, therefore monitoring how pain affects movement in a within-subject design (104). Also, the location and intensity of perceived pain can be partially standardised using experimental models (42,104). Thus, it is possible to test whether pain causes motor adaptations, and whether such adaptations outlast pain.

The responses to nociceptive inputs have been investigated considering a variety of motor outcomes at different levels of the motor system, such as corticospinal excitability, motor unit and muscle activity, kinematics, and kinetics (105–107). Overall, experimental pain models can be classified based on the temporal stimulation of nociceptors and on the tissue stimulated (42). Regarding the temporal characteristics, nociceptive stimuli can be divided into phasic and tonic (42). The former refer to brief

stimulations lasting less than or a few seconds and include electrical and thermal stimulation (42). Instead, tonic pain models consist in sustained nociceptive stimuli, which can last from a few minutes to hours based on the experimental pain model (42,104). In terms of stimulated tissues, experimental pain models usually target the skin (i.e., superficial pain) or musculoskeletal tissues (i.e., deep pain), resulting in different types of stimulated receptors (42,108). In the lumbar region, deep pain has been induced by stimulating different structures, including the erector spinae and the interspinous ligament (76,109). Due to the distinct spatial and temporal characteristics of nociceptive stimuli, experimental pain models present a range of advantages and limitations. Superficial pain models, which are non-invasive, are easier to deliver. Also, they allow for a more precise control over the intensity, area of stimulation, and duration, thereby enhancing reproducibility across studies and subjects (42). However, superficial pain models are less suitable for recreating a painful sensation like clinical pain, as demonstrated also by a lower involvement of the limbic area during pain processing compared to deep pain (79,110). In terms of temporal characteristics, phasic pain models like electrical stimulation guarantee an immediate onset of the pain sensation and allow to modulate and standardise the duration of the nociceptive stimulus (42). For example, phasic pain models are often used to assess the response to pain during both motor preparation and motor execution, providing important insights on the effects of pain on sensorimotor control (111,112). Instead, the temporal dynamics of tonic pain models is more difficult to control, and the pain sensation cannot be modulated based on external factors. Habituation, defined as the process by which an individual's response to a nociceptive stimulus decreases over time without

any change in the stimulus itself, represents a limitation of some experimental pain models, especially thermal and electrical stimulation (113).

An overview on the most common phasic and tonic experimental pain models to investigate motor adaptations to pain (hypertonic saline injection, capsaicin, thermal stimulation, and electrical stimulation) is presented below.

*Hypertonic saline injection (HSI)* consists in the injection of hypertonic saline solution (0.5 ml, 5.8%), typically in the belly of a muscle, but other locations have been also investigated, such a tendon and ligaments (42,109). Reported pain intensity after HSI is proportional to the volume, concentration, and infusion rate (114). Compared to thermal stimulation, HSI activates a broader population of nociceptors, mainly chemical receptors but also receptors with both low and high mechanical threshold belonging to C- and Aδ-fibres (42). Experimental pain induced by HSI is usually described as 'aching', 'cramping', 'tight', and 'spreading', and it usually lasts ten minutes, with a peak in the pain sensation reported after 1-2 minutes (108). A longer duration of the experience of pain is achieved through continuous infusion of the hypertonic saline solution (108). Beside reproducing pain in the stimulated area, HSI often results in referred pain (108). The injection of isotonic saline solution has been implemented in some studies as a control condition for HSI.

*Capsaicin* induces hyperalgesia through topical application on the skin, although intradermal and intramuscular injections are also available options (42). Capsaicin mainly binds to TRPV1 receptors activating C mechano-heat fibres (42). Moreover, this model induces pinprick hyperalgesia through the activation of Aδ and C afferent fibres,

as well as mechanical allodynia, primarily mediated by Aδ-fibres (115). Mechano-insensitive C nociceptors, also known as silent nociceptors, are key for the hyperalgesia induced by capsaicin (116). The topical model of capsaicin is a non-invasive method able to produce stable and long-lasting hyperalgesia.

*Thermal stimulation* consists in the application of cold, heat, or laser stimuli. Cold sensation is mediated by Aδ-fibres, whereas cold pain is mediated by C-fibres (117). Instead, heat sensation is mediated first by Aδ-fibres ('first pain' felt within less than 0.5s), and C-fibres giving a delayed pain sensation of longer duration and poorly localised (42). Aδ-fibres are activated when the skin is heated with fast rate. With laser stimulation, both Aδ and C-fibres are activated simultaneously, leading to a 'pricking' sensation (118).

*Electrical stimulation* can be delivered via surface or indwelling electrodes (42). The timing and intensity of electrical stimulation is easy to control, which make this model useful to characterise the temporal aspects of motor adaptations to pain, not only during motor execution but also motor preparation (111,112). Also, changes in the waveform type, frequency, and duration of the stimulation allows for the activation of different afferents and nerve structures, leading to different pain sensations (119). However, electrical stimulation is not selective on the type of stimulated receptor because it activates synchronously all peripheral nerve fibres bypassing the sensory nerve endings (42). Another limitation of electrical stimulation is the habituation observed in pain perception, leading researchers to use this method only for

reproducing phasic pain, as the nociceptive stimulus is applied for just a few seconds (112,120).

The effects of experimental pain on the motor system have been summarised in systematic reviews and meta-analyses, with changes observed both at the central and peripheral levels. Experimentally induced pain results in a reduction of corticospinal excitability, especially during tonic pain and when the pain is induced in a distal body region (105). However, when individual data were considered, the results appeared heterogeneous with around two thirds of participants showing a reduction and one third showing an increase in corticospinal excitability, often resulting in no group differences (105,121). Heterogeneity of findings is also present based on the painful body region (105). Although evidence from limb pain showed a reduction, tonic pain experimentally induced in the lumbar region resulted in an increase and no changes of corticospinal excitability of lumbar muscles (105). This conflicting evidence suggests that different neurophysiological mechanisms could be involved based on what body region is painful because of the differences in their functional role. At a more peripheral level of the nervous system, changes in muscle activity and motor unit recruitment were observed when pain was induced experimentally (106). Specifically, evidence supports a reduction of discharge rate of motor units in the painful muscle or in those proximal to the painful body region (106). Similarly, evidence supports a reduction in the activity of limb muscles, especially at higher levels of force production (107). To accomplish the task goal despite a reduced activity of the painful muscle, evidence suggests that the CNS redistributes the activity both within and between muscles, with adaptations depending on the available degrees of freedom (85). Similarly to the evidence on

corticospinal excitability, findings on muscle activity from the trunk region were more heterogenous with changes that appear different based on the muscle and performed task. For instance, a task involving trunk flexion-extension demonstrated an individual-specific reorganisation of muscle activity when pain was experimentally induced in the lumbar region (122). This reorganisation resulted in an overall increase in muscle activity across various muscles, but without a consistent pattern between individuals (122). In addition to the execution of task, there is evidence to suggest that pain induced experimentally in the lumbar region affects the recruitment of trunk muscles during both internal and external perturbations (123,124). The heterogeneity across studies suggests that different adaptations to pain might be present based on the biomechanical role of the painful muscle/body region and performed task.

Pain experimentally induced does not typically affect the achievement of the task goal. However, there is conflicting evidence regarding how pain influences the execution of movements, as observed through kinematic and kinetic analyses (107). This suggests that while the task can be accomplished, the way it is executed appears to be partially affected by the presence of pain. For example, pain experimentally induced in the shoulder resulted in lower shoulder elevation and elbow flexion during a reaching task, and changes in axioscapular muscle control (125). However, no changes were observed during other upper arm movements like throwing (126). Similarly, pain induced in the lower limb did not affect gait kinematics , but differences were observed during a postural control task (107). At the spinal level, experimental neck pain resulted in changes in the coordination of intervertebral movements (127), but contrasting evidence is present regarding head kinematics (128). Also, pain induced in the lumbar

region affected lumbar kinematics in some studies but not in others (129,130). Although several evidence suggests changes in muscle activity (111,122-124), kinematics seems to remain often unaffected. This can be due to the redundancy of the motor system, which allows for the achievement of task goals in a similar manner, though with modifications in the coordination across muscles. This is indirectly supported by a systematic review examining the effects of experimentally induced limb pain, which revealed minimal changes in kinematics, but with the main differences observed in kinetics, attributed to the reorganisation of muscles acting on the assessed joint (107). The absence of consistent changes in kinematics contrasts with clinical findings. However, several factors could explain this difference. First, it is possible that the nociceptive stimulus induced by tonic pain models is too short to induce kinematic changes. Secondly, heterogenous differences across subjects might result in no differences before and during pain. Finally, tonic pain model does not allow for the presence of motor solutions which are able to reduce the intensity of experienced pain.

Although evidence on the effects of experimental pain on muscle activity and kinematics have been summarised, this was limited to limb pain, and the findings cannot be directly applied to the trunk region. This limitation is due to variations in the biomechanical role and potential differences in neurophysiological mechanisms, as demonstrated by observed changes in corticospinal excitability between appendicular and axial muscles (105,121). Therefore, there is a need to summarise the evidence on the effects of pain induced in the lumbar region to understand (i) whether it causes motor adaptations; (ii) whether such motor changes are similar to those observed in the

clinical populations with LBP, and, more broadly, (iii) how they align with the proposed theories on motor adaptation to pain.

Additionally, several studies have investigated the effects of pain experimentally induced in the lumbar region on motor adaptations, but these were mainly limited to the use of tonic pain models which do not allow to reproduce MEP. Thus, the bidirectional relationship between pain and movement remains underexplored, as well as testing the effects of pain on movement at a higher level of causality, commonly described by counterfactual scenarios (92). To reproduce and investigate the effects of experimental MEP on movement, key characteristics of MEP need to be reproduced by the pain model. Specifically, these include bidirectionality and temporality since they are essential components of MEP and contribute to its subjective and heterogenous nature among the clinical population (53). Bidirectionality refers to the type of relationship existing between pain and movement since movement can provoke or relieve pain, and, as supported by evidence described in the previous sections of this thesis, pain affects movement. In the context of the theory on motor adaptations to pain (80), MEP can represent a central phenomenon because if people change the way they move to protect the body region from further pain, then changing the movement that is pain provocative would represent a logical consequence. However, how this happens is still unclear. Based on the same theory, MEP might lead to motor adaptations ranging from muscle activity redistribution to movement avoidance with the general aim of accomplishing the task goal while minimising the pain provoked by movement (87). Therefore, the pain provocative movement could represent a fundamental factor shaping motor adaptations to pain, but this has not yet been tested. Temporality,

another characteristic of MEP, describes its pattern over time which changes accordingly with the type and intensity of the performed movement (53). Because of its temporality, a better understanding of MEP requires its assessment at multiple time-points, differently from rest or recalled pain (53). A critical aspect shared by bidirectionality and temporality is how movement and pain are associated in the time domain since the strength of the motivational stimulus offered by pain to change how the movement is executed depends on this association. In other words, if pain is immediately provoked by the performed movement, this is expected to be modified, and the new motor strategy, if pain-free, is expected to be sustained. Conversely, pain provoked by repetitive loading might result in a more difficult understanding of the relationship that exists between pain and movement. As a result, the movement remains unchanged, and pain persists. Thus, bidirectionality and temporality are essential components in the association between pain and movement, and critical for the investigation of motor adaptations to MEP. Tonic pain models fail to reproduce bidirectionality and temporality, thus models where experimental pain is modulated by movement have been suggested.

## 1.8 Methodologies to induce movement-evoked pain

The assessment of motor adaptations to MEP can be conducted through different experimental pain models, some of which have already been applied to induce MEP in the lumbar region. Delayed onset muscle soreness (DOMS), nerve growth factor (NGF), and electrical stimulation are the most common. Since experimental pain induced by DOMS and NGF is commonly experienced for several days, pain elicited by these

models is also defined as sustained or persistent (106,131). Before selecting any experimental pain model, it is crucial to consider both its advantages and limitations to reproduce the bidirectional and temporal characteristics between pain and movement. This evaluation is essential to ensure that the selected model allows to test the research hypotheses of interest. For example, when testing a counterfactual scenario to assess the effects of MEP, the only variable allowed to change between testing is the direction of the pain provocative movement, while the intensity, location, and type of pain sensation remain invariant. An overview of the experimental pain models to reproduce MEP is provided below along with their advantages and limitations.

*Delayed onset muscle soreness (DOMS)* is an exercise-induced muscle pain model, characterised by a temporary but intense soreness resulting from eccentric exercise (42). This discomfort typically reaches its peak 24 to 48 hours following the activity. Pain is experienced during movement, including both muscle contraction and stretching, and application of mechanical pressure (42). The mechanisms of DOMS are still partially unclear but different hypotheses have been suggested, including damage of connective and/or contractile tissue, muscle spasm, and inflammation with release of endogenous substances known to sensitise nociceptors (132). An advantage of DOMS is that it does not typically present as pain at rest but only with movement. However, it is not possible to define whether the observed adaptations after inducing DOMS are attributed to pain, fatigue or tissue damage. Also, the amount of experienced pain and damaged tissue cannot be standardised, so that it is not possible to reproduce a pain of similar intensity and location experienced and modulated by different movements.

*Nerve Growth Factor (NGF)* is a neurotrophic substance, and when injected into the muscle it induces long-term mechanical sensitisation and time-dependent hyperalgesia provoked by muscle activity (42). The increase in muscle soreness is dose dependent and it has been reported up to seven days after the injection of NGF (133). Some studies also investigated the effects of intradermal injection of NGF revealing mechanical skin allodynia with an expansion of the sensitised area around the injection site lasting up to 14 days (134). Nerve growth factor share some of the limitations of hypertonic saline injection because it is not possible to standardise the location and intensity of perceived pain. Also, the pain experienced after the injection of NGF increases gradually up to two days (133,134), which it makes unfeasible to test motor adaptations when participants start to experience pain. Finally, the experience of pain from NGF is dependent on muscle contraction (42,134), which precludes the assessment of motor adaptations to pain provoked by different directions of movement.

*Electrical stimulation,* apart from being used to induce phasic pain as described in section 1.7, it can also be used as experimental pain model to reproduce MEP (135,136). Despite some limitations due to the unspecific stimulation of receptors, electrical stimulation presents several advantages. Firstly, it allows to optimise both the bidirectional and temporal characteristics of MEP, and to modulate the nociceptive stimulus proportionally to the performed movement (135,137). In other words, the nociceptive electrical stimulation allows to recreate a closed loop between movement (or any other biomechanical input) and the delivered stimulation, so that any changes in the motor strategy can result in a reduction or increase of perceived pain (135). Secondly, perceived pain can be standardised across participants in terms of intensity

and location. Recent studies also showed that the use of sinusoidal waveforms resulted in minimal habituation over time compared to the use of square waves, which have been used traditionally for inducing phasic pain (135). Thus, electrical stimulation is the only experimental pain model that allows to compare motor adaptations induced experimentally by tonic versus MEP. This comparison has been investigated in a recent study looking at changes in maximal torque production during tonic and MEP using the same experimental pain model, with findings revealing a larger torque reduction during MEP (137). Finally, the association of the nociceptive input to movement and not muscle contraction has another important implication. Given that the CNS plans and executes movement considering it as a whole rather than focusing on the recruitment of individual muscles (138), pain associated with movement and not muscle contraction can provide more meaningful insights into how pain affects or is integrated into motor planning and execution because it reflects the approach of the CNS to handle complex, goal-directed actions (138). When pain is associated with specific movements, it may alter the way the brain plans and executes these movements, potentially leading to changes in motor strategies to avoid pain (139). Therefore, MEP induced by electrical stimulation allows the identification and use of a motor strategy able to reduce the intensity of the nociceptive stimulus.

Evidence on the effects of experimentally induced MEP revealed changes on motor preparation and motor execution at multiple levels of the CNS in accordance with the theory on motor adaptations to pain (137,140–142). Studies using NGF identified motor adaptations both in cortical excitability and motor output (140–142). Interestingly, meta-analyses from individual level data found that the reduction of

corticospinal excitability observed 2 days after NGF injection was associated to lower pain intensity, but over time such sustained reduction was associated to higher pain severity, supporting the positive short-term effect of motor adaptations to pain, but with potential long-term consequences (80,121). Motor preparation is also affected by MEP with evidence suggesting that motor adaptations could be specific to the direction of the painful movement (141). In detail, opposite changes in corticospinal excitability have been found during motor preparation when a muscle has an agonist or antagonist role while performing a painful movement (141). In addition to changes at the corticospinal level, changes in biomechanical loading, force production, and muscle recruitment resulting from MEP might also contribute to long-term symptoms (140,142,143). This has been suggested by a study showing a shift in the direction of force production several days after NGF injection (140). Studies using electrical stimulation to induce MEP also demonstrated that individuals redistributed the biomechanical load and changed their movement in response to pain, regardless of the pain location or performed task (135,144). Sensorimotor control is also affected by MEP since a delayed recruitment of trunk muscles was observed during rapid arm movements when coupled with pain induced in the lumbar region (111).

Accordingly with the advantages and limitations of experimental pain models, further insights have been provided by inducing MEP with electrical stimulation. For example, different patterns of motor adaptations were observed from the moment pain was induced (111,135,136), highlighting the critical nature of this initial period characterised by dynamic changes and, potentially, by learning processes on the relationship between pain and movement that are not captured by using NGF or DOMS.

Moreover, the presence of motor adaptations to MEP was associated with a reduction in perceived pain (135,144). However, in one study such reduction was not related to changes in the nociceptive input, suggesting that the act of “taking action” could be sufficient to reduce the perceived threat to the tissues and experienced pain (144). Thus, whether and how the observed motor adaptations represent a purposeful strategy to reduce pain remain unclear.

In the past, the role of motor adaptations as a purposeful strategy to reduce pain was investigated by inducing tonic pain in different body locations. However, this approach led to contrasting results, offering both support and rejection to the hypothesis that motor adaptations are specific to the pain location (84,145,146). A better understating might come from testing MEP induced by opposite directions of movement. Findings from this counterfactual scenario could further support the causal effect of pain on movement and whether motor adaptations are specific to the pain provocative movement. Neurophysiological mechanisms tested during motor preparation seem to support this hypothesis (141), but no studies have investigated the specificity of MEP to change the way people move. Whether motor adaptations are specific to the painful movement could advance our understanding on the relationship between pain and movement. Firstly, it will support the crucial role of MEP on the observed motor differences, making MEP an important component to be considered in the management of patients, potentially explaining some of the observed clinical heterogeneity. Secondly, knowledge describing the effects of MEP experimentally induced could inform the investigation of MEP in the clinical population by generating hypothesis to be tested. For example, inducing MEP might reveal insights on the acute

motor strategies used to reduce and avoid the pain provoked by movement. Thus, this thesis will not only summarise the evidence on what is known on the effects of pain experimentally induced in the lumbar region on movement, but it will also implement an experimental MEP model to understand whether and how the direction of the pain provocative movement is key to the observed motor adaptations.

## 1.9 Thesis aims, objectives and hypotheses

The primary aim of this thesis was to investigate the effects of MEP experienced in the lumbar region on how people move, with a particular focus on kinematic changes. Changes in kinematics was selected as the main outcome of this thesis because there is substantial evidence to support kinematic differences in people with NScLBP. Evaluating kinematics is relevant in the context of MEP due to the bidirectional relationship between pain and movement. Also, kinematics affects the biomechanical loading exerted on the lumbar spine, with potential consequences in the presentation of symptoms in clinical populations. Finally, advancements in wearable technology have made kinematics an accessible and objective outcome measure, enabling contributions to clinical practice through easier assessments of movement patterns. This accessibility ensures that the findings of this thesis can significantly influence future research and clinical approaches in the management of LBP. The secondary aim of this thesis was to determine if such motor adaptations are specific to the direction of the pain provocative movement, and if they represent a purposeful strategy to reduce pain in accordance with the theory on motor adaptation to pain. To address these main objectives, three studies were conducted by investigating the relationship between MEP

and movement at different levels of causality. An overview of the structure of the thesis is presented in Figure 1.2. The specific aims for each study presented in individual chapters are as follows:

- *Chapter Two* aimed to synthesise the evidence on the effects of pain induced in the lumbar region on kinematics and muscle activity through a systematic review. Findings from such systematic review are essential to support or refuse a causal relationship between pain in the lumbar region and movement, and to provide the background for the development of an experimental study using MEP. The hypothesis for this Chapter was that pain experimentally induced in the lumbar region causes motor adaptations.

- *Chapter Three* aimed to investigate whether pain induced in the lumbar region and modulated by movement in different directions leads to different motor adaptations. This Chapter also aimed to determine if these motor adaptations are a purposeful strategy to reduce pain. The hypothesis for this Chapter was that motor adaptations are specific to the movement direction that provokes pain, and that such adaptations are effective at reducing pain. Findings from this Chapter can provide evidence on the causal relationship between pain and movement based on a counterfactual scenario, supporting the importance of the direction of MEP in determining motor adaptations.

- *Chapter Four* aimed to subgroup people with chronic LBP based on their pain response to trunk movements, and to investigate if these subgroups show

distinct kinematics during functional tasks when compared to each other and to a control group of asymptomatic individuals. The hypothesis for this Chapter was that MEP in a specific direction influences how people move, leading to restricted spinal kinematics in the direction of pain-provocative movements when compared to individuals with LBP who experience pain in a different direction, and to a control group without LBP. Although this Chapter only investigates the relationship between pain and movement in terms of association (i.e., first level to prove causality), it is essential to translate and integrate experimental findings obtained in *Chapter Two* and *Chapter Three* with those obtained from clinical LBP.

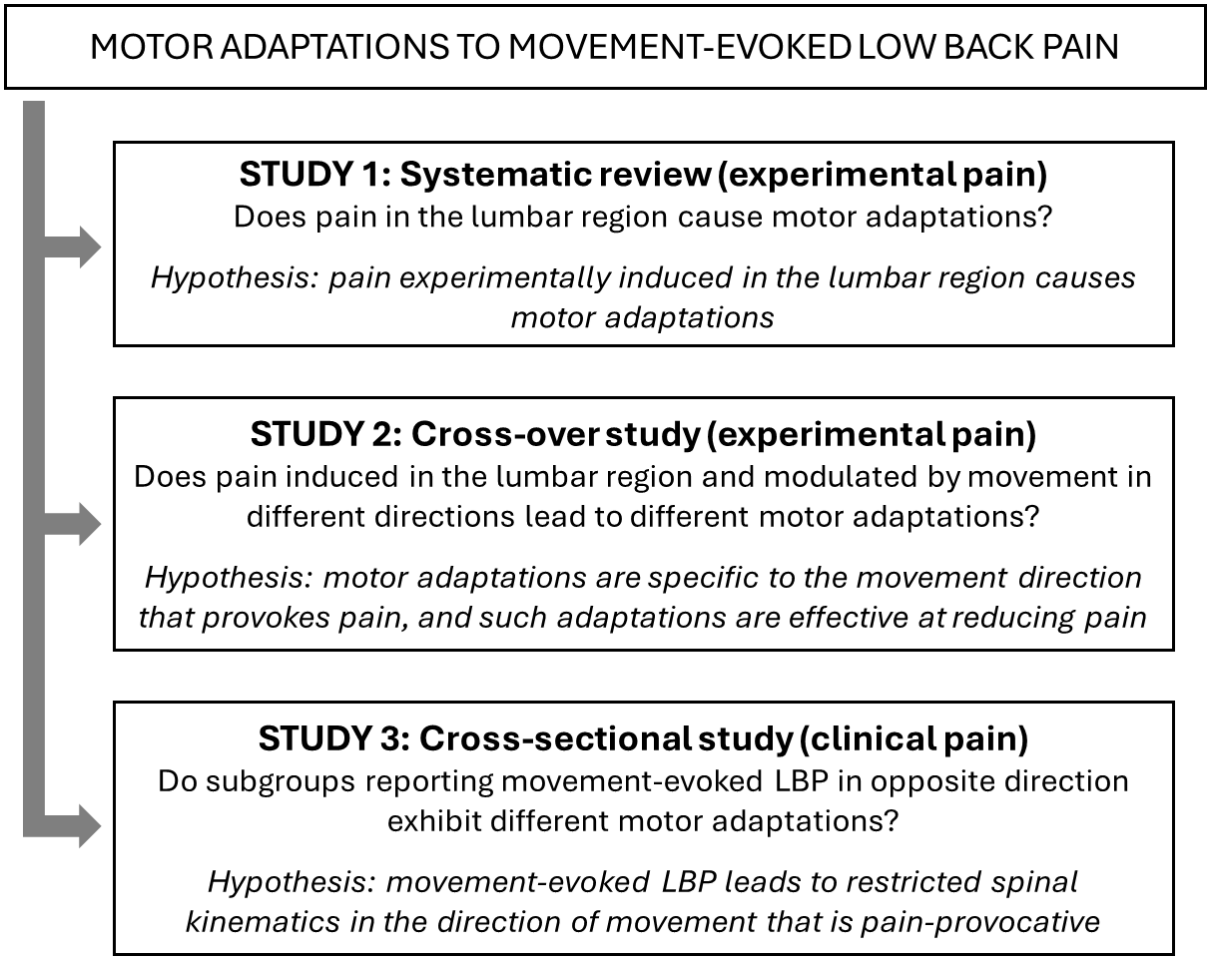


**Figure 1.2** *Thesis structure and main content of each individual study*

# CHAPTER 2 – NEUROMUSCULAR ADAPTATIONS TO EXPERIMENTALLY INDUCED PAIN IN THE LUMBAR REGION: SYSTEMATIC REVIEW AND META-ANALYSIS

This Chapter fully presents the content of a manuscript previously published by the author of this thesis (147). It includes text from the published work, with adjustments made to fit with thesis's objectives and minimise redundancy. Furthermore, the methodology used in this Chapter was also presented in a protocol paper published before conducting the systematic review (148).

Publications:

1. **Devecchi V**, Falla D, Cabral HV, Gallina A. Neuromuscular adaptations to experimentally induced pain in the lumbar region: protocol for a systematic review and meta-analysis. Syst Rev. 2021 Oct 15;10(1):270.
2. **Devecchi V**, Falla D, Cabral HV, Gallina A. Neuromuscular adaptations to experimentally induced pain in the lumbar region: systematic review and meta-analysis. Pain. 2023 Jun 1;164(6):1159-1180.

## 2.1 Abstract

Experimental pain models are frequently used to understand the influence of pain on the control of human movement. This Chapter aims to assess the effects of experimentally induced pain in the lumbar region of healthy individuals on kinematics and muscle activity. Databases were searched from inception up to January 31, 2022. In total, 26 studies using either hypertonic saline injection (n = 19), heat thermal stimulation (n = 3), nociceptive electrical stimulation (n = 3), or capsaicin (n = 1) were included. The identified adaptations were task dependent, and their heterogeneity was partially explained by the experimental pain model adopted. Reduced ROM of the lumbar spine in the presence of pain was supported by low quality of evidence. Meta-analyses revealed an increase of erector spinae activity (standardised mean difference = 0.71, 95% confidence interval [CI] = 0.22-1.19) during full trunk flexion and delayed onset of transversus abdominis to postural perturbation tasks (mean difference = 25.2 ms, 95% CI = 4.09-46.30) in the presence of pain. Low quality of evidence supported an increase in the activity of the superficial lumbar muscles during locomotion and during voluntary trunk movements during painful conditions. By contrast, activity of erector spinae, deep multifidus, and transversus abdominis was reduced during postural perturbation tasks. Given the agreement between these findings and the adaptations observed in clinical populations, the use of experimental pain models may help to better understand the mechanisms underlying motor adaptations to LBP.

## 2.2 Introduction

As described in *Chapter One*, pain influences the neuromuscular system at multiple levels. Current theories argue for non-stereotypical changes of the neuromuscular system in response to pain, and adaptations may range from subtle changes in motor unit recruitment to movement avoidance (80,87). When compared to asymptomatic individuals, several neuromuscular adaptations have been reported in people with NScLBP. For example, differences in the ROM and movement variability of the spine (149), intensity and distribution of muscle activity (128,150), timing of muscle activity (96), and corticospinal excitability (151) have all been identified. A recent systematic review identified that changes in spine kinematics and muscle activity are potential biomarkers to differentiate people with NScLBP from an asymptomatic population (103). However, the mechanisms underlying these adaptations remain unclear (87), and results from different studies investigating clinical NScLBP are often conflicting as they show opposite neuromuscular changes (152). In accordance with current theories on motor adaptations to pain, the goal of protection from pain or injury, or threatened pain or injury, can be achieved by changing neuromuscular strategies in a manner that is individual and task-specific (87,100). More broadly, this heterogeneity of adaptations can be attributed to the complexity of clinical pain since it is characterised by the interplay of several multidimensional factors (67,153).

Experimental pain models can provide direct evidence of the causal effects of a noxious stimulus on the neuromuscular system. As measures of neuromuscular control can be obtained from the same person before and during the experience of

experimental pain, these models allow to conduct within-subject comparisons to characterise individual-specific adaptations to pain, hence addressing the heterogeneity due to inter-individual variability. From a neurophysiological point of view, the availability of different experimental pain models offers several advantages because pain can be induced in different anatomical structures and modulated in time in different ways (104). For example, phasic, tonic, and persistent pain can be induced using electrical stimulation, hypertonic saline injection, and NGF, respectively (42,104). Finally, experimental pain models can be used to examine the influence of pain on movement without the impact of psychological and emotional factors usually associated with the subjective experience of chronic pain (42,108). From a clinical perspective, the different pain models may be used to reproduce different features of pain experienced by individuals with clinical NScLBP and investigate whether the noxious stimulus results in adaptations similar to those observed in individuals with clinical NScLBP (103).

Some of the effects of experimental pain on the neuromuscular system have already been summarised. Recent reviews have shown that experimental pain has an inhibitory effect on motor unit discharge rate and corticospinal excitability (105,106), although the pattern of changes may be influenced by the anatomical structure stimulated and the pain model adopted (106). One systematic review examined the influence of experimentally induced limb pain on kinematics and muscle activity (107). However, considering the differences in biomechanics and sensorimotor functions between appendicular and axial regions, the effects of pain experimentally induced in the low back may differ from what observed when pain is induced in the limbs.

This Chapter aims to synthesise the current evidence on the effects of pain induced in the lumbar region of healthy adults on kinematics and muscle activity through a systematic review. By confirming or refusing a causal relationship between pain in the lumbar region and movement, this Chapter represent a necessary step to inform and support the need of investigating the primary aim of this thesis. Further, this Chapter aims to investigate if neuromuscular adaptations are also induced remote to the lumbar region (2.a), if they outlast the duration of pain (2.b), and if they depend on the type of experimental pain model adopted (2.c).

## 2.3 Methods

The present review was conducted following a pre-defined published protocol (148) registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020220130) on 25/11/2020. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA, Appendix 4) statement 2020 was adopted to report this systematic review (154).

### *2.3.1 Eligibility criteria*

The PICOS framework (Population – Intervention – Comparator – Outcome – Study Design) was used to define the eligibility criteria.

*Population*. The population of interest was represented by healthy adults (≥ 18 years) without a history of LBP. When different groups were included in the same study (e.g., people with and without LBP), data were extracted only from the one of interest.

*Intervention*. Interventions of interest were represented by exogenous pain models applied over the lumbar region. Therefore, injection or topical application of algesic

substances (i.e., hypertonic saline, capsaicin, glutamate, and NGF), thermal stimulation, and electrical stimulation were eligible for inclusion. Endogenous pain models (e.g., DOMS) were not included in this review because the effect of pain on neuromuscular control risks being biased by potential confounders, such as fatigue and muscle fibre damage. When the experimental pain was delivered with a phasic modulation (e.g., electrical or thermal stimulation), pain needed to be induced in at least 50% of measured trials to make the study eligible for inclusion (otherwise the intervention of interest may have been more related to fear of pain rather than pain).

*Comparator*. In studies investigating the effect of experimental pain, measurements are usually conducted over four time points (or conditions): baseline (BASE), before any interventions are delivered; control (CTR), when a control intervention is delivered (e.g., isotonic saline injection or innocuous thermal stimulation); PAIN, when an experimental pain condition is delivered; and when the experience of the noxious stimulus is completely or almost resolved (POST-PAIN). To address the primary review question, both the BASE and CTR conditions were considered eligible for comparison with the PAIN condition. Moreover, the POST-PAIN condition was compared with the BASE and PAIN to investigate if the adaptations outlasted the experience of symptoms (secondary review question – 2.b). In the POST-PAIN condition, the level of pain (e.g., minimal pain or no pain at all) did not represent an element of restriction, and it was used as a factor in a subgroup analysis in case of heterogeneity of findings. To be included in the analyses, the POST-PAIN condition needed to be evaluated on the same day of PAIN.

*Outcomes*. Kinematics and muscle activity measured during voluntary or postural perturbation tasks represented the outcomes of interest. Postural tasks involve applying internal (e.g., rapid arm movements) or external (e.g., moving platforms) perturbations to challenge postural control, while assessing the motor response necessary to maintain or regain a steady state. The assessment of body kinematics included ROM, speed, quality and variability of movements. For the assessment of muscle activity, the intensity and onset of muscle activation (assessed by electromyography), as well as muscle recruitment (assessed by ultrasound or muscle functional MRI) were considered. No restrictions were imposed regarding the assessment of different body regions to understand if pain in the lumbar region also induces adaptations at remote sites (secondary review question – 2.a).

*Study Design*. Studies conducting within-subject comparisons were eligible for this review. Hence, repeated measure or randomised crossover studies represented the design of interest. Although the language of studies did not represent an element of restriction in the search strategy, only studies reported in English, Italian, or Portuguese were considered eligible.

### *2.3.2 Information sources*

Studies published prior to the 31st of August 2021 were searched initially by one reviewer (VD), and the search was updated up to the 31st of January 2022 by the same reviewer. MEDLINE (OVID interface), EMBASE (OVID interface), CINAHL (EBSCO interface), and ZETOC were the databases searched, in addition to Internet sites (PubMed and Web of Science, Clarivate Analytics) and grey literature databases

(OpenGrey and Ethos). Hand-searching was also conducted for relevant journals (PAIN, Journal of Neurophysiology, Journal of Pain, European Journal of Pain, and Musculoskeletal Science and Practice) and conference proceedings (International Society of Electromyography and Kinesiology, International Association for the Study of Pain, International Society of Biomechanics). Reference lists of included studies and reviews on experimental pain models were searched as well.

### *2.3.3 Search strategy*

We imposed no date, region, or language restrictions on the search. The search strategy was developed by one reviewer (VD) in collaboration with an experienced librarian. A comprehensive reporting for each database is included in the published protocol (148) and in Appendix 1. The search was slightly adapted for different databases, but consistency was ensured. Interventions and body region stimulated were the concepts considered into the search strategy, and they were connected as follow:

("experimental pain" OR "pain model") AND ("back pain" OR "low back")

Where "experimental pain" includes all free-text words commonly adopted to report the use of experimental pain in a study (e.g., "experimental pain", "pain induced", "induced pain", etc.) and "pain model" identifies the interventions (e.g., hypertonic saline, capsaicin, glutamate, electrical stimulation, etc.). Terms referring to the same concepts were separated by the Boolean operator "OR". Proximity searching was used when possible.

### *2.3.4 Selection process*

At every stage of the screening process, title and abstract of all records were stored on EndNote X9 (Clarivate Analytics). Duplicates were firstly removed by the software, followed by verification by one reviewer (VD). To facilitate the screening process between reviewers, all records were also exported on the web-based application Rayyan (155). Both stages of the selection process (title-abstract and full-text screening) were conducted independently by two reviewers (VD and HC) using a piloted screening tool. A third reviewer (AG) was consulted to mediate disagreement both during the title-abstract and full-text screening. Agreement between reviewers was quantified using the kappa statistic. When multiple records of the same study were available, they were collated in a single one (Appendix 2).

### *2.3.5 Data collection process and data items*

Data extraction was performed by one reviewer (VD) using a piloted extraction form. Accuracy verification of extracted data was conducted by a second reviewer (HC). A third reviewer (AG) was consulted in case of disagreement. When data were only available in figures, they were extracted with WebPlotDigitizer (version 4.4) software (156). Relevant data were extracted for each element of the PICOS framework, including characteristics of the sample, intervention delivered, comparator condition, outcome of interest, and study design. Outcomes of interest were collected for each available time point (i.e., BASE, CTR, PAIN, POST-PAIN). A detailed list of items is reported in the published protocol (see Table, “Characteristics extracted from included studies” in Appendix 3) (148).

### *2.3.6 Study risk of bias assessment*

Risk of bias (RoB) of included studies was conducted by two independent reviewers (VD, HC). When necessary, a third reviewer (AG) was consulted for arbitration. In contrast to what we anticipated in the study protocol (148), we only used the ROBIN-I tool to assess RoB. We preferred this approach to facilitate the comparison between studies since only four studies out of 26 had a crossover design. Our choice is also supported by the fact that most of the domains are the same or similar between the Cochrane risk of bias tool (RoB2) for crossover trial (157) and the ROBIN-I tool (158). Moreover, the GRADE system allowed the quality of evidence to be rated from the start as high quality when the ROBIN-I is used. The overall RoB of studies appraised with the ROBINS-I can be “low”, “moderate”, “serious”, and “critical” (158). The assessment was summarised and graphically presented for each RoB domain, along with the overall score. Furthermore, overall RoB was also reported in data synthesis to facilitate the evaluation of the strength of evidence and explore if RoB may represent a source of heterogeneity across findings.

### *2.3.7 Data synthesis and Meta-Analysis*

Data synthesis and reporting of findings was conducted to investigate whether pain induced in the lumbar region results in neuromuscular adaptations (primary review question), and if such adaptations outlast the duration of the noxious stimulus (secondary review question – 2.b). To ensure methodological homogeneity and facilitate the interpretation of findings, results from individual studies were grouped based on the outcome domain, muscle/body region investigated, and task category. Based on the

role of trunk muscles, five task categories were identified: locomotion, voluntary trunk movements, postural perturbation tasks, submaximal trunk contractions, and others (when a task cannot be included in any of the previous categories). Studies were included in a quantitative synthesis (with or without meta-analysis) if sufficient data were available. When meta-analysis was precluded, tabulation and graphical synthesis were provided using a vote-counting system and forest plots, respectively (159). Synthesis without meta-analysis were conducted in accordance with recent guidelines to facilitate the interpretation of findings and the identification of patterns in data (159). Results from individual studies were also narratively described. Quantitative syntheses and forest plots were developed using the package 'meta' in R software, version 4.1 (160). Results of individual studies were presented along with the adopted experimental pain model to understand if the latter could represent a potential factor for heterogeneity (secondary review question – 2.c).

Quantitative syntheses were conducted using effect measures for continuous outcomes. When the outcome of interest was reported across studies with different measures or assessed during different tasks, results were reported using the standardised mean difference (SMD) and 95% Confidence Intervals (161). Instead, when homogeneity was ensured, the mean difference (MD) was preferred. Since the design of included studies consisted of within-subject comparisons, SMD was computed from the mean and standard deviation (SDdiff) of within-subject changes (161). Therefore, the following equations were used for SMD calculation and related variance (v(SMD)) (162):

$$SMD = \frac{\bar{X}_{condition} - \bar{X}_{comparator}}{SD_{diff}}$$

$$v(SMD) = \frac{1}{n} + \frac{SMD^2}{2n}$$

where *n* is the sample size, $\overline{X}_{condition}$ is the group mean for PAIN or POST conditions, $\overline{X}_{comparator}$ is the group mean for BASE or CTR conditions, and $SD_{diff}$ is the standard deviation of the difference. For studies that expressed $\overline{X}_{condition}$ as a proportion of $\overline{X}_{comparator}$ (e.g., % change from BASE, with BASE representing 100% for each participant), the $\overline{X}_{comparator}$ corresponding to the standard deviation of the condition (PAIN) was used to compute the SMD.

Although the mean of change can be easily obtained from the mean values measured during the conditions of interest (i.e., $\overline{X}_{condition} - \overline{X}_{comparator}$), the $SD_{diff}$ might not always be reported (163). When a study reported the *p*-value of the comparison between conditions, its value was used to obtain the *t*-statistic (imputed in a Microsoft Excel spreadsheet by entering "=tinv(*p,df*)", where *p* is the reported p-value and *df* is the degree of freedom and equals *n*-1) (164) and directly calculate the SMD as follows (164):

$$SMD = \frac{t}{\sqrt{n}}$$

Such an approach allowed us to obtain the SMD and its variance without the need for computing the $SD_{diff}$, therefore allowing us to calculate SMD and v(SMD) when $SD_{diff}$ was not reported. When a specific p-value was not provided (e.g., $p<0.05$), we adopted a conservative approach by using its upper bound (e.g., 0.05) (164). When neither the p-

value nor $SD_{diff}$ were reported, $SD_{diff}$ was imputed from $SD_{condition}$ and $SD_{comparator}$ according to the formula (163):

$$SD_{diff} = \sqrt{SD_{condition}^2 + SD_{comparator}^2 - (2 \times r \times SD_{condition} \times SD_{comparator})}$$

Where *r* is the correlation coefficient between $\overline{X}_{condition}$ and $\overline{X}_{comparator}$. Considering no studies provided the r value, we adopted a conservative approach (*r* = 0.5) to estimate the $SD_{diff}$ (161).

Random-effect meta-analysis with an inverse-variance method was used for quantitative synthesis because not all studies estimated the same intervention effect (pain characteristics and experimental pain models varied across studies) (161). Statistical heterogeneity was quantified using the $I^2$ statistic, a measure that rates the level of heterogeneity as not important ($I^2$ < 40%), moderate (30% < $I^2$ < 60%), or substantial ($I^2$ > 50%) [17].

In forest plots without meta-analysis, findings were summarised using SMD and CI 95% to facilitate the interpretation of findings across studies (159). For the vote-counting system, findings were described based on the direction of change of the outcome (i.e., increase, decrease, no change). Since the same study could have investigated different conditions for a task (e.g., walking speed (165)), forest plots without meta-analysis can be useful to visually represent the data and identify causes for heterogeneity both within- and between-studies. Therefore, heterogeneity in forest plots without meta-analysis and tables was visually inspected and, if present, pre-specified subgroup analyses (i.e., experimental pain model and RoB) were considered

to explain it. Otherwise, unexplained heterogeneity was a reason to downgrade the certainty of evidence.

### *2.3.8 Certainty of evidence*

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to evaluate the certainty of evidence about the effects of induced pain in the lumbar region on the outcome domains of interest (i.e., muscle activity and kinematics) (166). After grouping based on the outcome domain, certainty of evidence was evaluated for trunk muscle group and investigated task. Study limitations, inconsistency, indirectness, imprecision, and publication bias were the domains that could affect and downgrade the quality of evidence (167). Instead, when a large effect estimate or dose response gradient (e.g., correlation between level of pain and neuromuscular adaptation) was present, the certainty of evidence was upgraded (167). Explanatory reasons for downgrading or upgrading the quality of evidence were also provided. Study limitations were rated in accordance with the RoB tools previously described. Moreover, quality of evidence was downgraded for inconsistency when heterogeneity of findings across studies remained unexplained despite the use of pre-specified subgroup analyses (i.e., experimental pain model or RoB). Overall, main findings of individual studies and certainty of evidence were synthesised in a summary of findings table where the strength of evidence was rated as “High”, “Moderate”, “Low”, and “Very low” (167).

## 2.4 Results

### *2.4.1 Study selection*

The results of the search and selection process are reported in detail in Figure 2.1. In total, the database search retrieved 15019 records and the hand-searching an additional 19 records. After removal of duplicates, 8556 records were screened by title and abstract by the two reviewers with an agreement of K = 0.9. Full-text screening was conducted on 60 reports (43 from databases and 17 from hand-searching) and the agreement between reviewers was K = 1.00. After collating records of the same study, a total of 26 studies were included in this review.

Two studies that may appear relevant for the present review were excluded because pain was delivered during less than 50% of trials (112,168) or pain was not delivered during the assessment of the outcome of interest (169). In six studies, the applied intervention (i.e., exogenous pain model) did not met the inclusion criteria for this review since it was not delivered to the lower back, or the adopted pain model was not eligible (170–175). Finally, two studies were excluded because the outcomes of interest for this review were not assessed (86,176).

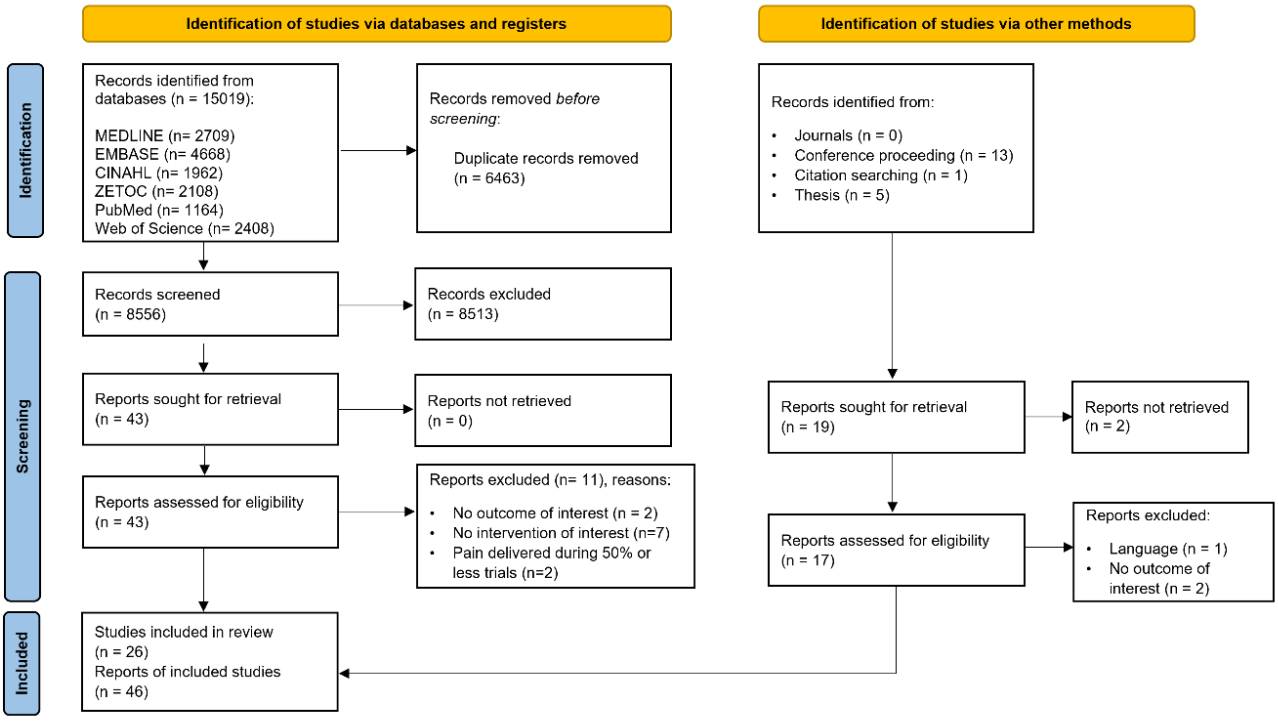


**Figure 2.1** *PRISMA flow diagram of included studies.*

### *2.4.2 Study characteristics*

The characteristics of the 26 studies included in this review are described in Table 2.1. Four different experimental pain models were adopted, specifically, hypertonic saline injection (n = 19) (76,77,122–124,177–190), heat thermal stimulation (n = 3) (129,130,191), nociceptive electrical stimulation (n= 3) (111,192,193), and capsaicin (n= 1) (194). Of the 19 studies using hypertonic saline injection, 7 included a control condition consisting of isotonic saline solution (123,124,177,180,184,185,190). Similarly, 2 studies used innocuous thermal stimulation as a control condition for heat thermal stimulation (129,191). Of the 26 included studies, only one investigated motor adaptations to MEP, focusing specifically on the changes in muscle activity during rapid arm movements associated with nociceptive electrical stimulation (111). Kinematics,

intensity of muscle activity, and muscle timing were the outcomes of interest investigated in 11, 20, and 6 studies, respectively. Kinematics and muscle activity of the lower limbs were assessed in 5 studies (129,181,189,191,193). Twenty-two studies adopted a repeated measure design whereas 4 studies used a crossover design. The average age of recruited participants was equal to or less than 30 years old in 23 studies; in the other three studies it was 32, 38 and not specified (range between 20-55 years old). Regardless of the experimental pain model adopted, the average reported pain intensity ranged from 21 to 65 out of 100 (Numeric Rating Scale or Visual Analogue Scale were used to measure pain intensity). A POST-PAIN condition was assessed in 10 studies (111,122,124,180–182,188,190,193,194), and in 3 of them the participants still experienced minimal pain (from 9 to 14 out of 100) (182,188,194).

**Table 2.1** *Characteristics of included studies*

| **First author** (year) | **Design & conditions** | ***n*** (F/M) | **Age** *(years)* mean ± SD | **Experimental pain model** (control, if any) | **Body region** (side) **Tissue** | **Average pain level** mean ± SD | **Task investigated** | **Outcome domains** | **Outcome measurement tool** | **Body region and muscles investigated** |
|---|---|---|---|---|---|---|---|---|---|---|
| Abboud (2018) | **Crossover**<br>1/2: PAIN<br>1/2: BASE | 20 (4/16) | 28.2 ± 5.4 | PAIN: HTS | Spinous process - L3<br>Skin | NRS<br>43 ± 7.5 | External trunk perturbations while sitting | Kinematics<br>Muscle activation and timing | 3D motion capture<br><br>HD-sEMG<br>Bipolar sEMG | Thoracolumbar region<br><br>ES (bilat)<br>OE / RA (bilat) |
| Arendt-Nielsen (1996) | **RM**<br>1: BASE<br>2: PAIN | 10 (0/10) | 25, range (23-30) | PAIN: HSI | Long - L3 (right)<br>Muscle | NRS<br>54 ± 23[a] | Walking (4 km/h) | Muscle activation | Bipolar sEMG | LO (T12 & L2)<br>IL (L2)<br>sMF (L4) |
| Bialy (2019) | **RM**<br>1: BASE<br>2: PAIN | 42 (16/26) | 22.3 ± 1.5 | PAIN: NES | Lower back (bilaterally)<br>Skin | VAS<br>60 ± 0 | Rapid arm abduction while standing | Muscle activation | Ultrasound | Contralateral TrA, OI, OE |
| Boudreau (2011) | **RM**<br>1: BASE<br>2: CTR<br>3: PAIN | 10 (6/4) | 23 ± 1.05 | PAIN: HSI<br>CTR: ISO | ES - L2 (right)<br>Muscle | NRS<br>39 ± 5 | External perturbations while standing | Muscle activation and timing | Bipolar sEMG | Bilaterally:<br>ES (T12, L2, L4)<br>OE |
| Dickx (2008) | **RM**<br>1: REST<br>2: NO PAIN + exercise<br>3: PAIN + exercise | 15 (0/15) | 23.3 ± 0.8 | PAIN: HSI | Long - L4 (right)<br>Muscle | VAS<br>53 ± 4 | Submaximal trunk extension, prone position (40% 1 RM) | Muscle activation | mfMRI | Bilaterally:<br>dMF (L3-L4)<br>sMF (L3-L4)<br>LO (L3-L4)<br>Psoas (L3-L4) |
| Dickx (2010) | **RM**<br>1: BASE<br>2: PAIN | 15 (6/9) | 24 ± 2 | PAIN: HSI | Long - L4 (right)<br>Muscle | VAS<br>60 ± 15 | Lifting task, prone position | Muscle activation | Ultrasound | Bilaterally:<br>dMF (L3-L4, L4-L5, L5-S1) |
| Dubois (2011) | **RM**<br>Random BASE, CTR, PAIN | 12 (9/3) | 38.6 ± 11 | PAIN: HTS<br>CTR: ITS | Spinous process - L5<br>Skin | NRS<br>34 ± 13 | Trunk flexion-extension while standing | Kinematics<br><br>Muscle activation | 3D motion capture<br>Bipolar sEMG | Lumbar, pelvic, hip motions<br>Bilaterally:<br>ES (L3-L4) |

| **First author** (year) | **Design & conditions** | ***n*** (F/M) | **Age** *(years)* mean ± SD | **Experimental pain model** (control, if any) | **Body region** (side) **Tissue** | **Average pain level** mean ± SD | **Task investigated** | **Outcome domains** | **Outcome measurement tool** | **Body region and muscles investigated** |
|---|---|---|---|---|---|---|---|---|---|---|
| Hirata (2015) | **Crossover**<br>1: BASE<br>2/3: CTR<br>2/3: PAIN<br>4: POST-PAIN | 12 (5/7) | 25 ± 4 | PAIN: HSI<br>CTR: ISO | Long - L2 (right)<br>Muscle | VAS<br>26 ± 4 | Submaximal trunk extension while sitting (5-10-20 % MVC) | Muscle activation | Bipolar sEMG | Bilaterally:<br>LO (L1)<br>sMF (L5)<br>RA, OE |
| Henchoz (2012) | **RM**<br>Random CTR or PAIN (low or high pain expectancy) | 22 (10/12) | 30.4 ± 9.3 | PAIN: HTS<br>CTR: ITS | Spinous processes (L4-L5)<br>Skin | NRS:<br>32 ± 11 | Trunk flexion-extension while standing | Kinematics<br>Muscle activation | 3D motion capture<br>Bipolar sEMG | Hip and lumbar regions<br>Bilaterally:<br>ES (L2-L3 and L4-L5) |
| Hodges (2013) | **RM**<br>1: BASE<br>2: PAIN<br>3: POST-PAIN | 17 (0/17) | 25 ± 6 | PAIN: HSI | Long - L4 (right)<br>Muscle | NRS<br>61 ± 27[a] | Trunk flexion-extension while sitting | Muscle activation | Bipolar sEMG | Bilaterally:<br>RA, OI, OE<br>TES, LES<br>LD |
| Hodges (2003) | **RM**<br>1: BASE<br>2: CTR<br>3: PAIN<br>4: POST-PAIN | 7 (2/5) | 28.6 ± 3.6 | PAIN: HSI<br>CTR: ISO | Long - L4 (right)<br>Muscle | VAS<br>62 ± 10[a] | Rapid arm movements (L)<br>Repetitive arm movements | Muscle activation and timing | Bipolar sEMG<br>Bipolar iEMG | Deltoid<br>Right side:<br>TrA, OE, OI<br>dMF, sMF (L4) |
| Jacobs (2011) | **RM**<br>1: BASE<br>2: PAIN<br>3: POST-PAIN | 14 (6/8) | 28 (range 19-47) | PAIN: NES | PSIS (bilaterally)<br>Skin | NRS<br>50 ± 0 | Sit-to-stand | Kinematics<br>Muscle timing | 3D motion capture<br>Bipolar sEMG | Hip, knee, ankle<br>Right side:<br>RA, OI, ES<br>TA, Gmax, RF, BF |
| Kiesel (2012) | **RM**<br>1: BASE<br>2: PAIN<br>3: POST-PAIN | 17 | college-aged | PAIN: HSI | Long - L4 (left)<br>Muscle | VAS<br>48 ± .4 | Arm lifting while standing<br>Weight shifting | Muscle activation | Bipolar iEMG | Bilaterally:<br>dMF (L4) |

| **First author** (year) | **Design & conditions** | ***n*** (F/M) | **Age** *(years)* mean ± SD | **Experimental pain model** (control, if any) | **Body region** (side) **Tissue** | **Average pain level** mean ± SD | **Task investigated** | **Outcome domains** | **Outcome measurement tool** | **Body region and muscles investigated** |
|---|---|---|---|---|---|---|---|---|---|---|
| Kiesel (2008) | **RM**<br>1: BASE<br>2: PAIN | 7<br>(0/7) | 26 ± 7.3 | PAIN: HSI | Long - L4<br>(NR)<br>Muscle | VAS<br>> 40 | Abdominal draw-in &<br>lifting task | Muscle activation | Ultrasound | TrA<br>sMF (L4) |
| Lamoth (2004) | **Crossover**<br>1: BASE<br>2/3: PAIN<br>2/3: CTR | 12<br>(4/8) | 21 (range 18-25) | PAIN: HSI<br>CTR: ISO | Long - L3<br>(right)<br>Muscle | NRS<br>61 ± 19[a] | Walking (2.2, 3.8, 4.6, 5.4 km/h) | Kinematics<br><br>Muscle activation | 3D motion capture<br>Bipolar sEMG | Thoracic, lumbar, pelvic<br>Bilaterally:<br>ES (T12, L2, L4) |
| Larsen (2016) | **RM**<br>1: BASE<br>2: PAIN (bilat)<br>3: CTR (bilat)<br>4: PAIN (unilat) | 19<br>(4/15) | 26 (range 19-39) | PAIN: HSI<br>CTR: ISO | Long - L2<br>(right or bilaterally)<br>Muscle | VAS<br>PAIN (bilat):<br>65 ± 11<br>PAIN (unilat):<br>50 ± 10 | External perturbations while standing | Muscle activation | Bipolar sEMG | Bilaterally:<br>IL (L2)<br>LO (L1)<br>sMF (L5)<br>RA, OE, OI |
| Larsen (2018) | **RM**<br>1: BASE<br>2/3: PAIN<br>Unilateral or bilateral | 26<br>(16/10) | 23.6 ± 4.4 | PAIN: HSI | Long - L2<br>(dominant side or bilaterally)<br>Muscle | VAS<br>PAIN (bilat):<br>47 ± 3<br>PAIN (unilat):<br>21 ± 3 | 10 steps up and steps down | Muscle activation | Bipolar sEMG | Dominant side:<br>RA, OE, OI<br>IL (L2), LO (L1)<br>sMF (L4), Gmax, Gmed |
| Moe-Nilssen (1999) | **RM**<br>1: BASE<br>2: PAIN | 23<br>(20/3) | 26 ± 7.5 | PAIN: HSI | Long – L1<br>(left)<br>Muscle | NRS<br>61 ± 15 | Walking | Kinematics | Triaxial accelerometer | Lumbar spine (L3) |
| Moseley and Hodges (2005) | **RM**<br>1: BASE<br>2: PAIN<br>3: POST-PAIN | 16<br>(9/7) | 24 ± 5 | PAIN: NES | PSIS<br>(bilaterally)<br>Skin | NRS<br>49 ± 9 | Rapid arm movement while sitting | Muscle timing | Bipolar sEMG | Right side:<br>OE, TrA/OI<br>Deltoid |

| **First author** (year) | **Design & conditions** | ***n*** (F/M) | **Age** *(years)* mean ± SD | **Experimental pain model** (control, if any) | **Body region** (side) **Tissue** | **Average pain level** mean ± SD | **Task investigated** | **Outcome domains** | **Outcome measurement tool** | **Body region and muscles investigated** |
|---|---|---|---|---|---|---|---|---|---|---|
| Moseley (2004) | **RM**<br>1: BASE<br>2/3: ATTENTION<br>2/3: STRESS<br>4: PAIN | 8<br>(3/5) | 32 ± 7 | PAIN: HSI | ES – L4<br>(right)<br>Muscle | NRS<br>62 ± 11 | Rapid arm movement while standing | Muscle timing | Bipolar iEMG<br><br>Bipolar sEMG | dMF, sMF<br>OE, OI, TrA<br>Deltoid |
| Ross (2015) | **RM**<br>1: BASE<br>2: PAIN<br>3: POST-PAIN | 14<br>(0/14) | 21.8 ± 2.8 | PAIN: CPS | Low back<br>(bilaterally)<br>Skin | VAS:<br>37 ± 17 | Trunk flexion-extension while standing | Kinematics<br><br>Muscle activation | 3D motion capture<br><br>Bipolar sEMG | Lower limb & lower back<br>Right side:<br>RA, OE, OI<br>ES (thoracic)<br>ES (lumbar)<br>sMF, LD |
| Ross (2017) | **RM**<br>1: BASE<br>2: PAIN<br>3: POST-PAIN | 16<br>(8/8) | 20.9 ± 2.4 | PAIN: HSI | Interspinous ligament<br>L4-L5 | VAS:<br>46 ± 19 | Trunk flexion-extension while standing | Kinematics | 3D motion capture | T12-S1 segments |
| Smith (2005) | **RM**<br>1: BASE<br>2: PAIN | 12<br>(4/8) | 26 ± 4 | PAIN: HSI | Long – L3<br>(right)<br>Muscle | NRS:<br>44 ± 19 | Breathing manipulation while standing | Kinematics | Inclinometers | Knee, hip, lumbar spine (sagittal) |
| van den Hoorn (2015) | **RM**<br>1: BASE<br>2/4: PAIN (lumbar)<br>3/5: POST-PAIN (lumbar)<br>2/4: PAIN (calf)<br>3/5: POST-PAIN (calf) | 17<br>(6/11) | 21 ± 2 | PAIN: HSI | ES – L3<br>(right)<br>Muscle | NRS:<br>53 ± 18 | Walking (3.4 and 6.3 km/h) | Kinematics<br><br>Muscle activation | 3D motion capture<br>Bipolar sEMG<br><br><br><br><br>Bipolar iEMG | Spine and lower limb<br>Right side: RA, ES(L3), TFL, Gmed, Gmax, GRA, SM, BF, RF, VL, VM, GM, GL, SOL, TA<br>OE, OI, IL(L3), LO |

| **First author** (year) | **Design & conditions** | ***n*** (F/M) | **Age** *(years)* mean ± SD | **Experimental pain model** (control, if any) | **Body region** (side) **Tissue** | **Average pain level** mean ± SD | **Task investigated** | **Outcome domains** | **Outcome measurement tool** | **Body region and muscles investigated** |
|---|---|---|---|---|---|---|---|---|---|---|
| Wong (2016) | **Crossover**<br>1: BASE<br>2/3: CTR<br>2/3: PAIN<br>4: POST-PAIN | 9 (6/3) | 25.4 ± 2.4 | PAIN: HSI<br>CTR: ISO | Interspinous ligament L3-L4 and L4-L5 | NRS: 58 ± 14 | Spinal stiffness test with mechanical indentation | Muscle activation | Bipolar sEMG | Bilaterally: OE, TrA/OI ES (L3) |
| Zedka (1999) | **RM**<br>1: BASE<br>2: PAIN (NES)<br>3: PAIN (HSI) | 5 (1/4) | Range: 20-55 | PAIN: HSI | ES – L3 (right) Muscle | > 40/100 | Trunk flexion - extension while standing | Kinematics<br>Muscle activation | Gyroscope<br>Bipolar sEMG | L3 segment<br>Bilaterally: ES (L3) |

[a] peak value of pain intensity. RM, repeated measure design. Pain models and control conditions: CPS, capsaicin; HSI, hypertonic saline injection; HTS, heat thermal stimulation; ISO, isotonic saline injection; NES, nociceptive electrical stimulation; ITS, innocuous thermal stimulation. Average pain level: NRS, numeric rating scale; VAS, visual analogue scale. Outcome measurement tool: HD-sEMG, high-density surface electromyography; iEMG, intramuscular electromyography; sEMG, surface electromyography. Muscles: BF, biceps femoris; ES, erector spinae; GL, gastrocnemius lateralis; Gmax, gluteus maximus; Gmed, gluteus medius; GM, gastrocnemius medialis; GRA, gracilis; IL, iliocostalis; LD, latissimus dorsi; LES, lumbar erector spinae; MF, multifidus; OE, obliquus externus; OI, obliquus internus; LO, longissimus; RA, rectus abdominis; RF, rectus femoris; SM, semimembranosus; SOL, soleus; TA, tibialis anterior; TES, thoracic erector spinae; TFL, tensor fasciae latae; TrA, transversus abdominis; VM, vastus medialis; VL, vastus lateralis.

### *2.4.3 Risk of bias*

The overall RoB assessed with ROBINS-I was moderate in 16 studies, and serious in 9 studies (Table 2.2). Only one study was at low RoB. The domains that affected the internal validity of included studies were D1 (confounding), D4 (deviation from intended intervention), and D6 (measurement of outcomes). A comprehensive summary is reported in Figure 2.2. Six studies were at serious RoB due to confounding because they alternated different experimental pain conditions which increased the risk of a carryover effect. For example, in one study (181) pain was induced in two body regions (low back and calf) during the same session. In another study (129), phasic pain and control intervention were repeatedly alternated across trials. Serious RoB due to deviation from intended interventions (D4) was identified in 3 studies because of other co-interventions not controlled for (e.g., injection of other chemical substances) (185,190,192). Finally, 2 studies were at serious RoB in the measurement of outcome (186,192).

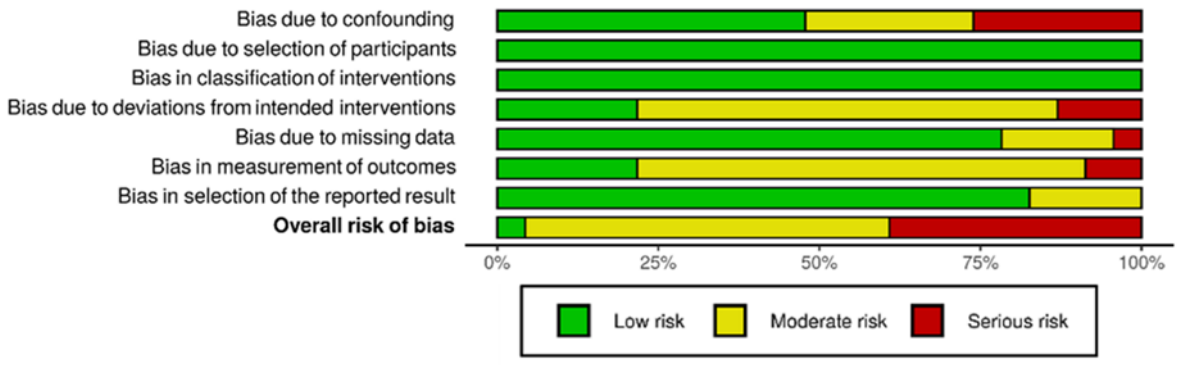


**Figure 2.2** *Summary of the risk of bias across domains. Studies with repeated measure design and assessed with ROBINS-I tool are considered.*

**Table 2.2** *Risk of bias of studies with repeated measure design and assessed with ROBINS-I tool.*

| Study | First author, year [comparison] | Risk of bias domains | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D2 | D3 | D4 | D5 | D6 | D7 | Overall |
| | Abboud, 2018 | - | + | + | - | + | + | - | - |
| | Arendt-Nielsen, 1996 | + | + | + | - | + | - | + | - |
| | Bialy, 2019 | + | + | + | X | - | X | + | X |
| | Boudreau, 2011 [CTR vs PAIN*] | + | + | + | + | + | + | + | + |
| | Dickx, 2008 | - | + | + | - | + | - | - | - |
| | Dickx, 2010 | - | + | + | - | + | - | + | - |
| | Dubois, 2011 [CTR vs PAIN*] | - | + | + | + | - | + | + | - |
| | Henchoz, 2013 [CTR vs PAIN*] | X | + | + | - | + | + | + | X |
| | Hirata, 2015 [CTR vs PAIN*] | - | + | + | + | - | + | - | - |
| | Hodges, 2003 [CTR vs PAIN*] | + | + | + | - | + | + | + | - |
| | Hodges, 2013 | + | + | + | - | + | - | + | - |
| | Jacobs, 2011 | - | + | + | + | + | - | + | - |
| | Kiesel, 2008 | + | + | + | - | - | - | + | - |
| | Kiesel, 2012 | + | + | + | - | + | - | + | - |
| | Lamoth, 2004 [CTR vs PAIN*] | - | + | + | + | + | + | - | - |
| | Larsen, 2016 [CTR vs PAIN*] | X | + | + | + | + | + | + | X |
| | Larsen, 2018 | + | + | + | X | + | - | + | X |
| | Moe-Nilssen, 1999 | + | + | + | - | + | X | + | X |
| | Moseley, 2004 | X | + | + | - | + | - | - | X |
| | Moseley, 2005 | - | + | + | + | + | - | - | - |
| | Ross, 2015 | - | + | + | - | + | - | - | - |
| | Ross, 2017 | X | + | + | - | + | - | + | X |
| | Smith, 2005 | - | + | + | - | - | - | + | - |
| | van den Hoorn, 2015 | X | + | + | - | X | - | + | X |
| | Wong, 2016 [CTR vs PAIN*] | + | + | + | + | - | + | + | - |
| | Zedka, 1999 | X | + | + | X | + | - | + | X |

When not specified, comparisons between baseline (BASE) and PAIN conditions.
* Comparison between control (CTR) and PAIN conditions.

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviation from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

**Judgment**
X Serious
- Moderate
+ Low

### *2.4.4 Results of syntheses and certainty of evidence*

Trunk kinematics

The effect of experimental pain induced in the lumbar region on trunk and lower limb kinematics was assessed in 11 studies with an overall RoB between moderate and serious (77,129,130,181,184,186,188,189,191,193,194). Experimental pain models adopted were hypertonic saline injection (n=6), heat thermal stimulation(n=3), capsaicin (n=1), and nociceptive electrical stimulation (n=1). Outcomes of interest were ROM, lumbar to hip angles ratio, trunk movement variability, and trunk movement stability. Trunk acceleration was investigated in one study (186). Outcome measures of trunk movement variability and stability were obtained from standard deviation, principal component analysis, local divergence exponent, and cross-correlation measures across trunk angle waveforms. Results from individual studies along with summary of findings are presented in Table 2.3. Meta-analysis for kinematic outcomes was precluded because of the large heterogeneity across the evaluated tasks. However, quantitative data are illustrated with forest plots in Figure 2.3.

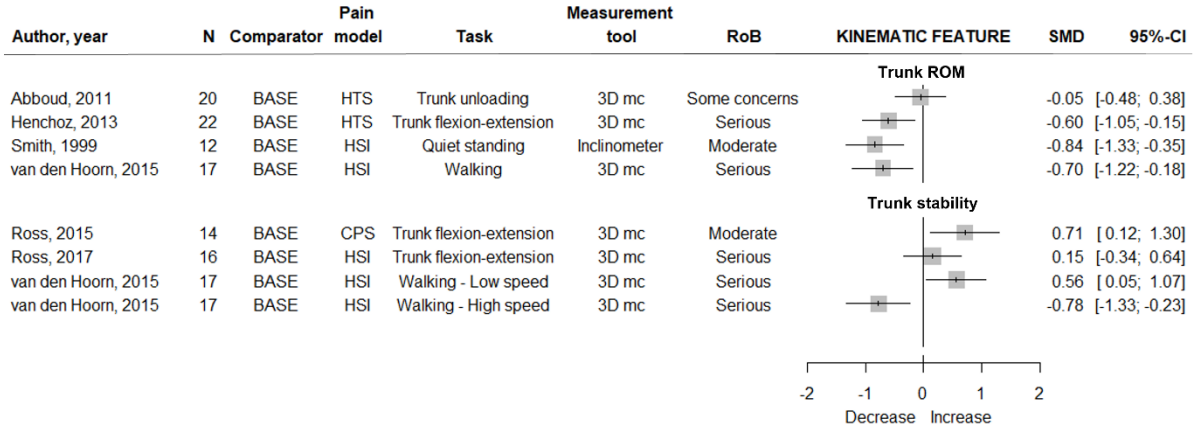


**Figure 2.3** *Forest plots with main findings on trunk kinematics during different tasks.*
*Note: the study van den Hoorn, 2015 is reported twice to illustrate the different adaptation of trunk stability while walking at different speeds. Comparators: BASE, baseline. Pain models: HSI, hypertonic saline injection; HTS, heat thermal stimulation; NES, nociceptive electrical stimulation. Kinematics assessed with 3D motion capture (mc) in most of the studies. ROM, range of motion*

**Table 2.3** *Main findings and quality of evidence on the effects of experimentally induced pain in the lumbar region on trunk kinematics*

| Study | *N* | Comp | Pain mode | Task | Meas Tool | RoB | Results | Main findings & certainty of evidence | Comments |
|---|---|---|---|---|---|---|---|---|---|
| *ROM and Lumbar/Hip ratio* | | | | | | | | | |
| Abboud et al. (2018) | 20 | BASE | HTS | Trunk perturbation | 3D motion capture | Some concerns | = ROM<br>= Peak velocity | Decreased lumbar ROM. Quality: **LOW** [a, b]<br>Alteration lumbar/hip coordination. Quality: **LOW** [a, b] | Quality of evidence rated down because of limitations (risk of bias) and publication bias. Evidence from few studies with a small sample size. |
| Dubois et al. (2011) | 12 | ITS | HTS | Trunk flex/ext | 3D motion capture | Moderate | ↓ overall L/H ratio<br>↑ L/H ratio (early ext) | | |
| Henchoz et al. (2013) | 22 | ITS | HTS | Trunk flex/ext | 3D motion capture | Serious | ↓ lumbar ROM<br>↓ L/H ratio in (flex and late ext)<br>↑ L/H ratio in early ext | | |
| Jacobs et al. (2011) | 14 | BASE | NES | Sit-to-stand | 3D motion capture | Moderate | ↓ peak hip extension | | |
| Smith et al., (2005) | 12 | BASE | HSI | Quiet breathing | Inclinometers | Moderate | ↓ lumbar ROM<br>↑ knee ROM | | |
| van den Hoorn et al., (2015) | 17 | BASE | HSI | Walking | 3D motion capture | Serious | = knee and ↓ hip<br>↓ lumbar ext / ↑ lumbar flex<br>↓ lumbar rot & lat flex (pain side)<br>= lumbar rot & lat flex (no pain side) | | |
| Zedka et al., (1999) | 5 | BASE | HSI | Trunk flex/ext | Gyroscope | Serious | ↓ spinal ROM | | |
| *Trunk stability and variability* | | | | | | | | | |
| Lamoth et al., (2004) | 12 | ISO | HSI | Walking | 3D motion capture | Some concerns | = kinematics pattern & variability<br>= segments coupling | Inconsistent and limited evidence | Different reasons for inconsistency, such as task characteristics, experimental pain model, and psychological factors. |
| Ross et al., (2015) | 14 | BASE | CPS | Trunk flex/ext | 3D motion capture | Moderate | ↓ local dynamic stability | | |
| Ross et al., (2017) | 16 | BASE | HSI | Trunk flex/ext | 3D motion capture | Serious | = local dynamic stability (mediated by PCS) | | |

| Study | *N* | Comp | Pain mode | Task | Meas Tool | RoB | Results | Main findings & certainty of evidence | Comments |
|---|---|---|---|---|---|---|---|---|---|
| van den Hoorn et al., (2015) | 17 | BASE | HSI | Walking | 3D motion capture | Serious | ↓ gait stability (speed 0.94m/s)<br>↑ gait stability (speed 1.67 m/s)<br>↑ trunk variability (speed 0.94 m/s<br>↓ trunk variability (speed 1.67 m/s) | | |
| *Lumbar spine acceleration* | | | | | | | | | |
| Moe-Nilssen et al., (1999) | 23 | BASE | HSI | Walking | Triaxial accelerometer | Serious | ↓ trunk acceleration (AP and ML axes) | Limited and poor quality of evidence | Negative correlation between experienced pain and trunk acceleration |

Experimental pain models adopted: HSI, hypertonic saline injection; HTS, heat thermal stimulation; NES, nociceptive electrical stimulation; CPS, capsaicin. Control condition: BASE, baseline; ISO, isotonic saline injection; ITS, innocuous thermal stimulation.
Reasons for rating down the quality of evidence: a Study limitation (risk of bias); b Publication bias.

Overall, there is low quality of evidence to support a reduction of lumbar ROM induced by experimental pain induced in the lumbar region during voluntary trunk movements. No meaningful conclusions can be drawn on trunk variability and stability because of the large inconsistency across studies and the limited number of tasks investigated.

Consistent findings across four studies out of five reported a reduction of lumbar ROM (77,129,130,181,189). Quantitative data were available from four studies only (Figure 2.3). Changes of lumbar ROM occurred with an overall reduction of the lumbar/hip ratio during a trunk flexion-extension task (129,191). However, an increase of lumbar/hip ratio resulting from larger lumbar movement (as specified by authors) was reported during the first quartile of the extension phase (129). Although different pain models were adopted, reduced ROM of hip movements were reported in two studies assessing walking and sit-to-stand (181,193). In one study, experimental heat pain resulted in no changes of lumbar ROM and velocity after external trunk perturbations (130).

Findings on trunk stability and variability were inconsistent across four studies, even when the same task was investigated (Figure 2.3) (181,184,188,194). No differences regarding the pattern of trunk kinematics, its variability, and segment coupling while walking at different speeds were reported in one study (184). Instead, another study found an increase and a decrease of trunk variability when participants walked at 0.94 and 1.67 m/s, respectively (165). Inconsistent findings were obtained by Ross et al. in two studies investigating the same task (trunk flexion/extension while standing), but different pain models (188,194). Specifically, experimental pain induced

by capsaicin resulted in a decrease of trunk stability, whereas no changes were reported with hypertonic saline injection.

Intensity of muscle activity – Trunk Muscles

Twenty studies assessed the effects of experimental pain induced in the lumbar region on the intensity of muscle activity (76,77,122–124,129,130,177–185,190–192,194). Specifically, experimental pain models adopted were hypertonic saline injection (n=15), heat thermal stimulation (n=3), nociceptive electrical stimulation (n=1), and capsaicin (n=1). Overall RoB ranged between moderate and serious, except for one study rated at low risk. Forest plots with meta-analysis were used to describe activation changes of lumbar muscles during trunk flexion-extension while standing (Figure 2.4). Forest plots without meta-analyses were presented for other tasks (Figure 2.5 and 2.6) because of methodological heterogeneity across studies due to differences in how the task was performed or in the assessment of the outcome of interest. When muscle activation was collected from different superficial lumbar muscles, methodological consistency in data synthesis was ensured by reporting results of the same spinal level (L2-L3) and from the painful side.

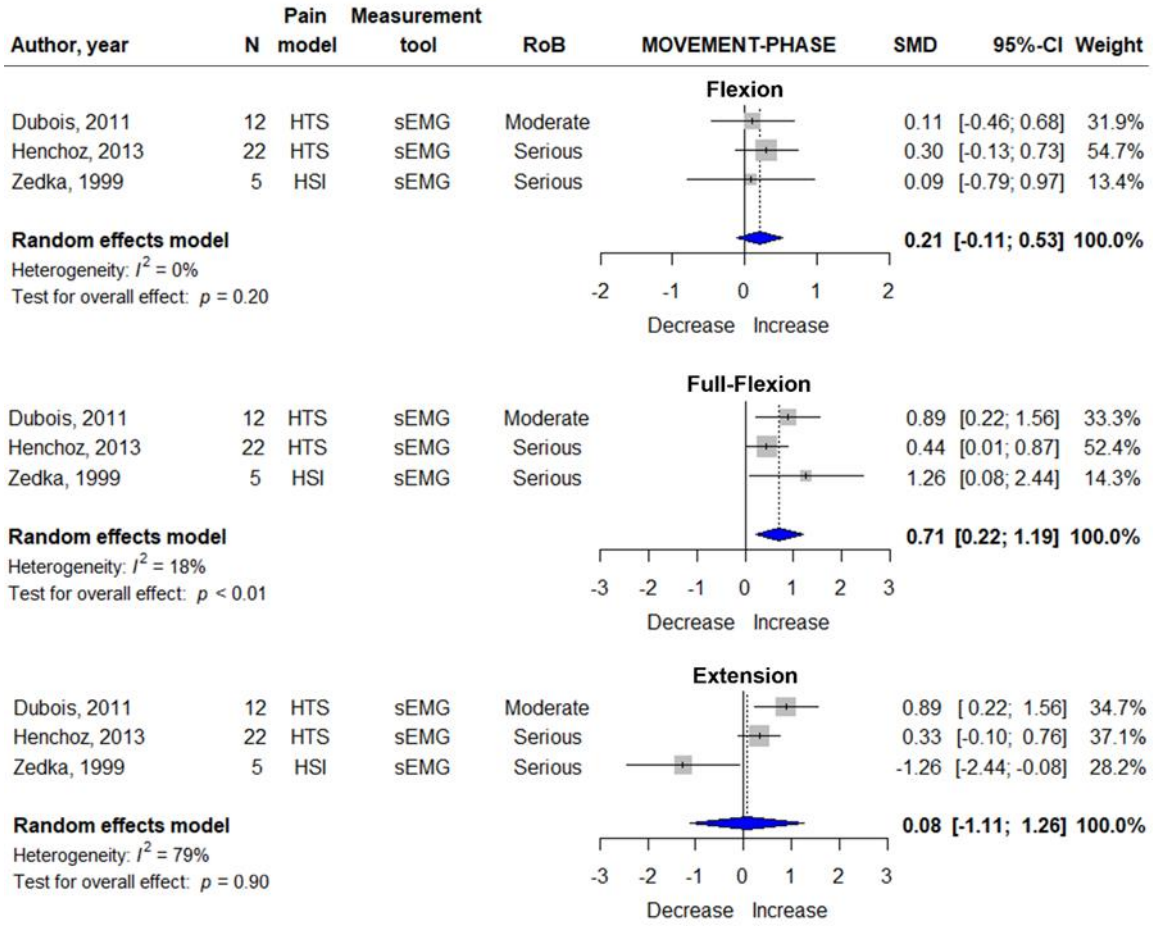


**Figure 2.4** *Meta-analyses on erector spinae activation during a trunk flexion-extension task while standing.*
*Note: standardised mean difference (SMD) and 95% confidence interval (95% CI) are reported. Data are presented for flexion, full-flexion, and extension phases. Muscle activation recorded with surface EMG (sEMG). Pain models: TS, thermal stimulation; HSI, hypertonic saline injection*

*Voluntary trunk movements*. Overall, there is low quality of evidence to support an increase of superficial lumbar muscle activity during voluntary trunk movements. Evidence on abdominal muscle activity was too limited to draw meaningful conclusions. No studies investigated deep muscle activity during voluntary trunk movements. The effects of experimental pain induced in the lumbar region on muscle activation were analysed in 5 studies with moderate (n = 3) and serious (n = 2) RoB (77,122,129,191,194). Meta-analysis was conducted from 3 studies investigating

changes of erector spinae activation during a flexion-extension task while standing (Figure 2.4) (77,129,191). A significant increase of erector spinae activation with experimental pain was observed in full forward flexion (SMD: 0.71 [95% CI 0.22, 1.19], $p < 0.01$; $I^2 = 18\%$). During flexion and extension, results from pooled studies showed no changes of EMG amplitude (SMD: 0.21 [95% CI -0.11, 0.53], $p = 0.20$; $I^2 = 0\%$ and SMD: 0.08 [95% CI -1.11, 1.26], $p = 0.90$; $I^2 = 79\%$, respectively). Erector spinae amplitude during the extension phase was characterised by high heterogeneity across studies, potentially explained by the different pain models adopted since muscle activity decreased in one study using hypertonic saline injection (77), and increased in two studies using thermal stimulation (129,191).

Two studies that investigated the effects of experimental lumbar pain during voluntary trunk movements could not be pooled in quantitative synthesis as data were not available (122) or they were obtained from different outcome measures (i.e., index of rotation stiffness)(194). Trunk flexion-extension while sitting was evaluated in one study and, despite the high between-subject variability, a net increase of EMG activity in superficial abdominal and back muscles was found (122). Opposite findings showing a reduction of trunk muscle activation (described as muscular contribution to spine rotational stiffness) were obtained from the investigation of a trunk flexion-extension task after application of capsaicin (194). Although the use of different experimental pain models can partially explain differences between these studies (122,194), inconsistency remains when results are compared with other two studies that measured muscle activation during the extension phase (77,191).

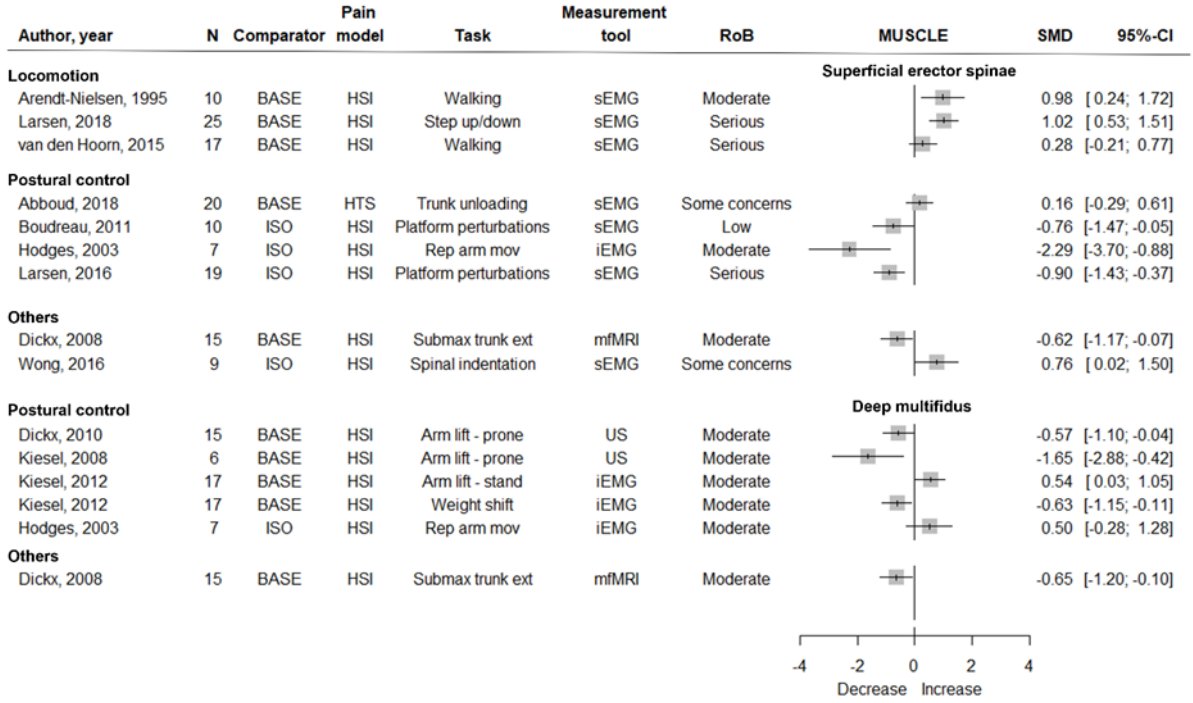


**Figure 2.5** *Forest plots with the main findings on amplitude changes of superficial back muscles and deep multifidus during different tasks.*
*Note: the study Kiesel, 2012 is reported twice to illustrate the different adaptation of deep multifidus activity during different tasks. Comparators: BASE, baseline; ISO, isotonic saline injection. Pain models: HSI, hypertonic saline injection; HTS, heat thermal stimulation. Measurement tool: sEMG, surface EMG; iEMG, intramuscular EMG; US, ultrasound; mfMRI, muscular functional MRI.*

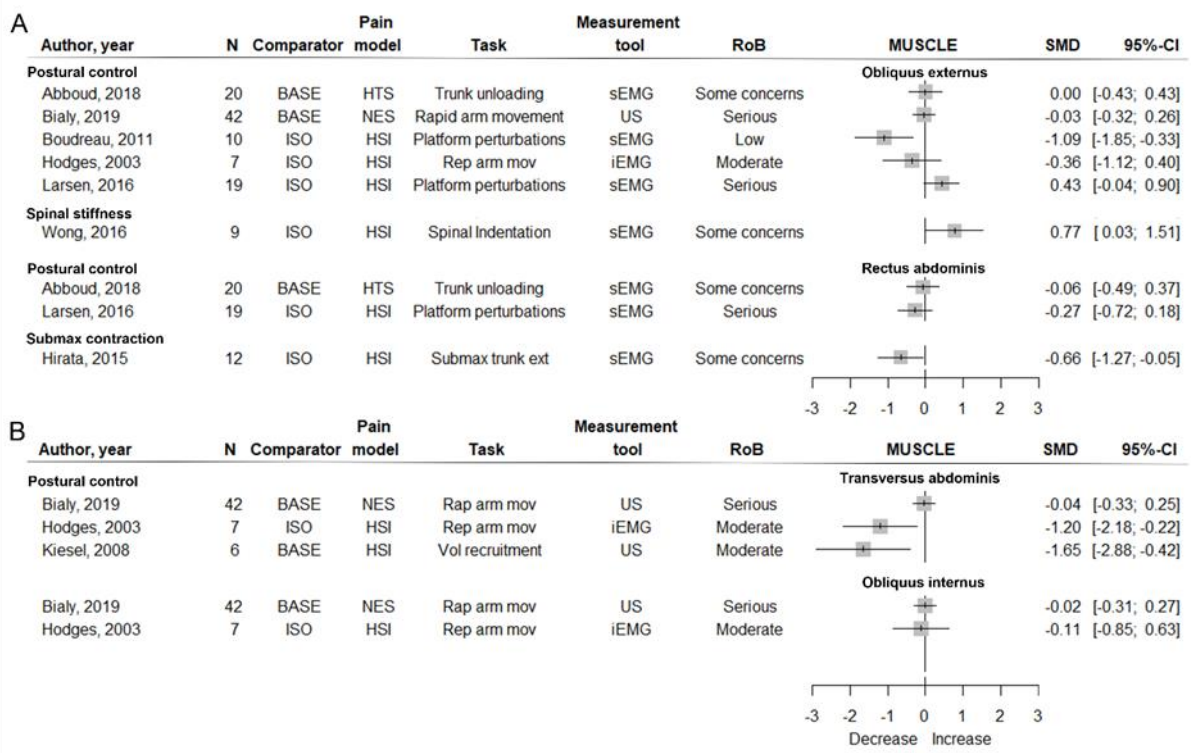


**Figure 2.6** *Forest plots with main findings on activation changes of superficial (A) and deep (B) abdominal muscles during different tasks.*
*Comparators: BASE, baseline; ISO, isotonic saline injection. Pain models: HSI, hypertonic saline injection; HTS, heat thermal stimulation; NES, nociceptive electrical stimulation. Deep abdominal muscles assessed with intramuscular EMG (iEMG) or ultrasound (US).*

*Locomotion*. Despite some inconsistency potentially introduced by differences in the analysis of outcome measures, we found low level of evidence that experimental pain results in an increased activation of superficial lumbar muscles during locomotion (Table 2.4). Two studies showed a trend of greater activation of the superficial abdominal muscles, but evidence is too limited to be able to draw meaningful conclusions. Similarly, one study only evaluated the amplitude of activation of deep trunk muscles after hypertonic saline injection (181), and no meaningful conclusions can be drawn.

Four studies investigated the effect of experimental pain induced with hypertonic saline injection on trunk muscle amplitude during locomotion (Figure 2.5) (76,181,184,185). Risk of bias was serious in two studies, moderate in one study and with some concerns in another crossover study. Two studies found an overall increase of erector spinae activation during walking (76,184). This adaptation was phase-dependent, with the greatest increase identified during the swing phase. Similar findings showing an overall increase of activity in superficial lumbar and abdominal muscles were reported in another study investigating a step up/step down task (185). Influenced by high between-subject variability and heterogeneity of muscle synergies during pain, results from van den Hoorn et al. showed no amplitude changes of lumbar and abdominal muscles during walking (181). In contrast to the other studies analysing specific phases of gait, van den Hoorn et al. considered the entire gait cycle.

*Postural perturbation tasks*. There is low quality of evidence to support a reduction of activation of superficial and deep lumbar muscles during postural perturbations tasks (Table 2.4). However, there was some inconsistency explained by differences in the pain models adopted and type of perturbations. Low quality of evidence supports the absence of changes of activation of the superficial abdominal muscles, and a reduction in the amplitude of transversus abdominis activity during postural perturbation tasks is supported by limited evidence (Table 2.5). The effects of experimental pain induced in the lumbar region on postural and stabilisation control of superficial and deep trunk muscles were investigated in 8 studies (Figure 2.5 and 2.6) (123,124,130,177,178,182,183,192). Risk of bias in repeated measure studies was low (n=1), moderate (n=4), serious (n=2), and with some concerns in one crossover study. In

two studies assessing external perturbations induced by movable platforms, EMG amplitude decreased in superficial lumbar and abdominal muscles after unilateral hypertonic saline injection (123). However, opposite change (i.e., increased amplitude) was observed when it was applied bilaterally (123). Heat thermal stimulation was investigated in one study, and no changes of trunk muscle activation were found during external trunk perturbations while sitting (130).

Internal perturbations produced by arm movements resulted in heterogeneous adaptations, including increase, no change, and a reduction of muscle activity. While Hodges et al. (124) found reduced EMG amplitude of transversus abdominis and erector spinae during repetitive arm movements, no changes of abdominal muscle activity were reported in another study investigating a similar task when pain was induced using nociceptive electrical stimulation and transversus abdominis, obliquus externus, and obliquus internus were assessed using ultrasound (192). Despite using the same experimental pain model (hypertonic saline injection) and similar task, Kiesel et al. also found different results compared to Hodges et al. by showing an increase of deep multifidus activation (182). Internal perturbations induced by weight shifting were investigated in one study that showed a reduction and no change of deep multifidus amplitude with forward and backward movements, respectively (182). During an arm lifting task from a prone position, two studies found that pain induced with hypertonic saline injection reduced deep multifidus recruitment, as assessed with ultrasound at different lumbar levels (178,183).

*Submaximal trunk extension*. Given the limited and inconsistent findings, no meaningful conclusions can be drawn on the effects of experimental pain on

submaximal trunk extension tasks. Two studies assessed muscle activation during submaximal trunk extension after hypertonic saline injection (Figure 2.5 and 2.6) (179,180). Overall RoB was moderate and with some concerns. Although a decrease of longissimus and deep multifidus activity was reported in one study during a dynamic trunk extension at 40% MVC (179), no changes in the amplitude of erector spinae activity was observed in another study during isometric trunk extension at different intensities (5-10-20% MVC) (180). Instead, the authors found a reduction of rectus abdominis activity when trunk extension was performed at 20% MVC (180).

*Other tasks*. One crossover study with some concerns of RoB investigated the response of trunk muscles during mechanical indentation (190). Specifically, a mechanical indentation device was used to apply a progressive load over the L3 spinal process while participants were prone. Compared with isotonic solution, hypertonic saline injection into the interspinous ligament resulted in an increase of surface EMG amplitude of abdominal and lumbar muscles in response to mechanical indentation (190). Moreover, higher pain intensity was correlated with trunk muscle activity and spinal stiffness.

Intensity of muscle activity – Limb Muscles

Insufficient and inconsistent findings were available to understand if pain in the lumbar region also induces adaptations at remote sites. Two studies investigated the effects of experimental pain induced in the lumbar region on the activation of lower limb muscles, one during walking after hypertonic saline injection (181) and another one inducing nociceptive electrical stimulation during a sit-to-stand task (193). One study

found a reduction of calf muscle activity (medial and lateral gastrocnemius) during walking (181), whereas opposite results were reported in another study that showed an increase of rectus femoris, biceps femoris, and gastrocnemius activity (193).

Muscle Timing

There is low quality of evidence to support a delay of transversus abdominis timing of activation during internal perturbations. However, such finding needs to be interpreted with caution since all included studies are from the same research group and further independent replication of results is necessary. A meaningful conclusion cannot be drawn for other muscles because of the large inconsistency across studies.

Meta-analysis of the effects of experimental pain induced in the lumbar region on muscle timing was conducted by pooling three (111,124,169) and two (124,169) studies assessing abdominal and back muscles, respectively (Figure 2.7). Methodological consistency was ensured since all studies evaluated rapid arm movements and compared BASE and PAIN conditions. Meta-analysis from three studies revealed delayed onset of transversus abdominis (MD: 25.20 [95% CI 4.09, 46.30], p = 0.02; $I^2$ = 75%) and no changes of obliquus externus timing of activation (MD: -5.96 [95% CI -30.27,18.36], p = 0.63; $I^2$ = 69%). For deep multifidus, meta-analysis showed no changes of muscle timing (MD: -13.78 [95% CI -33.45, 5.89], p = 0.17; I2 = 42%).

Data from four studies on muscle timing were not pooled in meta-analysis because they investigated different tasks and muscles (130,177,193). Two studies evaluated the effects of experimental pain induced in the lumbar region on muscle timing of trunk muscles during external perturbations (130,177). Boudreau et al. showed

a delay of erector spinae and obliquus externus activity after hypertonic saline injection, but Abboud et al. found no changes using heat thermal stimulation. Finally, one study inducing pain by means of nociceptive electrical stimulation revealed a reduction in how fast the external obliquus was recruited during rapid arm movements (192). Such an outcome measure (i.e., tissue deformation index) was calculated as the percentage of change of muscle thickness over time, and it could not be pooled with other studies.

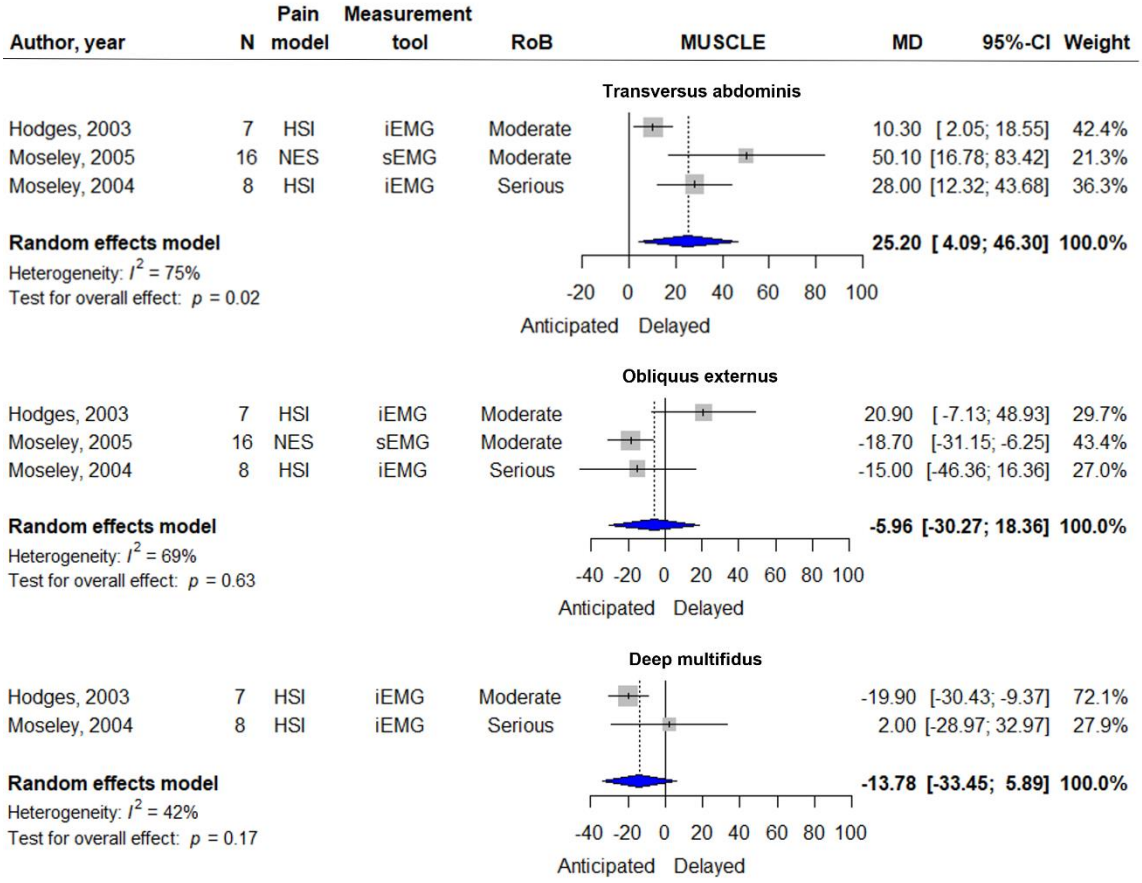


**Figure 2.7** *Meta-analyses of transversus abdominis (TrA), oblique externus (OE), and deep multifidus (dMF) timing during rapid arm movements.*
*Note: results are obtained after from comparisons between PAIN and BASE conditions. Mean difference (MD) values reported in ms. Pain models: HSI, hypertonic saline injection; NES, nociceptive electrical stimulation. Measurement tools: sEMG, surface EMG; iEMG, intramuscular EMG*

**Table 2.4** *Effects of experimentally induced pain in the lumbar region on lumbar muscle activity - summary of findings and certainty of evidence*

| | **Muscles**<br>▪ Task<br>*N studies (n participants)* | **Muscle Activation changes – Lumbar muscles**<br>*Increased* | *No change* | *Decreased* | **Findings & certainty of evidence** | **Comments** |
|---|---|---|---|---|---|---|
| EMG AMPLITUDE | **Superficial muscles:**<br>▪ Locomotion<br>4 (65) | Arendt-Nielsen[H]<br>Lamoth[H]<br>Larsen (2018)[H] | van den Hoorn[H] | - | ▪ Increased activation (phase-dependent) of superficial lumbar muscles during locomotion. **LOW** quality of evidence.[a, b] | Heterogeneity may be explained by risk of bias (carry-over effect) in van den Hoorn. Positive association between pain and increase of muscle activation in Larsen et al., 2018. |
| | ▪ Voluntary trunk movements<br>5 (70) | Dubois[T]<br>Henchoz[T]<br>Hodges(2013)[H]<br>Zedka[H] | - | Ross(2015)[C]<br>Zedka[H] | ▪ Increased activation (phase-dependent) of superficial lumbar muscles during voluntary trunk movements. **LOW** quality of evidence.[a, b] | Heterogeneity partially explained by *a priori* subgroup analysis (different pain model adopted by Ross et al.). Zedka et al. reported opposite and phase-dependent changes. |
| | ▪ Postural perturbation<br>4 (56) | - | Abboud[T] | Boudreau[H]<br>Hodges(2003)[H]<br>Larsen(2016)[H] | ▪ Decreased activation of superficial lumbar muscles during postural perturbation tasks. **LOW** quality of evidence.[b, d] | Inconsistency in the relationship between pain and changes of muscle activation (Larsen et al., 2016). Heterogeneity explained by *a priori* subgroup analysis (pain model). |
| | ▪ Submax contraction<br>2 (27) | - | Hirata[H] | Dickx(2008)[H] | ▪ Inconsistent and limited evidence | |
| | **Deep muscles:**<br>▪ Postural perturbation<br>4 (46) | Kiesel(2012)[H] | Hodges(2003)[H] | Dickx(2010)[H]<br>Kiesel(2012)[H]<br>Kiesel(2008)[H] | ▪ Reduced activation of deep lumbar muscles during postural perturbation. **VERY LOW** quality of evidence.[b, c, d] | Task-dependent inconsistency on deep multifidus changes (Kiesel et al., 2012). |
| | ▪ Submax contraction<br>1 (15) | - | - | Dickx(2008)[H] | ▪ Limited evidence | |
| | | **Muscle timing changes – Lumbar muscles**<br>*Delayed* | *No change* | *Anticipated* | | |
| EMG ONSET | **Superficial muscles:**<br>▪ Postural control<br>3 (37) | - | Abboud[T]<br>Boudreau[H]<br>Hodges(2003)[H] | - | ▪ No timing changes of superficial lumbar muscles during postural perturbations. **MODERATE** quality of evidence.[b] | |
| | **Deep muscles:**<br>▪ Postural perturbation<br>2 (15) | - | Moseley(2004)[H] | Hodges(2003)[H] | ▪ Inconsistent and limited evidence | |

Experimental pain models adopted: H, hypertonic saline injection; T, heat thermal stimulation; E, nociceptive electrical stimulation; C, capsaicin.
Certainty of evidence rated accordingly with GRADE (high, moderate, low, very low), and reasons for rating down the quality of evidence are:
[a] Study limitation (risk of bias); [b] Publication bias; [c] Imprecision; [d] Inconsistency.

**Table 2.5** *Effects of experimentally induced pain in the lumbar region on abdominal muscle activity - summary of findings and certainty of evidence*

| | **Muscles**<br>▪ Task<br>N studies (n part) | **Muscle Activation changes – Abdominal muscles**<br>*Increased* | <br>*No change* | <br>*Decreased* | **Findings & certainty of evidence** | **Comments** |
|---|---|---|---|---|---|---|
| EMG AMPLITUDE | **Superficial muscles:**<br>▪ Locomotion<br>2 (43) | Larsen (2018)[H] | van den Hoorn[H] | - | ▪ Inconsistent and limited evidence | |
| | ▪ Voluntary trunk movements<br>2 (31) | Hodges(2013)[H] | - | Ross(2015)[C] | ▪ Inconsistent and limited evidence | |
| | ▪ Postural perturbation<br>5 (98) | - | Abboud[T]<br>Bialy(2019)[E]<br>Hodges(2003)[H]<br>Larsen(2016)[H] | Boudreau[H] | ▪ No changes of superficial abdominal muscle activation during postural perturbation tasks.<br>**LOW** quality of evidence. [a, b] | |
| | ▪ Submax contraction<br>1 (12) | - | - | Hirata[H] | ▪ Limited evidence | |
| | **Deep muscles:**<br>▪ Postural perturbation<br>3 (56) | - | Bialy[E] | Hodges(2003)[H]<br>Kiesel(2008)[H] | ▪ Reduced activation of TrA during postural perturbation tasks.<br>**VERY LOW** quality of evidence. [a, b, c] | |
| | ▪ Submax contraction<br>0 (-) | - | - | - | ▪ No evidence | |
| | | **Muscle timing changes – Abdominal muscles**<br>*Delayed* | <br>*No change* | <br>*Anticipated* | | |
| EMG ONSET | **Superficial muscles:**<br>▪ Postural perturbation<br>3 (25) | Boudreau[H] | Hodges(2003)[H]<br>Moseley(2004)[H] | - | ▪ Inconsistent and limited evidence | Changes of superficial abdominal muscles affected by large inconsistency. |
| | **Deep muscles:**<br>▪ Postural perturbation<br>3 (31) | Hodges(2003)[H]<br>Moseley(2005)[E]<br>Moseley(2004)[H] | - | - | ▪ Delayed activation of TrA timing during internal perturbations.<br>**LOW** quality of evidence. [a, b] | Consistent findings on TrA only. |

Experimental pain models adopted: H, hypertonic saline injection; T, heat thermal stimulation; E, nociceptive electrical stimulation; C, capsaicin.
Certainty of evidence rated accordingly with GRADE (high, moderate, low, very low), and reasons for rating down the quality of evidence are:
[a] Study limitation (risk of bias); [b] Publication bias; [c] Imprecision; [d] Inconsistency.

Muscle activity and kinematics during the POST-PAIN condition

Ten studies included a POST-PAIN assessment to investigate whether neuromuscular adaptations outlast the duration of the noxious stimulus (111,122,124,180–182,188,190,193,194). A summary of findings is presented in Table 2.6. Although some adaptations were reported during the PAIN condition, measures of trunk muscle activity and kinematics returned to baseline values in six studies (111,122,181,188,190,194). Instead, three studies inducing pain with hypertonic saline injection found that neuromuscular adaptations outlasted pain and were still present to some degree during the POST-PAIN condition (124,180,182). Despite the large heterogeneity of tasks, outcomes investigated, and timing of assessment, only adaptations of deep trunk muscle activity outlasted pain. Moreover, one study assessed the onset delay of transversus abdominis during rapid arm movements and subgroups of participants who resolved and not resolved from the adaptations identified while in pain were observed (187).

Trunk kinematics was assessed during the POST-PAIN condition in three studies evaluating walking and trunk flexion-extension movements after hypertonic saline injection or capsaicin (181,188,194). No changes were reported during trunk flexion-extension when POST-PAIN and BASE conditions were compared (188,194). Instead, different findings were identified during walking (181). Specifically, trunk stability and variability returned at baseline values while walking at low speed, but not at a higher speed (0.94 and 1.76 m/s, respectively).

**Table 2.6** *Neuromuscular changes evaluated across conditions: BASE, PAIN and POST-PAIN*

| Study | N | Pain model | Task | Pain during POST PAIN condition | Timing of assessment | Outcome (body region) |
|---|---|---|---|---|---|---|
| *Neuromuscular adaptation returned to baseline values* | | | | | | |
| Hodges et al., (2013) | 15 | HSI | Trunk flex/ext while sitting | NRS: 0 | NR | Net muscle activation (back & abdominal muscles) |
| Moseley et al., (2005) | 16 | NES | Rapid arm movement | VAS: 0 | Immediately after PAIN | Onset delay (TrA) |
| Ross et al., (2015) | 14 | CPS | Trunk flex/ext | VAS: 14 ± 12 | 1 hour | Trunk stability and muscle contribution to spinal stiffness (lumbar spine) |
| Ross et al., (2017) | 16 | HSI | Trunk flex/ext | VAS: 9 ± 10 | 1 hour | Trunk stability |
| van den Hoorn et al., (2015) | 17 | HSI | Walking | NRS: 0 | 4 minutes after full recovery | ROM (lumbar spine)<br>Trunk stability and variability (0.94m/s speed) |
| Wong et al., (2016) | 9 | HSI | Mechanical indentation | NRS: 0 | 25 minutes | Muscle activation<br>(lumbar & abdominal muscles) |
| *Neuromuscular adaptation outlasted pain* | | | | | | |
| Hodges et al., (2003) | 7 | HSI | Rapid arm movement | VAS: 0 | 10 minutes | Onset delay (TrA) |
| Kiesel et al., (2012) | 17 | HSI | Weight shift | VAS < 10/100 | NR | Muscle amplitude (dMF) |
| van den Hoorn et al., (2015) | 17 | HSI | Walking | NRS: 0 | 4 minutes after full recovery | Muscle activation (GM)<br>Spinal stability and variability (1.67m/s speed) |

Abbreviations: CPS, capsaicin; dMF, deep multifidus; GM, gastrocnemius medialis; HSI, hypertonic saline injection; NES, nociceptive electrical stimulation; NR, not reported; TrA, Transversus Abdominis.

## 2.5 Discussion

Findings from this Chapter demonstrates that experimental pain induced in the lumbar region of healthy individuals alters spine kinematics and muscle activity. In contrast to the findings from a previous review which revealed no kinematic changes and a reduction of muscle activity during experimental limb pain (107), findings of this Chapter indicate that experimental lumbar pain results in a reduction of the ROM of the lumbar spine and contrasting changes of trunk stability and variability. Evidence on muscle activity adaptations revealed a reduction in the activation of the deep trunk muscles, delayed activation of the transversus abdominis, and task-dependent increased or decreased activation of the superficial lumbar muscles. Overall, inconsistency of neuromuscular adaptations across participants and studies could be partially explained by the task and experimental pain model examined.

### *2.5.1 Does experimentally induced pain in the lumbar region induce neuromuscular adaptations in healthy adults?*

The identified adaptations can be interpreted in accordance with current theories that suggest that motor adaptation to pain is a purposeful strategy to protect the painful region and limit pain (80,87). In this regard, reduced ROM and an increase of muscle activity during voluntary trunk movements and locomotion might be interpreted as a protective behaviour, e.g. a strategy to avoid end range positions perceived as threatening and to ensure spine stability (minimise spine movements). Meta-analyses in this review support the presence of these adaptations, as well as a consistent increase of activity of lumbar extensor muscles during full trunk flexion. This Chapter further summarised evidence revealing an overall increase in muscle activity and spinal

stiffness during voluntary trunk movements and mechanical indentation (122,190). From a biomechanical perspective, higher and sustained activation of trunk muscles can increase loading on the spine. Evidence from biomechanical models and longitudinal studies suggests that an increase of spine loading resulting from sustained muscle activity might lead to intervertebral disc degeneration and represent a risk factor for the development of NScLBP (195–198). During postural perturbation tasks, instead, the observed strategy (i.e., reduced/delayed activity of trunk muscles) might be adopted to avoid a sudden recruitment of the painful muscle. Such a motor solution might lessen the experience of pain during the task, but with secondary consequences on spine stability and potential tissue strain (199,200). Despite being consistent with a strategy to protect the painful tissue, the observed muscle activity adaptations were not stereotypical as suggested by earlier theories on motor adaptations to pain (74,75). Instead, the task-specific adaptations observed might constitute one potential source of the heterogeneity across studies investigating people with NScLBP. Additionally, a few studies also showed individual-specific responses to experimental pain (122,181). Overall, both an increase and a decrease of trunk muscle activity may represent a purposeful strategy to reduce pain and protect the painful area. However, in the long term such changes could have a negative impact on the spine, especially when considering the biomechanical demands of the performed task (80). Differently from muscle activity, changes in lumbar kinematics were more consistent across studies, suggesting that the reduction in the ROM could represent a biomechanical solution to protect the painful area.

Although evidence on the effect of experimental pain was obtained from asymptomatic people, psychological factors might also play a role in the modulation of kinematics and muscle activity during the experience of pain. Indeed, an influence of psychological factors on motor strategies was reported both in clinical and asymptomatic populations (201,202). Studies included in the present review used psychological factors to identify subgroups and explain different patterns of adaptations. For example, higher stability of trunk movements and persistent adaptations after the resolution of pain were observed in participants with higher fear of movement and pain catastrophising (187,188). Moreover, expectation of higher pain intensity resulted in an increase of muscle activity during a trunk flexion task (129). There is evidence to suggest that psychological and cognitive factors need to be considered to understand and partially explain some of the inter-individual variability encountered in the investigation of motor adaptations to pain in the lumbar region.

### *2.5.2 Are neuromuscular adaptations induced both locally and remote to the lumbar region?*

Given the limited and contrasting evidence, no meaningful conclusions can be drawn on the effects of pain induced in the lumbar region at remote sites. Future studies should address this gap in the literature considering the regional interdependence observed in clinical populations (203,204), and the impact that pain has on muscle synergies (83). An example of regional interdependence is provided by the strong relationship that exists between NScLBP and the development of hip osteoarthritis-related pain (203). Such findings are not surprising considering that neuromuscular adaptations are not restricted to the painful body region in people with

NScLBP (205). The influence of NScLBP on muscle synergies have been described in previous studies. Specifically, muscle synergies explaining most of the activation variance in healthy people were mainly represented by lumbar muscles, whereas the activation variance in individuals with NScLBP was mainly explained by activation of leg and thoracic muscles. In other words, people with NScLBP relied more on leg and more global muscle strategies during lifting (206), reaching (207), and prone hip extension (208). In one study of this review, muscle synergies related to lower limb actions were unaffected by pain during walking. The contrasting findings with clinical LBP might be explained by the different role of the trunk during the investigated task (181). Future studies are required to understand how experimental pain in the lumbar region affects motor strategies in joints along the kinetic chain, including the knee, hip, and thorax, especially for tasks that require voluntary trunk movements.

### *2.5.3 Do neuromuscular adaptations outlast the duration of the noxious stimulus?*

In most studies, motor strategies returned to baseline in the post-pain condition. In two studies, however, adaptations of multifidus and transversus abdominis activity outlasted the presence of pain (124,182). As the onset of the transversus abdominis activity evaluated during rapid arm movements remained delayed in people with higher fear of movement and catastrophising thoughts (187), psychological factors may partly explain the heterogeneity in whether motor adaptations outlast the duration of the noxious stimulus. The absence of motor adaptations during the post-pain condition might be explained by the short-lasting nature of the experimental pain models adopted and the lack of association between pain and movement. When reported, pain induced

by hypertonic saline injection lasted between two and ten minutes (76,124,184,190), whereas nociceptive electrical stimulation or thermal stimulation were delivered just for a few seconds (time required to perform one trial of movement/perturbation) (130,191,192). Additionally, associative learning resulting from the relationship between pain (negative feedback) and movement has been suggested as a potential mechanism to influence persistent changes in motor behaviour (209,210). Although promising results have been shown, they are limited to simple tasks of the upper arm (211,212). Future studies are needed to understand which physical, psychological, and cognitive factors might result in retention of motor adaptations acquired during pain in the lumbar region.

### *2.5.4 Do neuromuscular adaptations depend on the type of experimental pain model?*

Subgroup analyses conducted using experimental pain model as a main factor were able to explain some of the inconsistency across studies. Different changes of erector spinae activity were identified using superficial (skin) and deep (muscle) pain models. Whereas two studies reported an increase or no change of muscle activity using cutaneous pain (130,191), other studies using muscle pain revealed a consistent reduction in muscle activity during similar tasks (trunk extension and postural perturbations, respectively) (77,177). Different neurophysiological mechanisms could be involved and explain the identified discrepancy of adaptations between superficial and deep pain models. First, a recent review supported the neurophysiological effects of muscle pain on both cortical and spinal mechanisms, whereas skin pain showed only minimal effects at a cortical level (105). Second, decreased muscle spindle firing rate

was observed after hypertonic saline injection in the muscle, but not in the skin (213). Finally, muscle pain results in larger unpleasantness and higher activation of brain areas involved in emotional responses when compared with superficial pain (79,110). Although consistent findings showed a reduction of motor unit discharge rate after hypertonic saline injection (106), there is limited evidence that superficial pain induces similar adaptation.

Based on the identified differences of adaptations across experimental pain models, pain induced by means of hypertonic saline injection seems the one that better replicates adaptations observed in a clinical population (see below). However, nociceptive electrical stimulation and capsaicin, as well as hypertonic saline injection in tissues other than muscle, were used as experimental pain models in only a few studies. Further research is needed to identify their role in investigating motor adaptations to lumbar pain.

### *2.5.5 Similarities to clinical pain and implications*

The neuromuscular adaptations identified in this Chapter are in accordance with movement and muscular activity biomarkers that discriminate people with NScLBP from asymptomatic individuals summarised in a recent review (103). Adaptations include changes of lumbar ROM and lumbo-pelvic coordination during trunk sagittal bending, muscle activity changes (amplitude and timing) during postural perturbation tasks, and the reduction of the flexion relaxation phenomenon during full trunk flexion (103). Moreover, the phase-dependent nature of muscle activity adaptations during gait, as well as the factors influencing trunk variability and stability (i.e., psychological

features and mechanical demand of the performed task) were also identified in previous reviews on clinical LBP (150,214). Findings of reduced lumbar flexion during trunk sagittal bending were consistent across studies and agree with the few studies available on motor adaptation in people with non-specific acute LBP (215,216).

The task- and muscle-specific adaptations observed in this review suggest that specific rehabilitation interventions may be required to effectively target motor dysfunctions in individuals with clinical LBP. For instance, the delayed and reduced activation of deep trunk muscles and erector spinae during postural perturbation tasks suggests that it may be beneficial to promote the recruitment of these muscles with specific motor control exercises (217,218). Instead, interventions promoting a reduction of muscle activity may be effective for voluntary trunk movements requiring end-range postures and locomotion in order to also restore a full, pain-free range of lumbar motion. Inconsistent findings in some of the outcomes also suggest that individuals may adopt different neuromuscular strategies to increase spine stability (122). Given the adaptations summarised in this review, findings of this Chapter provide support for further clinical trials assessing the effect of motor control exercises addressing task- and muscle-specific adaptations on long-term clinical outcomes.

### *2.5.6 Limitations*

Findings of the present review are affected by some limitations. Although subgroup analyses were conducted to address inconsistency across studies, some heterogeneity might have remained unexplained because of differences in the location of pain experienced by participants, the presence of referred pain resulting from

hypertonic saline injection (reported in four studies), and differences in the amount of nociceptive stimulation required to induce the same pain intensity among participants. Future studies should assess if these differences may partially explain the variability of neuromuscular adaptations and use experimental pain models able to better standardise these factors. The small sample size of included studies also affected the quality of evidence. However, within-subject comparisons provide higher statistical power since they allowed to partially control for the inter-individual variability that usually affects case control studies. On the other hand, multiple interventions applied during the same session and with a short wash-out period could have led to carry-over effects across the experimental conditions. Finally, the results of this Chapter mainly apply to young adults since the average age of participants was less than 30 years old. Only two studies recruited people with average age of 32 and 38 years old (111,191). Future studies should investigate if findings on motor adaptations to experimental lumbar pain also apply to older populations.

## 2.6 Conclusions

Findings from this Chapter support that pain experimentally induced in the lumbar region results in adaptations of spine kinematics and trunk muscle activity. Although heterogeneous, the identified adaptations may protect the painful region and potentially limit the experience of pain in the short-term. The tasks performed and the type of experimental pain model used accounted for some of the heterogeneity between studies. Most of the adaptations to experimental pain summarised in this review are in accordance with muscular activity and movement biomarkers identified in people with NScLBP. Such consistency further supports the role of experimental pain induced in the

lumbar region to understand motor adaptations in people with clinical LBP, which can help to unravel the causal mechanisms underpinning the association between pain and movement.

Although findings from this Chapter provide important evidence on the causal relationship between pain and movement, two areas of research resulted largely unexplored. First, only one study assessed the effects of MEP on movement, which means that the bidirectional relationship between pain and movement has not been thoroughly investigated. Second, most of the evidence focused on local changes without considering whether the CNS redistributes movement to other joints. Thus, the next Chapter attempts to address these gaps in the literature by investigating the effects of MEP induced in the lumbar region on movement. Furthermore, lumbar kinematics was chosen as the main outcome to investigate in *Chapter Three* and *Chapter Four* since a reduction in lumbar ROM was the most consistent findings across the studies included in the systematic review.

# CHAPTER 3 – DIRECTION MATTERS: A CROSSOVER STUDY ON MOTOR ADAPTATIONS TO MOVEMENT-EVOKED PAIN INDUCED IN THE LUMBAR REGION

## 3.1 Abstract

People with NScLBP often experience pain evoked by movement (i.e., MEP). Although pain changes how people move, it remains unclear whether motor adaptations to LBP are specific to the pain-provocative movement. By using a crossover experimental design, this Chapter aimed to understand whether pain modulated by movement in different directions induces distinct motor adaptations, and if these adaptations are consistent with a purposeful strategy to minimise pain. Thirty healthy adults performed a repetitive box lifting task in two experimental sessions. Experimental pain was induced in the lumbosacral region using nociceptive electrical stimulation, with intensity modulated proportionally to either lumbar flexion or extension. Within-subject changes in kinematics and centre of pressure were assessed both during and post-pain. During both sessions and over time, participants reduced the lumbar movement in the pain-provocative direction ($p<0.01$), but not in the non-pain-provoking direction ($p>0.078$). The reduction in lumbar flexion was strongly associated with perceived pain intensity ($p<0.001$) and persisted beyond pain resolution ($p=0.027$). Pain during lumbar flexion also induced other acute motor adaptations, including reduced elbow flexion ($p=0.027$) and anterior shift of the centre of pressure ($p<0.001$). This Chapter revealed that the direction of the pain-provocative movement is a determinant factor in motor adaptation to pain, with clinical implications in developing personalised, movement-based interventions for NScLBP. Further, motor adaptations were not simply

a generic acute response to pain but evolved to minimise pain, supporting the proposal that MEP is a motivational stimulus for adaptive behaviour driven by learning.

## 3.2 Introduction

As described in *Chapter One*, MEP is a phenomenon that is extremely common since approximately seventy percent of people with musculoskeletal disorders experience an increase of pain when they move (219). However, *Chapter Two* revealed that motor adaptations to movement-evoked LBP remain largely underexplored despite spontaneous and movement-induced pain are different. MEP differs from pain at rest or recalled pain since it is "acutely provoked and experienced in response to active or passive movement of the involved tissues" (52). Compared to pain at rest, MEP is more severe (220), strongly associated with measures of pain sensitivity (55), and potentially more responsive to intervention (221). In addition to the provocation of pain by movement (i.e., MEP), pain can also change how people move. Current theories suggest that motor adaptations to pain represent a purposeful strategy to protect the painful region from further pain and injury (80). This can be achieved in several ways, from a subtle redistribution of activity within a muscle to the complete avoidance of the painful movement (87). Despite the reciprocal interaction between pain and movement, the systematic review of *Chapter Two* has demonstrated that research has mainly focused on how pain influences movement, leaving motor adaptations to pain-provocative movements largely underexplored (50). Yet, this is particularly relevant for musculoskeletal disorders such as NScLBP given that certain movements can either exacerbate or alleviate symptoms by changing the load on spinal structures (61).

MEP is a commonly reported by people with NScLBP and leads to reduced motor function and greater disability (51,222). Although movement and exercise can provoke pain, they are also recommended by clinical guidelines as first-line treatment for LBP (14,223). However, there is controversial evidence about which specific type or approach is most effective (224). This is due to the large clinical heterogeneity in NScLBP, which has promoted the development of personalised movement-based interventions aiming at the identification and replacement of pain-provocative movements with pain-free ones (225,226). Recent trials supported the efficacy of this personalised approach by showing larger reduction in pain and disability when a movement-based classification was considered to inform treatment (16). One possibility is that individualised interventions based on pain-provocative movements are more effective than one-size-fits-all treatments because motor adaptation differs between people who report LBP associated to different movements (227–230) . For instance, pain that increases with lumbar flexion or lumbar extension may result in different, opposite changes in motor strategy since motor adaptations are thought to be a purposeful strategy to avoid pain. This association between MEP and direction-specific motor adaptation can be tested directly in humans using those experimental pain models described in *Chapter One*.

*Chapter Two* showed that pain induced in the lumbar region results in reduced lumbar ROM and task-dependent changes of muscle activity. However, most of the included studies used tonic pain models which can only support a causal effect of pain on motor adaptation. Such unidirectional perspective is in contrast with the clinical presentation of MEP in LBP, where the interaction between pain and movement is

essentially bidirectional (50,51). In addition, tonic pain models do not offer a way to consistently modulate pain intensity by changing how someone moves, therefore could not be used to effectively investigate motor-adaptation to MEP. Recent pain models based on electrical stimulation allow to modulate intensity or duration of the painful stimuli by changing movement strategies, reproducing the temporal characteristics of MEP observed in clinical populations (135,137). These MEP models could provide new insights to understand motor adaptations to MEP in the lumbar region because they can modulate the nociceptive input based on the direction of movement, while also allowing people to change the way they move to reduce pain. Furthermore, MEP models allow to investigate the relationship between movement and pain within a counterfactual scenario answering to the question "how people would change the movement if pain is experienced in the opposite direction", which provide a higher level of evidence on the causal relationship between movement and pain.

Based on findings from *Chapter Two* confirming the causal relationship between pain and movement, this Chapter addresses the primary and secondary aims of the thesis. Specifically, this Chapter aims to investigate whether pain induced in the lumbar region and modulated by movement in different directions leads to different motor adaptations. Additionally, this Chapter also aims to determine if these motor adaptations are a purposeful strategy to reduce pain. The hypothesis for this Chapter is that motor adaptations are specific to the movement direction that provokes pain, and that such adaptations are effective at reducing pain.

## 3.3 Methods

### *3.3.1 Study design*

In this crossover study participants attended two experimental sessions separated by at least 3 days. In each session, participants performed 15 sets of a standardised box lifting task while experiencing pain experimentally induced in their lumbosacral region using nociceptive electrical stimulation; pain was associated with lumbar flexion in one session (Pain Flexion session), or lumbar extension in the other (Pain Extension session). To control for potential order effects, the order of sessions was randomised among participants (random.org), and the team-member who enrolled participants was blind to the random allocation sequence. Joint angles of the lower body, upper body, trunk and the displacement of the centre of pressure were the main outcomes of interest.

This study was approved by the Research Ethics Committee at the University of Birmingham (ERN_19-1018, Appendix 5) and conformed to the latest Declaration of Helsinki. Before the experimental procedures, all participants provided written informed consent and completed a pre-test health screening to confirm their fitness for exercise without any contraindications. All experiments were conducted at the School of Sport, Exercise and Rehabilitation Sciences (University of Birmingham) from 30/09/2021 to 02/04/2022. This study is reported following the CONSORT guidelines for crossover studies (231) (Appendix 6).

### *3.3.2 Participants*

Thirty healthy volunteers (14 female, age: 23 ± 3 years; height: 172.9 ± 8.8 cm; mass: 69.3 ± 11.0 kg) were recruited from the staff and student population at the University of Birmingham, UK. The sample size was determined using G*Power, based on data from a prior study that evaluated changes in lumbar ROM in healthy participants both before and after inducing pain in the low back region (129). A total of 24 participants were required to achieve an effect size (Cohen's d) of 0.60, a significance level (α) of 0.05, and a power (1−β) of 0.80. To account for potential dropouts between sessions or incomplete datasets, we recruited 30 participants.

Participants were included in the study if they were aged between 18 to 50 years old. This age range was chosen to minimise the potential confounders such as age-related fatigue. Participants were required to have no history of lower back pain that required treatment or affected their function. Participants were excluded if they presented with neck, upper or lower limb pain within the last year, a history of major spinal pathologies (i.e., infection, cancer, inflammatory disorders, fracture), prior spinal surgery, current pregnancy, presence of implanted medical devices or metal around the back, pelvis, or hip joints. Participants with major pathologies (neurological, neuromuscular, etc.) or those taking antidepressant drugs were also excluded.

### *3.3.3 Nociceptive electrical stimulation*

Pain was elicited in the lumbosacral region by electrical stimulation using two surface electrodes (TE0N1S3545, SpesMedica, Genoa, Italy) placed on the sacrum at the level of S2, with a 2 cm interelectrode distance (border to border) and aligned with

the midline of the spine. This location was chosen to prevent muscle twitching, and the electrodes were downsized from 35 x 45 mm to a 20-mm diameter to further minimise current dispersion across the skin. A constant current stimulator (Digitimer DS5 Isolated Bipolar Constant Current Stimulator, Welwyn Garden City, Hertfordshire, UK) was used to deliver sinusoidal waveforms at 4 Hz. The stimulator was controlled through a custom-written Simulink model (version 2021b, MathWorks), generating an analog signal (i.e., sinusoidal waveforms) at 2000 samples per second using a PCI-6229 board with a 16-bit resolution. The stimulation parameters were chosen to minimise pain habituation (135).

The stimulation intensity was determined before the start of the lifting task by an ascending stimulation protocol in steps of 0.5 mA. During this protocol which was applied during quiet standing, each painful electrical stimulus was delivered for 2 seconds, followed by a rest period of approximately 5 seconds. Participants verbally rated their pain intensity using a numeric rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain imaginable). The minimum and maximum stimulation intensity were identified as the stimulation amplitudes that induced a pain intensity of 1/10 and 5/10 respectively. The maximum pain intensity was similar to previous studies investigating movement-evoked LBP in a clinical population (64). To control for potential habituation, the stimulation intensity necessary to induce a pain of 5/10 was reassessed after every 3 sets and adjusted if necessary.

### *3.3.4 Lifting task and pain modulation*

After completing the ascending stimulation protocol, participants stood on a force plate (Kistler, 9286AA) facing a shelving unit, with their bare feet positioned at a standardised distance of 125% of their foot length from the shelving unit. The width of the stance was freely chosen by participants, and this was then recorded and maintained across all sets and sessions. Participants were asked to move a box (size: 39x28.5x16 cm, mass ~1kg) between two shelves positioned at eye and knee level. The mass of the box was low and equal across all participants to assess the effects of pain on neuromuscular control while reducing the potential influence of confounders such as fatigue. The task mainly required movements in the sagittal plane, and participants were asked to continuously move the box between shelves to the pace of a metronome set at 24 beats per minute, with each beat signalling when to place the box on the lower or upper shelf. This ensured 2.5 seconds for both lifting and lowering of the box. A period of familiarisation was provided before starting the assessment. In both sessions, participants completed 15 sets of 10 lifting cycles each, always starting and ending at the lower shelf. Two minutes of rest were provided between sets. Standardised instructions were given to participants so that they were only aware that nociceptive electrical stimulation would not be delivered during the first two sets. Specifically, all participants were told “during the first two sets you will not feel any pain, and from sets 3 to 15 you may or may not feel pain of constant or variable intensity”. These instructions were provided to ensure that participants were naïve to how the stimulation was modulated. The first two sets represented the baseline condition (Base), and the

recorded ROM was used as a reference for the modulation of the stimulation in the following sets.

To adjust the nociceptive electrical stimulation (output) in near real-time and proportional to the amount of lumbar movement performed (input), a closed-loop system was implemented (Figure 3.1). The lumbar movement was collected by an electrogoniometer connected to a single-channel amplifier (Forza, OT Bioelettronica, Italy) with a gain of 100V/V and digitised with a 16-bit converter (PCI-6229 board, National Instruments, USA). Once digitally converted, the input signal was processed in a custom-written Simulink model to scale the amplitude of the sine wave sent to the electrical stimulator and delivered to the participant (nociceptive electrical stimulation, output). To scale the amplitude of the sine wave, the total range of lumbar motion collected with the electrogoniometer during Base was divided into three intervals (flexion, neutral, and extension). During Pain Flexion for instance, the stimulation was set at the minimal pain intensity when the lumbar angle was in the neutral and extension interval, and the stimulation intensity increased linearly with the lumbar angle when the lumbar angle was within the flexion interval. If the participant reached or exceeded the maximal flexion angle recorded when performing the task without painful stimulation, the nociceptive electrical stimulation delivered was equal to the stimulation intensity that induced a pain of 5/10. This modulation of the painful stimulation allowed to exacerbate pain during repeated movement, similarly to what is reported by people with NScLBP (64). After each set, participants rated their level of fatigue using the 0-10 modified Borg scale and they rated the average intensity of pain

experienced during the painful phase of the task, without providing information about when the stimulation was provided (NRS, 0-10).

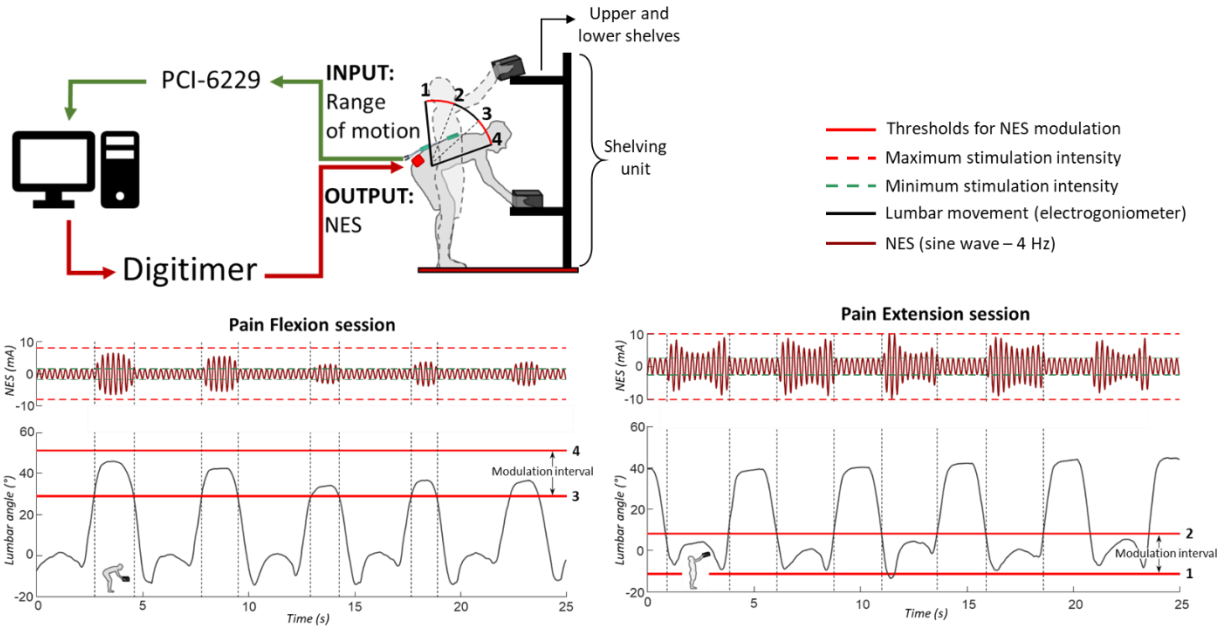


**Figure 3.1** *Experimental set-up showing the closed-loop associating lumbar movement to the delivered nociceptive electrical stimulation.*
*Lumbar range of motion was collected using an electrogoniometer, digitally converted by a PCI-6229 board, and processed in real-time using Simulink (MATLAB). During the baseline condition, the total range of lumbar movement was recorded and then used to linearly scale the delivered stimulation between its maximum and minimum stimulation intensity (dashed lines). The total range of lumbar motion (from 1 to 4) collected during baseline was evenly divided into three equal parts. In the Pain Extension session, pain modulation occurred when the lumbar movement was within the 1-2 interval. Instead, in the Pain Flexion session the pain modulation occurred when the lumbar movement was within the 3-4 interval. If the range of lumbar motion exceeded the one recorded during baseline, the stimulation intensity was limited to the maximum threshold (accordingly with the session type).*

### *3.3.5 Equipment for movement analysis*

During the lifting task, participants were equipped with wearable Inertial Measurement Units (IMUs, Noraxon USA Inc., Scottsdale, Arizona, USA) to assess lower limb, upper limb, and trunk kinematics. The IMUs were placed in accordance with

manufacturer guidelines and secured with double-sided tape. IMUs are wearable devices that measure and report body movements by combining information from embedded sensors, including accelerometer, gyroscope, and magnetometers. Based on their placement, data from individual sensors are combined to compute joint angles using the algorithms implemented by the data acquisition software (myoRESEARCH, version 3.12, Noraxon USA Inc., Scottsdale, Arizona, USA). IMUs of the Noraxon have shown good reliability and concurrent validity when compared to the gold standard during both lower limb and trunk movements, especially on the sagittal plane (232,233). Specifically, joint angles showed clinically acceptable reliability (differences lower than 5º) and root mean square differences ranged from 1.4° to 2.6° during uniplanar movement (232,233).

A flexible electrogoniometer (M180B, Biometrics Ltd, Gwent, UK) was placed and secured using double-sided tape on the upper and lower part of the lumbar spine (approximately between T12/L1 and L5/S1) to measure its movement in the sagittal plane; this signal was used to modulate the nociceptive electrical stimulation delivered by means of a pair of electrodes placed on the sacrum. A triaxial accelerometer (Noraxon USA Inc., Scottsdale, Arizona, USA) was secured in the centre of the box to identify the start and end of lifting cycles. The displacement of the centre of pressure was the main outcome extracted from the force plate (Kistler, 9286AA, Switzerland) with signals sampled at 200 Hz and digitised with a 16-bits converter (PCI-6229 board, National Instruments, USA). The centre of pressure was computed from the force and torque signals using a custom-written Simulink model, and visually inspected online.

### *3.3.6 Data processing*

Joint angles and box acceleration signals were sampled at 100 Hz and acquired using the myoRESEARCH software (version 3.12) and exported in MATLAB (version 2022b, MathWorks, USA) for offline processing. The signal representing the vertical acceleration of the box was smoothed with a Butterworth lowpass filter at 30 Hz (6th order). The obtained signal was differentiated to extract the jerk, and its peaks were automatically identified and visually inspected to define the start and end of each cycle. The first half of the first cycle (lifting phase) and the second half of the last cycle (lowering phase) were excluded from the analysis so that for each set nine cycles were considered (starting and ending from the upper shelf). Data from the force plate were sampled at 200 Hz and digitised using a PCI-6229 board with 16-bit resolution controlled by a custom-written Simulink model for the extraction of the centre of pressure (CoP). Once digitised, the signal from the electrogoniometer was filtered with a Butterworth 1st order lowpass filter with a cut-off frequency of 10 Hz.

The waveform of joint angles and CoP were filtered with a Butterworth lowpass filter (4th order, 10 Hz), and divided in cycles based on the accelerometer signal. All smoothed waveforms were interpolated to create 101 samples representing 0-100% of a lifting cycle. Within each cycle, the instants representing the peak of lumbar flexion and extension were identified and used to extract the position at the other joints at the same instants. This allowed us to assess the motor strategy adopted by participants in relation to MEP. The peak in lumbar flexion corresponded to the instant when participants put the box on the lower shelf. Instead, the peak in lumbar extension corresponded to the phase of the cycle when participants had to move the box between

their upper body and the top shelf. During each cycle, there were two peaks of lumbar extension and the highest one was used for statistical analyses. An overview of the raw signal during Base is presented in Figure 3.2 from one representative participant.

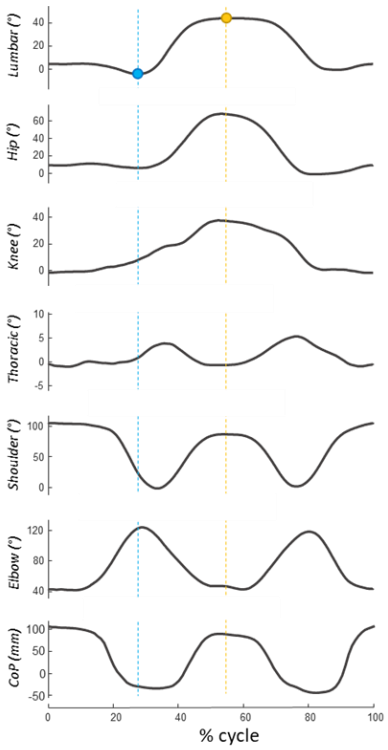


**Figure 3.2** *Raw data from one participant during the baseline condition.*
*All joint angles and centre of pressure (CoP) along the anteroposterior axis are presented. Positive values indicate a flexion movement and vice versa. For the CoP positive and negative values indicate an anterior or posterior shift, respectively. The instants with the extension and flexion peaks are indicated in blue and yellow, respectively. The extension peak occurred during the phase of movement when participants extended their lower back before placing the box on the top shelf.*

The first two sets represented the Base since no pain was induced and the ROM was used as a reference. Sets 3rd and 4th represented the early adaptation condition (Early) to investigate the acute neuromuscular response to MEP, and sets 12th and 13th

were the late adaptation condition (Late). Finally, sets 14th and 15th were the post-pain (Post) condition since the nociceptive electrical stimulation was not delivered.

Joint angles and CoP during both the peak in lumbar flexion and lumbar extension were extracted and averaged across cycles within the same condition (i.e., Base, Early, Late, Post) and session (i.e., Pain Flexion or Pain Extension). Similarly, perceived pain was averaged between sets 3-4 (i.e., Early) and 12-13 (i.e., Late). Also, Borg ratings were averaged across sets within the same condition and session.

### *3.3.7 Statistical analysis*

All analyses were conducted in IBM SPSS Statistics (version 29.0). Based on the data normality (Shapiro-Wilk test), parametric or non-parametric analyses were considered for inferential statistics. Different data transformations (i.e., logarithmic, square root, reverse) were applied to joint angles and CoP data based on their distribution inspected by means of QQ-plots and histogram plots. Shapiro-Wilk test was conducted to confirm that data were normally distributed after transformation. Greenhouse-Geisser corrections were applied to control for violations of sphericity in repeated measures. Data are reported as mean and standard deviation or median and quartiles depending on their distribution. All p-value are presented after Bonferroni correction because three comparisons were assessed for each variable of interest (i.e., Early, Late, and Post were compared to Base).

To evaluate the between-session reliability of the stimulation intensity to induce a pain of 1/10 and 5/10, we used the intraclass correlation coefficient (ICC) calculated using the two-way mixed effects model and absolute agreement for average measures.

We assessed whether there was a systematic bias between sessions by comparing the maximum stimulation intensity (paired t-test or Wilcoxon signed-rank test).

Perceived pain during Early was compared between sessions using paired t-test or Wilcoxon signed-rank test. The same approach was conducted to test within-session changes in perceived pain between Early and Late. Perceived fatigue during each condition was compared between sessions using paired t-test or Wilcoxon signed-rank test. Finally, Friedman test was used to test for differences in perceived fatigue between conditions within each session. When significant, this was followed by a Wilcoxon signed-rank test with Bonferroni correction (three comparisons) comparing Base with the other conditions.

Joint angles and CoP during Base were compared between sessions with paired t-test or Wilcoxon signed-rank test. Two-way repeated measure analyses of variance (ANOVA) were used to assess the main and interaction effects of session (Pain Flexion and Pain Extension) and condition (Base, Early, Late, Post) on joint angles and CoP. Post-hoc analysis was performed as follows. When an interaction effect was present, pairwise comparisons were used to identify changes from baseline within each session, e.g.: if in Pain Flexion the data during Early, Late or Post differed from Base. Within-subjects simple contrasts were used to test if the changes from Base differed between sessions, e.g.: if in Early the change from Base of the peak in lumbar flexion was larger during Pain Flexion compared to Pain Extension. When main effects of conditions were significant without significant interaction with session, pairwise comparisons were applied to the main effects.

To evaluate if the adaptations in the lumbar region represent a purposeful strategy to reduce pain, we assessed if the perceived pain intensity during Late was associated with the change in lumbar kinematics between Base and Late, separately for the two sessions. The correlation was conducted using Pearson rho or Spearman rank correlation depending on data distribution, presence of outliers, and linearity of the relationship.

## 3.4 Results

### *3.4.1 Stimulation intensity, perceived pain and fatigue*

The stimulation intensity required to induce a pain intensity of 5/10 did not differ between Pain Extension (median [1st quartile, 3rd quartile]: 8.5 [5.6, 12.5] mA) and Pain Flexion (8.0 [5.1, 12.0] mA) sessions (difference: 0.25 [-1.0, 0.5] mA; Wilcoxon signed-rank test, N = 30, z = 1.48, p = 0.140). ICC values [95% confidence interval] to evaluate between-session reliability were 0.85[0.68, 0.93] for the stimulation intensity needed of to induce a pain intensity of 5/10, and 0.60[0.19, 0.81] for the stimulation intensity needed to induce a pain of 1/10.

Perceived pain during Early did not differ between Pain Extension (3.22 ± 1.01) and Pain Flexion (3.18 ± 1.13) sessions (t = -0.12, p = 0.90). During Pain Flexion, reduction of perceived pain intensity from Early (3.18 ± 1.14) and Late (2.68±1.33) conditions narrowly missed significance (difference: -0.5 ± 1.44, t = 1.90, df = 29, p = 0.068). Changes were characterised by large inter-individual variability; out of 30 participants, 12 reported a reduction of perceived pain of at least 1 out of 10, 14 reported minimal changes (smaller than ± 1 out of 10), and 4 reported higher pain during

Late compared to Early. No difference in perceived pain was observed during Pain Extension between Early (3.22 ± 1.01) and Late (3.13 ± 1.54) conditions (difference: 0.09 ± 1.39, t = 0.36, df = 29, p = 0.72). Also for this condition, large variability in the responses was observed among participants with 9 reporting a reduction of perceived pain of at least 1 out of 10, 12 reported minimal changes (smaller than ± 1 out of 10), and 9 reported higher pain during Late compared to Early. During all conditions, perceived fatigue did not differ between sessions ($p > 0.40$). Additionally, within both sessions perceived fatigue differed between conditions ($p<0.001$), but the median increase in perceived fatigue between Base and Post was minimal (Pain Extension: 0 [0 – 1.38], $p < 0.001$, and Pain Flexion: 0.63 [0 – 1], $p < 0.001$).

### *3.4.2 Effects of movement-evoked pain on joint angles and centre of pressure*

Data from all participants were included in the analyses. None of the outcomes of interest differed at Base between Pain Flexion and Pain Extension during the peak in lumbar flexion ($p > 0.11$) or the peak in lumbar extension ($p > 0.34$). Outcomes of interest with different patterns of changes between the two sessions are illustrated in Figures 3.3 (peak lumbar flexion) and 3.4 (peak lumbar extension). Average waveforms of the lumbar angle during both sessions and for different conditions are presented in Figure 3.5. All values are reported in the Table 3.1 for the peak lumbar flexion and Table 3.2 for the peak lumbar extension. Below, the analyses on the data extracted at peak lumbar flexion and at peak lumbar extension are presented separately. As a reminder, peak lumbar flexion refers to the flexion component of the task, and it was the pain provocative phase of movement during the Pain Flexion session. In the opposite

direction, peak lumbar extension refers to the extension component of the task and it was the pain provocative phase of movement during the Pain Extension session. A summary of the direction of changes is summarised in Table 3.3.

Peak in lumbar flexion

Two-way repeated measures ANOVA identified an interaction effect of session and condition on lumbar angle ($F(3,87)$: 6.74, $p = 0.004$). Pairwise comparisons in Pain Flexion revealed a reduction of lumbar flexion compared to Base during Late (-5.63±8.41, $p < 0.001$) and Post (-5.13±6.36 $p < 0.001$), but not during Early (-1.67±6.63, $p = 0.53$). No changes compared to Base were observed during Pain Extension ($p = 1$). Planned contrasts support a larger reduction of peak lumbar flexion when pain was modulated in flexion than when pain was modulated in extension (Early: $F(1,29) = 8.23$, $p = 0.008$; Late: $F(1,29) = 10.42$, $p = 0.009$; Post: $F(1,29) = 7.73$, $p = 0.027$). Despite the significant difference with Base and between sessions, the reduction of lumbar flexion during Late was characterised by large inter-individual variability. Specifically, of the 30 participants tested, 7 showed minimal changes (within ± 2°), 19 a reduction and 4 an increase of lumbar flexion compared to Base.

Hip angle data were assessed after logarithmic transformation. Two-way repeated measures ANOVA identified an interaction effect of session and condition on hip angle ($F(3,87)$: 6.78, $p < 0.001$). Pairwise comparisons revealed that during Early, participants performed the task with reduced hip flexion during both Pain Flexion (-6.31±9.26, $p = 0.009$) and Pain Extension (-2.99±5.36, $p = 0.015$). During Pain Extension, the reduction of hip flexion was also present during Late (-4.56±8.61, $p = 0.033$) and

Post (-3.65±6.52, p= 0.018) whereas in Pain Flexion no changes were observed (p = 1). The reduction of hip flexion between Base and other conditions did not differ between sessions (planned contrasts: p > 0.14).

Elbow angle data were assessed after logarithmic transformation. Two-way repeated measures ANOVA identified an interaction effect of session and condition on the elbow angle (F(3,87): 5.26, p = 0.004). During Pain Flexion, pairwise comparisons identified a lower elbow flexion in Early compared to Base (-6.74±9.74, p = 0.006). The reduction of elbow flexion was larger during Pain Flexion than Pain Extension during Early (planned contrast: F(1,29) = 7.83, p = 0.027), but did not differ in Late (F(1,29) = 0.002, p = 1) or Post (F(1,29) = 0.81, p =1). Two-way repeated measures ANOVA identified a main effect of condition on elbow angle (F(3,87) = 5.63, p =0.005). Pairwise comparisons revealed a difference from Base for both Late (F(1,29) = 10.23, p = 0.009) and Post (F(1,29) = 14.33, p < 0.001).

Data of the CoP were assessed after square root transformation. Two-way repeated measures ANOVA identified an interaction effect of session and condition for the CoP (F(3,87): 7.51, p <0.001). Pairwise comparisons identified during Early an anterior shift of the CoP compared to Base during Pain Flexion (7.56±13.93, p = 0.006). No changes were found for other conditions (p > 0.77) or during Pain Extension (p > 0.67). The anterior shift of the CoP was larger during Pain Flexion than Pain Extension only during Early (planned contrast: F(1,29) = 14.71, p < 0.001).

Two-way repeated measures ANOVA identified no main effect of condition or interaction effect for the knee (assessed after square root transformation, $p > 0.236$), thoracic ($p > 0.146$), and shoulder ($p > 0.098$) angles.

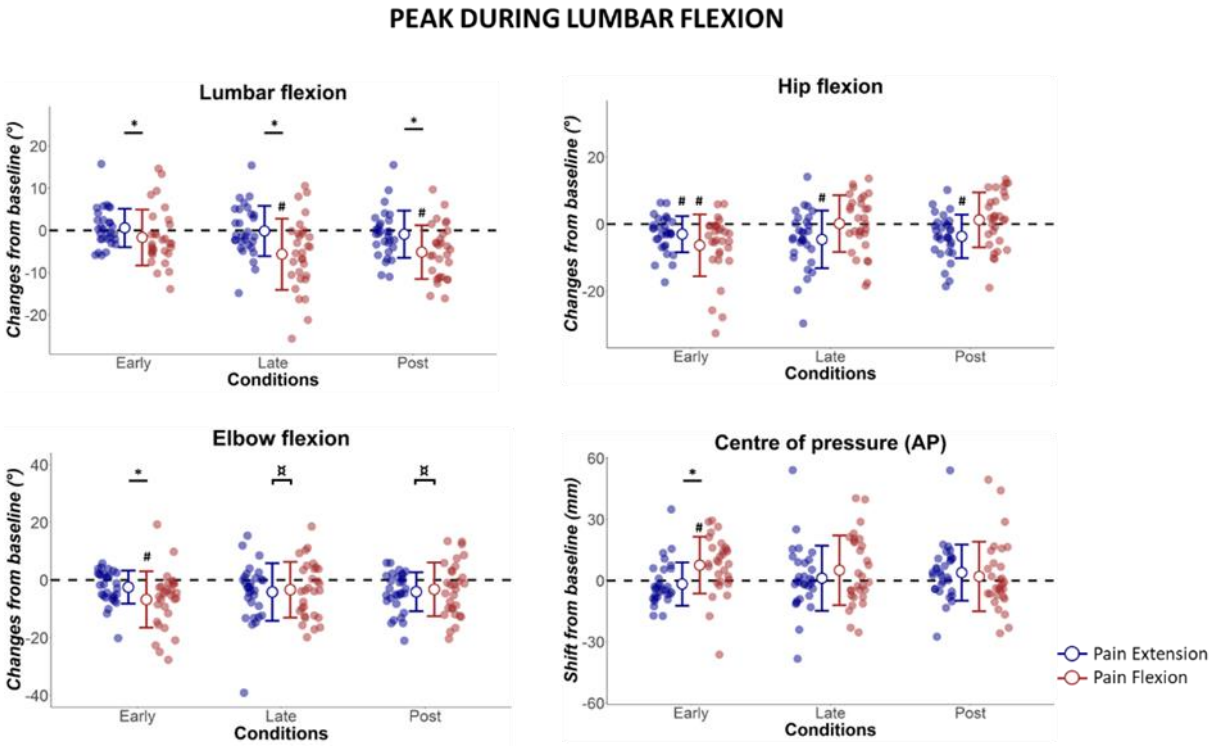


**Figure 3.3** *Changes from Base for multiple joint angles and centre of pressure during the peak in lumbar flexion.*
*Data are presented for all participants. * Interaction effect (session x condition) with significant planned contrasts between sessions ($p < 0.05$ after Bonferroni correction). # Pairwise comparisons revealed a significative difference from Base ($p<0.05$ after Bonferroni correction). ¤ Presence of a main effect of condition, with pairwise comparisons showing a significant difference from Base when sessions are pooled together ($p<0.05$ after Bonferroni correction).*

**Table 3.1** *Joint angles and centre of pressure (CoP) during the peak of lumbar flexion (mean ± SD)*

| ANGLE | SESSION | CONDITIONS | | | |
|---|---|---|---|---|---|
| | | BASE | EARLY | LATE | POST |
| Lumbar (°) | *Pain Flexion* | 32.5 ± 11.7 | 30.8 ± 11.9 | 26.9 ± 12.6 | 27.4 ± 11.4 |
| | *Pain Extension* | 30.8 ± 11.8 | 31.4 ± 12.4 | 30.7 ± 13.3 | 29.9 ± 13.2 |
| Hip (°) | *Pain Flexion* | 50.4 ± 19.8 | 44.1 ±21.9 | 50.5 ± 22.0 | 51.7 ± 21.8 |
| | *Pain Extension* | 52.9 ± 20.0 | 49.9 ± 21.1 | 48.3 ± 18.8 | 49.3 ± 18.8 |
| Knee (°) | *Pain Flexion* | 21.3 ± 24.2 | 21.6 ± 26.6 | 24.4 ± 30.9 | 20.9 ± 26.5 |
| | *Pain Extension* | 23.6 ± 25.9 | 22.2 ± 26.0 | 19.1 ± 21.6 | 18.5 ± 20.5 |
| Thoracic (°) | *Pain Flexion* | 12.9 ± 8.1 | 11.8 ± 11.2 | 11.9 ± 7.6 | 14.3 ± 10.5 |
| | *Pain Extension* | 12.3 ± 8.0 | 11.5 ± 8.0 | 13.3 ± 9.6 | 12.0 ± 8.6 |

| | | | | | |
|---|---|---|---|---|---|
| Shoulder (°) | *Pain Flexion* | 55.2 ± 14.1 | 52.0 ± 14.0 | 53.0 ± 9.8 | 52.2 ± 11.2 |
| | *Pain Extension* | 58.2 ± 9.2 | 59.0 ± 10.8 | 55.4 ± 13.5 | 57.0 ± 11.9 |
| Elbow (°) | *Pain Flexion* | 26.8 ± 12.5 | 20.1 ± 12.5 | 23.5 ± 14.0 | 23.7 ± 14.2 |
| | *Pain Extension* | 29.5 ± 15.9 | 27.0 ± 15.0 | 25.3 ± 15.3 | 25.4 ± 14.8 |
| CoP (mm) | *Pain Flexion* | 50.2 ± 30.5 | 57.8 ± 31.4 | 55.3 ± 26.8 | 52.2 ± 25.3 |
| | *Pain Extension* | 49.7 ± 33.9 | 48.0 ± 31.5 | 50.8 ± 27.2 | 53.6 ± 27.2 |

Peak in lumbar extension

Two-way repeated measures ANOVA identified an interaction effect of session and condition on lumbar angle ($F(3,87)$: 7.84, $p = 0.001$). Pairwise comparisons in Pain Extension revealed a reduction of lumbar extension compared to Base during Late (-2.48 ± 4.04, $p = 0.006$) but not during Early (0.06 ± 3.37, $p = 1$) or Post (-0.56 ± 2.88, $p = 0.87$). No changes compared to Base were observed during Pain Flexion ($p > 0.078$). A planned contrast comparing Base with Late showed a larger reduction of lumbar extension during Pain Extension compared to Pain Flexion ($F(1,29) = 13.38$, $p = 0.003$). Similarly to the peak in lumbar flexion, large inter-individual variability was observed in the changes between Late and Base. Changes during Late were minimal (within ± 2°) in 12 participants, 16 showed a reduction and two an increase of lumbar extension.

Hip angle data were assessed after square root transformation. Two-way repeated measures ANOVA identified a main effect of condition on hip angle ($F(3,87) = 8.40$, $p < 0.001$). Compared to Base, participants performed the task with more hip flexion during both Late ($F(1,29) = 13.28$, $p = 0.003$) and Post ($F(1,29) = 13.4$, $p <0.001$).

Knee angle data were assessed after square root transformation. A main effect of condition was found ($F(3,87) = 4.83$, $p = 0.011$). Pairwise comparisons revealed that during Post participants performed the task with a reduction of knee flexion ($F(1,29) = 15.41$, $p < 0.001$).

Similarly, two-way repeated measures ANOVA identified a main effect of condition on elbow angle ($F(3,87) = 5.75$, $p = 0.002$). Pairwise comparisons showed a reduction of elbow flexion compared to Base during Post ($F(1,29) = 12.65$, $p = 0.003$).

Although a main effect of condition on thoracic angle was found ($F(3,87)$: 6.41, $p = 0.002$), pairwise comparisons after Bonferroni corrections did not result in any difference between Base with the other conditions ($p > 0.078$).

Two-way repeated measures ANOVA identified a main effect of condition on the CoP ($F(3,87)$: 12.51, $p<0.001$). Compared to Base, a larger anterior shift of the CoP was observed during both Late ($F(1,29) = 7.02$, $p = 0.039$) and Post ($F(1,29) = 18.27$, $p < 0.001$).

Two-way repeated measures ANOVA identified no main effect of condition or interaction effect on shoulder angle ($p > 0.475$).

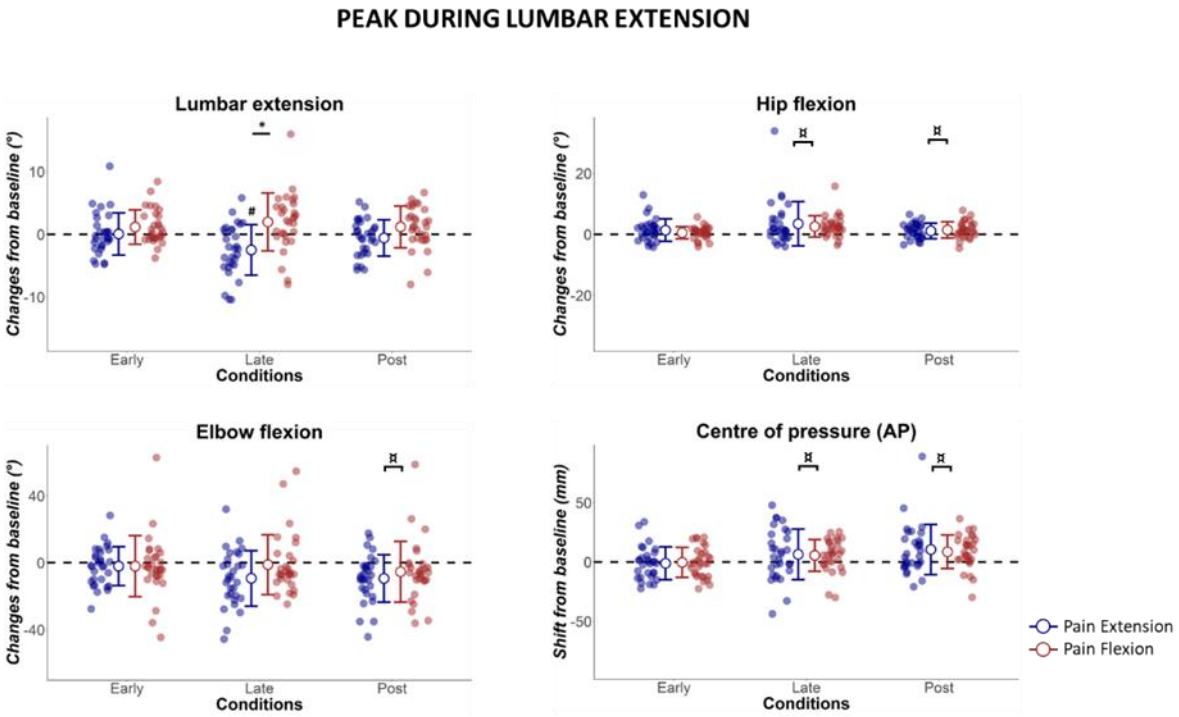


**Figure 3.4** *Changes from Base for multiple joint angles and centre of pressure during the peak in lumbar extension.*
*Data are presented for all participants. * Interaction effect (session x condition) with significant planned contrasts between sessions (p < 0.05 after Bonferroni correction). # Pairwise comparisons revealed a significative difference from Base (p<0.05 after Bonferroni correction). ¤ Presence of a main effect of condition, with pairwise comparisons showing a significant difference from Base when sessions are pooled together (p<0.05 after Bonferroni correction).*

**Table 3.2** *Joint angles and centre of pressure (CoP) during the peak of lumbar extension (mean ± SD)*

| Angle | Session | CONDITIONS | | | |
|---|---|---|---|---|---|
| | | BASE | EARLY | LATE | POST |
| Lumbar (°) | *Pain Flexion* | -2.3 ± 4.5 | -3.5 ± 5.1 | -4.3 ± 6.3 | -3.5 ± 5.7 |
| | *Pain Extension* | -2.3 ± 5.1 | -2.3 ± 5.1 | 0.2 ± 6.2 | -1.7 ± 4.5 |
| Hip (°) | *Pain Flexion* | 1.3 ± 3.2 | 1.9 ± 3.9 | 3.9 ± 4.3 | 2.8 ± 3.4 |
| | *Pain Extension* | 1.8 ± 3.8 | 3.2 ± 3.4 | 5.3 ± 6.9 | 2.9 ± 3.2 |
| Knee (°) | *Pain Flexion* | 4.7 ± 3.5 | 3.8 ± 3.2 | 3.3 ± 3.3 | 3.3 ± 3.4 |
| | *Pain Extension* | 4.8 ± 3.4 | 4.9 ± 3.7 | 5.6 ± 6.0 | 3.3 ± 3.2 |
| Thoracic (°) | *Pain Flexion* | -7.6 ± 5.1 | -5.8 ± 5.5 | -7.9 ± 5.7 | -8.5 ± 5.6 |
| | *Pain Extension* | -7.8 ± 5.7 | -7.5 ± 5.0 | -8.9 ± 4.9 | -8.1 ± 5.1 |
| Shoulder (°) | *Pain Flexion* | 52.3 ± 17.4 | 49.4 ± 15.7 | 52.6 ± 15.9 | 53.2 ± 15.8 |
| | *Pain Extension* | 53.4 ± 12.9 | 53.1 ± 14.4 | 55.7 ± 15.4 | 58.5 ± 14.8 |
| Elbow (°) | *Pain Flexion* | 83.5 ± 17.3 | 81.5 ± 21.3 | 82.4 ± 19.2 | 78.2 ± 19.2 |
| | *Pain Extension* | 86.6 ± 18.6 | 84.6 ± 19.9 | 77.4 ± 22.1 | 77.4 ± 20.5 |
| CoP (mm) | *Pain Flexion* | -24.3 ± 23.0 | -24.5 ± 24.5 | -18.7 ± 26.9 | -15.6 ± 27.4 |
| | *Pain Extension* | -24.9 ± 25.8 | -25.9 ± 28.4 | -18.4 ± 28.0 | -14.3 ± 25.6 |

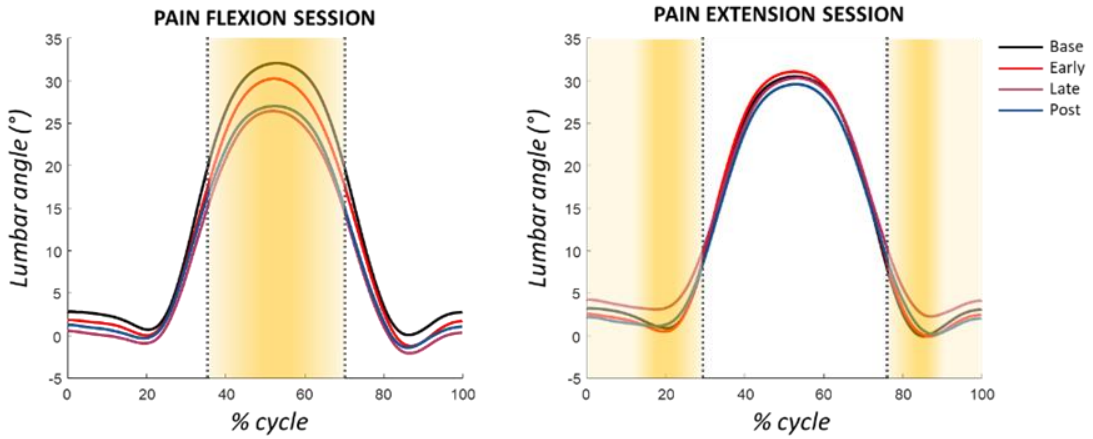


**Figure 3.5** *Average waveforms of the lumbar angle across conditions during both the Pain Flexion and Pain Extension sessions.*
*The area in yellow represents the pain modulation interval. Compared to Base, a reduction in the lumbar flexion peak is present during the Pain Flexion session across all conditions, especially during Late and Post-Pain. Although small, in the Pain Extension session there is a reduction of the extension peak in the Late condition compared to Base.*

**Table 3.3** *Changes of kinematics and centre of pressure (CoP) compared to baseline*

| | Outcome of interest | EARLY | | LATE | | POST | |
|---|---|---|---|---|---|---|---|
| | | ***Pain flexion*** | ***Pain extension*** | ***Pain flexion*** | ***Pain extension*** | ***Pain flexion*** | ***Pain extension*** |
| PEAK in LUMBAR FLEXION | Lumbar flexion | ↓ | - | ↓ | - | ↓ | - |
| | Hip flexion | ↓ | ↓ | - | ↓ | - | ↓ |
| | Knee flexion | - | - | - | - | - | - |
| | Thoracic flexion | - | - | - | - | - | - |
| | Shoulder flexion | - | - | - | - | - | - |
| | Elbow flexion | ↓ | - | ↓ | ↓ | ↓ | ↓ |
| | CoP *(anterior shift)* | ↑ | - | - | - | - | - |
| PEAK in LUMBAR EXTENSION | Lumbar extension | - | - | - | ↓ | - | - |
| | Hip flexion | - | - | ↑ | ↑ | ↑ | ↑ |
| | Knee flexion | - | - | - | - | ↓ | ↓ |
| | Thoracic flexion | - | - | - | - | - | - |
| | Shoulder flexion | - | - | - | - | - | - |
| | Elbow flexion | - | - | - | - | ↓ | ↓ |
| | CoP *(anterior shift)* | - | - | ↑ | ↑ | ↑ | ↑ |

Red cells indicate different adaptations between sessions, as determined by planned contrasts

### *3.4.3 Correlation between perceived pain and kinematics*

To evaluate if the adaptations in the lumbar region represent a purposeful strategy to reduce pain, and to investigate whether variability in lumbar kinematic

adaptations can explain the variability in pain intensity in Late, the association between pain intensity and lumbar kinematic changes was assessed. During Pain Flexion, a strong correlation was identified between the change from Base to Late of the lumbar flexion peak and the amount of perceived pain reported during the Late condition ($t = 4.37$, $df = 28$, $p < 0.001$, $r = 0.64$). Instead, during Pain Extension no correlation between changes in lumbar extension peak and perceived pain was found ($t = 0.71$, $df = 28$, $p = 0.48$, $r = 0.13$). Both correlations are illustrated in Figure 3.6.

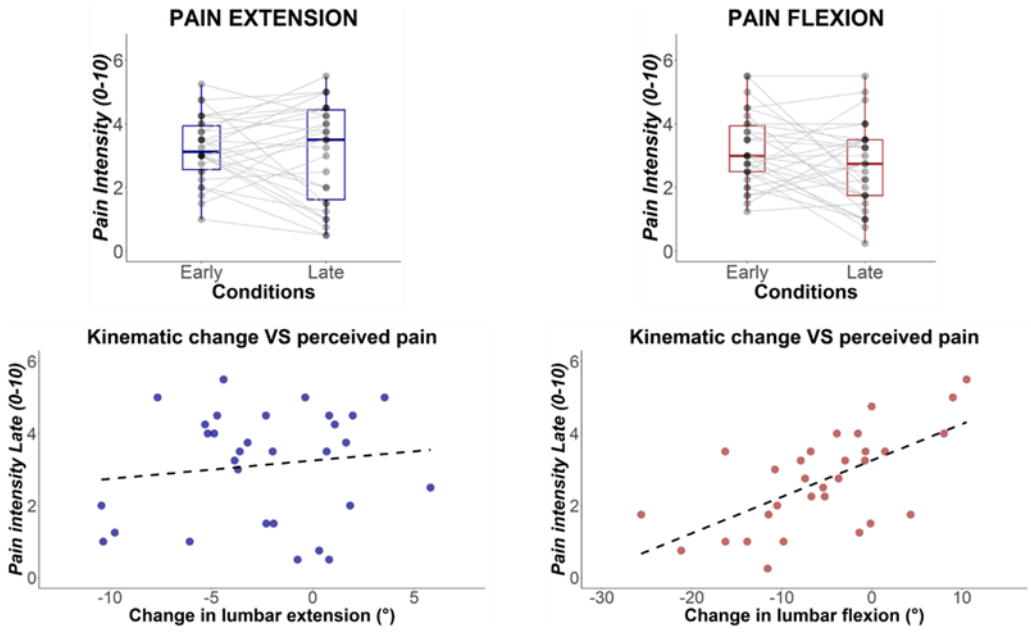


**Figure 3.6** *Perceived pain intensity and relationship with lumbar kinematics.*
*Top: perceived pain and its changes between Early and Late conditions. Bottom: Association between changes in lumbar kinematics (Base – Late) and perceived pain during Late. All data are presented for the Pain Extension (blue) and Pain Flexion (red) sessions.*

## 3.5 Discussion

When exposed to MEP, participants reduced the range of lumbar movement in the pain-provoking direction. The association between larger reduction of lumbar flexion and lower perceived pain supports the notion that the adaptations represent a

purposeful strategy to reduce pain. Findings of this Chapter show that pain in the same location, and of similar intensity, induce different motor adaptations depending on which movements modulate pain intensity. This data supports a counterfactual scenario where the existence of pain-provocative movements is a main determinant of motor adaptations to pain.

### *3.5.1 Motor adaptations to MEP evolve over time and become specific to the pain-provocative movement*

When exposed to pain that increased with lumbar flexion or extension, participants first adopted a multi-segment strategy, but over time this was limited to adaptation of the pain-provoking lumbar movement alone. This suggests that motor adaptations to MEP change as information regarding the relationship between pain and movement is acquired. The specificity of adaptation to the pain-provoking movement was also observed over time when pain was induced during lumbar extension.

Acute, non-specific adaptations induced by acute pain associated with lumbar flexion included larger elbow extension, a forward shift of the centre of pressure, and reduced hip and lumbar flexion. Such adaptations could represent a strategy to protect and unload the painful lumbopelvic region by reducing its ROM, by relying more on the arms to lift the box and reduce the distance between the centre of mass and the box, a strategy which may effectively reduce moments acting on the spine (85,234,235). Although *Chapter Two* did not find clear evidence for remote adaptations in response to tonic lumbar pain, a redistribution of load and muscle activity was observed when pain was induced in the lower limb in tasks that involved multiple degrees of freedom such as walking and double leg squat (85,234,235). This could explain why we observed

remote adaptations when pain was delivered during lumbar flexion, but not when pain was induced during lumbar extension, where biomechanical constraints limited the amount of available solutions to complete the task (place the box on the upper shelf). Our data suggests that, when multiple degrees of freedom are available, and until a strategy to reduce pain is identified, the CNS might prioritise a redistribution of load along the kinematic chain to unload and protect the painful area from further pain and/or injury.

Participants reduced the range of the painful movement over time, suggesting that they needed multiple repetitions to learn the association between movement and modulation of pain. Changes in motor adaptation over time in response to painful electrical stimulation have been described in several studies, and include progressively more delayed deep trunk muscles activation (111), a progressive restoration of the baseline contact heel duration during gait (136), and a progressive unloading of the painful leg during quiet stance (135). Similarly, injections of NGF induced a progressive reorganisation of motor cortical maps over several days (142,236). Our findings add to previous research showing that experimentally induced MEP can provide insights into the learning process involved when a new painful stimulus is experienced. Such learning processes can be described by the "pain perception – action cycle" where sensory-motor integration, informed by memory, allow to develop an internal prediction model aiming at the anticipation and avoidance of the pain provocative movement (237). Differently from other experimental pain model like DOMS and NGF, nociceptive electrical stimulation is better suitable to capture and describe the dynamic of such

"pain perception – action cycle". Overall, our findings suggest that pain is a motivational stimulus for adaptive behaviour driven by learning.

The reduction of lumbar movements associated with pain is consistent with the evidence of restricted ROM observed in the clinical populations and presented in *Chapter One*, and with the response to tonic experimental pain summarised in *Chapter Two*. This Chapter adds that motor adaptation is specific for the phase of the movement pain is experienced in, and that ROM of the painful movement is selectively restricted. The specificity of this motor adaptation is in line with neurophysiological evidence that, during motor preparation, corticospinal excitability of a muscle decreases when acting as an agonist to perform a painful movement, but it increases when acting as an antagonist to the painful movement (141). Compared to the multi-segment adaptation observed in the acute phase, a more selective adaptation has the advantages to minimise nociceptive input, while also limiting the metabolic costs associated to generalised motor adaptation (238). A reduction of lumbar ROM was consistent across participants, likely because it was the only solution to reduce the painful stimulus. Instead, a large inter-individual variability was observed for the other joints. This is confirmed by the larger values of standard deviation of the hip and knee joint angles during the painful conditions, as detailed in Table 3.1 and Table 3.2. Such variability is not surprising given that different biomechanical solutions can compensate for a reduced lumbar motion. While lifting a box, for instance, a reduction of lumbar flexion can be compensated by extending more the upper limbs or by increasing flexion of the knees. Thus, supported by previous neurophysiological studies, this Chapter provides

evidence that participants exposed to MEP over time selectively restrict the movement that induces pain, at least in the context of an acute noxious stimulus.

In contrast to most studies using tonic pain models, this Chapter revealed motor adaptations that outlasted pain duration when participants learnt a motor solution which was able to reduce their perceived pain (i.e., pain induced during lumbar flexion). Such findings suggest that although provocation of pain is a motivator to adapt, removal of the nociceptive stimulus does not motivate return to the original movement strategy. In the long term, altered movement strategies despite symptom remission (239) could lead to deconditioning, suboptimal loading, and restriction of sensory information from the lumbar region (87), factors which could contribute to pain persistence. As reduced movement limits the ability to discern whether the original motor strategy still induces pain, it is plausible that motor adaptation might persist until new information is acquired confirming that the once painful movement is now pain-free (240).

### *3.5.2 Are motor adaptations to MEP a purposeful strategy to reduce pain?*

The results of this Chapter partially support the hypothesis that changes in movement behaviour are a purposeful adaptation to reduce pain. When pain was associated to lumbar flexion, the amount of reduction in lumbar flexion was strongly correlated to a low perceived pain intensity. However, this was not observed when pain was associated to lumbar extension. This might be explained by several reasons: i) the reduction of flexion movement was twice that observed during extension which results in higher reduction of the nociceptive stimulus; ii) the flexion movement could be accomplished with more motor strategies compared to extension, which allowed

participants to redistribute the effort and movement across multiple joints; iii) participants received one long painful stimulation per cycle during flexion, and two short stimulations during extension.

Findings from this Chapter provide new evidence that motor adaptation is consistent with a purposeful strategy to limit pain. Previous research has attempted to address this question by inducing tonic pain in different body locations. That approach produced conflicting evidence with studies supporting (84) or refuting (145,146) the notion that motor adaptation is specific for pain location. A possible reason for these findings is that tonic pain, although specific to a region, cannot be reduce pain by changing the movement strategy, and thus removing the critical element of exposure to a less painful option. Here we provide evidence that, for an identical pain location, participants over time learned to limit the painful movement, and this resulted in low pain (at least for lumbar flexion) for those who adapted. This supports the notion that the goal of motor adaptation is to limit pain, at least in the short term (80), and highlight the role of painful movements as a determinant of motor adaptation to pain.

### *3.5.3 Clinical implications*

Findings of direction-specific motor adaptations to MEP provide the neurophysiological bases for the effectiveness of personalised movement-based interventions in people with NScLBP. The observation that some participants either did not exhibit motor adaptations which could reduce their pain, or that these adaptations were ineffective in tasks with higher biomechanical restrictions, highlights the need of approaches that enable patients to discover and perform pain-free movements tailored

to their specific needs. In this regard, findings support that motor adaptation to experimental pain can represent a useful strategy to limit pain in the short-term since participants who exhibited larger motor adaptation reported lower pain intensity. This aligns with a recent RCT (16) where people with clinical LBP reported lower pain intensity after they were trained to (i) reduce the amount of lumbar movement, (ii) redistribute the lumbar movement to other joints, and (iii) avoid end-range posture of the lumbar spine during pain provocative tasks. However, compensatory strategies need to be assessed carefully because they could lead to negative consequences in the long term, such as reduced movement and restriction of sensorimotor information.

Based on the evolution of motor adaptations observed over time, our data showed that (i) some individuals fail to identify a motor strategy able to reduce their pain, which could lead to avoid performing the task; (ii) some individuals identify a motor strategy that reduces their pain, but the motor adaptation persists when pain subsides, with potential long term negative consequences due to movement alterations; (iii) some individuals identify a motor strategy able to reduce their pain, and gradually return to the original motor pattern as their pain subsides. If this is confirmed in people with LBP, the first and second scenario would likely require different interventions to address not only the pain but also re-educating the motor system to reacquire full-range, pain-free movement. This is supported by evidence showing an improvement in pain and disability when both dysfunctional movement are corrected and full-range “less protective” movement are restored (16,241,242).

### *3.5.4 Methodological considerations*

The use of an experimental pain model to study motor adaptations to pain may limit the ecological validity of the present findings. Although nociceptive electrical stimulation lacks spatial specificity due to the activation of both nociceptive and non-nociceptive receptors, it represents the only method to assess the effects of pain of a similar intensity, induced in the same body region, and modulated by movements in opposite directions. Furthermore, nociceptive electrical stimulation cannot fully reproduce the qualitative characteristics and natural feeling experienced with clinical LBP.

## 3.6 Conclusion

The findings of this Chapter support the importance of directionality in determining motor adaptations to experimentally induced MEP, providing a high level of evidence on the causal effect of pain on movement. Specifically, the results showed that during a lifting task, experimental pain experienced in the same location and of a similar intensity induced different motor adaptations in the sagittal plane, depending on the direction of the pain-provocative movement. Also, the observed adaptations evolved over time, highlighting a learning process where healthy individuals adjusted their motor strategies in a purposeful way to reduce pain. This Chapter provides the neurophysiological basis for the need to assess pain directionality when developing personalised movement interventions for people with NScLBP. However, the specificity of motor adaptations based on the pain provocative movement require to be tested in the clinical population and across different tasks. Thus, such an investigation was conducted and is presented in the next Chapter.

# CHAPTER 4 – KINEMATIC DIFFERENCES BETWEEN INDIVIDUALS WHO REPORT LOW BACK PAIN INDUCED BY DIFFERENT MOVEMENTS

## 4.1 Abstract

People with NScLBP frequently report pain during specific lumbar movements. This has led to various classification systems that consider the relationship between pain and specific movement directions. This Chapter aims to evaluate the presence of MEP in people with LBP based on their perceived pain in response to trunk movements, and to investigate if kinematic differences are present and are specific to the direction of MEP. This cross-sectional study assessed kinematics during pain-provocative and functional tasks in 22 adults without and 40 with NScLBP. Changes in pain intensity during forward and backward bending were used to evaluate the presence of MEP, and what direction was more painful. Functional tasks included sit-to-stand, pelvic tilt, and lifting. Movement-evoked pain was reported by 36 (90%) of the participants with NScLBP, with 15 reporting larger MEP during flexion ($MEP_{flex}$, $p<0.001$) and 21 during extension trunk movements ($MEP_{ext}$, $p=0.005$). Those with higher $MEP_{ext}$ reported greater task-related fear of movement ($p=0.02$). Higher pain intensity reported at the end of trunk flexion movements correlated with smaller knee ($p=0.02$) and hip ($p=0.002$) angles, and greater lumbar flexion ($p=0.03$). No correlations were found between pain and kinematic features after trunk extension ($p>0.19$). Lumbar kinematics during sit-to-stand was similar between controls and people with NScLBP ($p=0.71$). However, people with prevalent $MEP_{flex}$ showed increased lumbar flexion during this task compared to those with $MEP_{ext}$ ($p=0.005$) and controls ($p=0.05$). No differences were observed for the

pelvic tilt task ($p>0.37$). Individuals with NScLBP showed reduced hip and knee flexion during lifting ($p<0.05$), especially in those with higher $MEP_{flex}$ ($p<0.05$). People with movement-evoked LBP exhibit distinct kinematic patterns during functional tasks, especially those reporting pain during forward bending, who show larger lumbar flexion and smaller hip and knee flexion.

## 4.2 Introduction

Based on findings from *Chapter Two* and *Chapter Three*, pain experienced in the lumbar region causes motor adaptations, and such adaptations are specific to the direction of movement that is pain provocative. Despite revealing important mechanisms underpinning motor adaptations to pain with potential clinical implications, these findings were obtained from experimental settings and need to be further investigated in the clinical population, ensuring that the obtained evidence is directly relevant and beneficial for patients with NScLBP.

As described in *Chapter One*, LBP remains a leading cause of disability globally, with a considerable socioeconomic burden (2). The etiology of LBP can be classified into three main categories: pain due to specific and serious pathology affecting the lumbar spine, pain resulting from nerve compression, and non-specific LBP (243). The latter, accounting for about 80% to 90% of LBP cases (3), is characterised by a complex interplay between biological, psychological, and social factors (1). For some individuals with NScLBP, movement and posture are key factors contributing to their pain, suggesting a mechanical driver of the disorder. Indeed, activities like prolonged positions in sitting or standing, repeated movements, and functional tasks have been associated with mechanical LBP (244,245). This association suggests that the presence

of movement dysfunction might contribute to the development and maintenance of LBP. To develop personalised interventions focusing on such movement impairments, different classification systems have been proposed to tailor individualised treatments according to specific patient subgroups (56,225). Findings from clinical trials support this approach by showing a larger reduction in pain and disability when treatments were delivered accordingly with movement-based classification (16). However, evidence remains controversial due to differences in the adopted classification system, and their validity and reliability (246).

Traditionally, LBP classification systems have relied on the opinion of experts or theoretical models (57). Recent evidence advocates for objective and data-driven methods where LBP subgroups are identified based on physical and psychological factors, including the response to MEP (57,70). This approach aligns with current theories which highlight the importance of considering the reciprocal interaction between pain and movement (50,51) – if movement provokes pain, then people are expected to change the way they move in order to avoid pain, as clearly shown in *Chapter Three*. In this regard, motor adaptations to pain are considered purposeful strategies to protect the painful body region from further pain and injury, but with negative long-term consequences (80). Changes in motor execution and cortical activity have been observed in people with NScLBP when performing a pain provocative movement (73). However, it remains unclear whether biomechanical strategies are differentially altered based on pain directionality in people reporting movement-evoked LBP.

A recent study identified LBP subgroups based on the pain response to repeated spinal bending in the sagittal plane (64). While LBP subgroups have been identified with distinct somatosensory features (70), evidence investigating and comparing kinematic changes in people reporting movement-evoked LBP during opposite trunk movements is limited to traditional classification systems. The existence of motor adaptations specific to the direction of MEP similar to those observed in *Chapter Three* could support the development of more effective and personalised interventions. For example, individuals with altered spinal kinematics in the pain provocative direction might benefit from specific interventions aimed at addressing this, which may not be relevant for other patients experiencing LBP in other movement directions. This rationale is supported by recent evidence revealing larger improvement in kinematics, pain and disability in those patients with smaller ROM at baseline (242,247), and an association between improved movement and pain reduction (248).

This Chapter addresses the primary and secondary aims of the thesis by investigating kinematics and MEP in the clinical population. Specifically, this Chapter aims to evaluate the presence of MEP in people with NScLBP during opposite trunk movements performed in the sagittal plane, and to investigate whether kinematic differences identified during functional tasks are specific to the direction of the pain provocative movement. The hypothesise of this study was that MEP in a specific direction influences how people move, leading to restricted spinal kinematics in the direction of pain-provocative movements when compared to individuals with NScLBP who experience pain in a different direction, and to a control group without NScLBP.

## 4.3 Methods

This cross-sectional study received ethical approval from the Research Ethics Committee at the University of Birmingham, United Kingdom (ERN_ 21-1772, Appendix 7) and conformed to the latest Declaration of Helsinki. All participants provided written informed consent. Data collection was conducted at the School of Sport, Exercise and Rehabilitation Sciences (University of Birmingham). This study is reported according to the STROBE recommendations for reporting of cross-sectional studies (249) (Appendix 8).

### *4.3.1 Participants*

Adults aged between 18 to 50 years old with and without history of chronic non-specific LBP were recruited between 22/09/2022 and 22/06/2023. The eligibility criteria applied to identify the control (CTR) and the NScLBP group are presented in Table 4.1. The sample size calculation was based on lumbar kinematics differences observed in a previous study, which examined various tasks among subgroups of participants with NScLBP reporting pain during trunk flexion and extension movements and a control group (229). We set a power (1-β) of 0.8 and an alpha level at 0.05. Given an eta squared of 0.154, a total sample size of 57 participants was suggested. To account for potential dropouts due to pain, technical issues, or non-responsiveness to MEP tasks, we aimed to recruit 60 participants, comprising 20 individuals without LBP and 40 with LBP. The number of people with LBP was twice that in the control group since a-priori it was impossible to estimate how many people would report MEP during trunk flexion and extension.

**Table 4.1** *Eligibility criteria for the control and chronic low back pain groups*

| ELIGIBILITY CRITERIA | CONTROL GROUP (CTR) | CHRONIC LOW BACK PAIN GROUP (cLBP) |
|---|---|---|
| **Inclusion criteria** | - No history of low back pain that was sufficient to seek treatment or modify function. | - Low back pain for at least the past three months<br>- Low back pain intensity ≥3/10<br>- Oswestry Disability Index > 10% |
| **Exclusion criteria (specific)** | - N/A | - LBP related to specific pathologies (infection, cancer, inflammatory disorders, fracture, radicular pain with neurological deficit) |
| **Exclusion criteria (common)** | - Previous/major surgery<br>- Neuropathic pain<br>- Recent/potential pregnancy<br>- Major pathologies (neurological, neuromuscular, etc.)<br>- Heart condition, chest pain, exercise limitation<br>- Pain in other body regions (rather than the low back) that was sufficient for them to seek treatment or modify function over the previous 12 months<br>- Inability to understand English | |

### *4.3.2 Questionnaires*

Before conducting the experimental session, participants were asked to complete a series of questionnaires to gather population statistics. Specifically, they completed the Oswestry Disability Index (ODI) questionnaire which is a reliable measure of disability relating to back pain (250), Tampa Scale for Kinesiophobia (TSK) to asses any fear of movement related to pain (251), and the Pain Catastrophising Scale (PCS) (252). Also, a general questionnaire was customised to assess LBP intensity over the past week (Visual Analogue Scale, VAS, with 0-10 cm as anchor points for no pain and the worst pain imaginable, respectively) and duration of symptoms. The VAS was also used to quantify the pain intensity over the last 24 hours at the time of recruitment.

### *4.3.3 Data collection*

Before starting data collection, participants were equipped with the same wearable IMUs (Noraxon USA Inc., Scottsdale, Arizona, USA) used in *Chapter Three* to assess lower limb and trunk kinematics. The IMUs were placed on the shank and thigh (bilaterally), pelvis (S1), lower thoracic spine (T12-L1) and upper thoracic spine (C7-T1) in accordance with manufacturer guidelines and secured with double-sided tape. Participants then performed two potentially pain provocative tasks to identify pain directionality and three functional tasks.

Pain provocative tasks

Movement-evoked pain was tested in participants with NScLBP by evaluating changes in back pain intensity during tasks requiring opposite spinal movements in the sagittal plane: picking up a pen (forward bending) and looking upwards (backward bending) (64). In the forward bending task, participants flexed their trunk to pick up a pen from the floor, returned upright and then placed the pen back down on the floor. This was repeated 20 times at their preferred manner and pace. For the backward bending task, participants were instructed to look at a ceiling marker 60 cm behind them in any way they preferred and at any speed, ensuring they didn't turn around. They repeated this movement 20 times. Five minutes of rest were provided between forward and backward bending tasks to ensure that the level of pain returned similar to the one reported before starting the task. Back pain intensity was collected asking participants to rate on a 0-10 VAS their perceived pain before starting and immediately after the tasks. After each task, participants also rated the level of fear of movement that they

experienced following instructions to “Please indicate the fear of movement you experienced during forward bending (or backward bending) on a scale of 0 (i.e., no fear) to 10 (i.e., the highest possible degree of fear)” (253). The sequence of tasks was randomised. Based on the reported changes in pain intensity, the pain provocative tasks allowed to identify people with higher MEP during forward bending ($MEP_{flex}$), during backward bending ($MEP_{ext}$), or with no MEP response for either task (noMEP).

Functional tasks

When the MEP tasks were completed, participants were asked to perform three functional tasks in the same order; (i) sit-to-stand, (ii) pelvic tilt, and (iii) lifting. These tasks were chosen because they represent everyday activities, and involve movements often reported as pain provocative in people with NScLBP. Indeed, these tasks challenge the lumbar region during both lumbar flexion and extension, which allow to investigate the role of pain directionality on motor adaptations.

Participants completed three sets of five sit-to-stand trials. This task involved standing in front of a chair, sitting down, pausing briefly, and then standing back up to the original position. Between each repetition, participants rested for a few seconds, and a couple of minutes of rest were provided between each set. Participants were allowed to perform the task at a self-paced speed.

For the pelvic tilt task, participants started in a neutral posture while seated, with their hips and knees flexed to 90 degrees. The exercise involved two sets of 10 repetitions of forward and backward pelvic tilt. Participants were encouraged to perform

full-range movements. The task was self-paced, with participants executing the movements continuously and a couple of minutes of rest was provided between sets.

For the box lifting task, participants performed the same task described in *Chapter Three*. In brief, participants stood in front of a shelving unit, positioning their feet at a distance from the shelves equal to 125% of their foot length. They chose their preferred stance width, and this was recorded and kept consistent across sets. The task consisted of moving a box (dimensions: 39x28.5x16 cm, weight ~1kg) between shelves positioned at eye and knee level. The weight of the box was light and the same for all participants in order to focus on the impact of pain on neuromuscular control while minimising confounding factors like fatigue. A triaxial accelerometer (Noraxon USA Inc., Scottsdale, Arizona, USA) was secured to the box to facilitate the identification of the start and end of lifting cycles. Participants were asked to follow the pace of a metronome set at 24 beats per minute, signalling when to place the box on the lower or upper shelf (i.e., 2.5 seconds for movement). After familiarisation, participants completed 3 sets of 10 lift cycles, starting and ending at the lower shelf, and with a two-minute rest between sets.

### *4.3.4 Data processing and analysis*

Kinematic data was acquired from the knee, hip, lumbar and thoracic spine as described in *Chapter Three*. Joint angles and box acceleration signals (in the lifting task) were obtained directly from the myoRESEARCH software (version 3.14), sampled at 100 Hz, and exported in MATLAB (version 2022b, MathWorks) for offline processing. Joint angle waveforms were filtered with a Butterworth lowpass filter (4th order, 10 Hz). For

the box-lifting task, the vertical acceleration signal was used to extract the beginning and end of each lifting cycle. To ensure consistency in the analysis, we excluded the initial lifting phase of the first cycle and the final lowering phase of the last cycle. Consequently, for each set, we considered nine complete cycles, beginning and ending at the upper shelf.

During the MEP tasks, we extracted the peak lumbar flexion in the “pick up a pen” task and the peak lumbar extension in the “look at the ceiling” task. Additionally, we extracted the value of the other joint angles at the same time instant. During the lifting task, this information was extracted for both peak flexion and extension. The peak lumbar flexion corresponded to the moment when participants placed the box on the lower shelf, while the peak lumbar extension occurred when they moved the box between their upper body and the top shelf. Since each cycle included two peaks of lumbar extension, only the highest peak was considered.

The highest peak of lumbar flexion was extracted during the sit-to-stand task, along with the hip and knee angles at that corresponding instant during each repetition. During the pelvic tilt task, only peak lumbar flexion (posterior pelvic tilt) and peak lumbar extension (anterior pelvic tilt) were extracted. Once extracted, discrete values of joint angles were averaged across repetitions of the same movement phase and task.

### *4.3.5 Statistical analysis*

All analyses were conducted in RStudio (160). Based on the data normality verified by Shapiro-Wilk test, parametric or non-parametric analyses were considered for inferential statistics. Data are reported as mean and standard deviation or median and

quartiles depending on their distribution. Homogeneity of variance was tested using the Levene Test. For all tasks, each joint angle was firstly compared between CTR and cLBP groups using independent t tests or Wilcoxon Rank Sum test. Secondly, people with cLBP who reported higher MEP in flexion or extension (i.e., $MEP_{flex}$ and $MEP_{ext}$) were considered and compared with the CTR group using either a one-way ANOVA or Kruskal-Wallis test. If significant effects were observed, post-hoc analyses were conducted using Tukey's Honest Significant Difference Test or the Pairwise Wilcoxon Rank Sum Test, applying the Bonferroni correction for three comparisons. For the MEP tasks, it was evaluated in the cLBP group the association between joint angles with perceived pain at the end of the pain-provoking task and task-specific fear of movement using Pearson rho (*r*) or Spearman rank correlation depending on data distribution, presence of outliers, and linearity of the relationship after visual inspection.

## 4.4 Results

Sixty-two participants were recruited for this study, including 22 without and 40 with LBP. All demographic characteristics are presented in Table 4.2.

**Table 4.2** *Demographic and clinical characteristics*

| VARIABLE | | cLBP | | | CTR vs LBP p-value | CTR vs $MEP_{flex}$ vs $MEP_{ext}$ Post-hoc: p-value |
|---|---|---|---|---|---|---|
| | CTR *(n = 22)* | ALL *(n = 40)* | $MEP_{flex}$ *(n = 15)* | $MEP_{ext}$ *(n = 21)* | | |
| Age | 28.8 ± 7.1 | 28.6 ± 8.6 | 28.9 ± 10.5 | 28.6 ± 7.5 | 0.63 | - |
| Gender | 11F/11M | 19F/21M | 6F/9M | 11F/10M | 1 | - |
| Height | 172.5 ± 9.6 | 170.6 ± 11.1 | 172.1 ± 12.6 | 169.5 ± 9.3 | 0.50 | - |
| Weight | 69.7 ± 16.7 | 73.6 ± 15.1 | 79.1 ± 14.0 | 69.3 ± 13.4 | 0.26 | - |
| TSK (17 – 68) | 28.8 ± 5.4 | 37.0 ± 6.6 | 38.8 ± 6.6 | 35.3 ± 6.4 | < 0.001 | CTR-cLBP-E: 0.007<br>CTR-cLBP-F: <0.001 |
| PCS (0 – 52) | 5.8 ± 10.1 | 15.0 ± 11.9 | 17.1 ± 13.2 | 12.2 ± 9.5 | < 0.001 | CTR-cLBP-E: 0.007<br>CTR-cLBP-F: 0.004 |
| | | | | | | $MEP_{flex}$ vs $MEP_{ext}$ |
| Pain duration (m) | - | 27.2 ± 41.6 | 39.6 ± 64.0 | 22.4 ± 16.4 | | 0.83 |
| Pain (0-10, 24h) | - | 39.5 ± 22.3 | 42.7 ± 24.4 | 35.1 ± 21.8 | | 0.34 |
| Pain (0-10, wk) | - | 44.2 ± 18.3 | 49.3 ± 13.5 | 38.4 ± 20.7 | | 0.07 |
| ODI (0-50) | - | 16.3 ± 6.9 | 16.9 ± 7.6 | 16.8 ± 6.8 | | 0.96 |

*Note: four participants in the cLBP group did not report movement-evoked pain*

### *4.4.1 Movement-evoked pain tasks*

Based on changes in perceived pain after the pain provocative tasks, twenty-one cLBP participants reported higher MEP during forward bending ($MEP_{flex}$, n=21), fifteen during backward bending ($MEP_{ext}$, n=15), and four did not report MEP in either direction ( noMEP, n=4). No differences in demographic characteristics, pain intensity, or disability were present across people reporting MEP in different directions. Also, back pain intensity reported before starting the flexion task did not differ from the one reported before starting the extension task (p=0.10). The increase in perceived pain during forward bending was larger in people with higher $MEP_{flex}$ compared to $MEP_{ext}$ ($p<0.001$) as expected. Similarly, during backward bending the increase in perceived pain was larger in people with higher $MEP_{ext}$ compared to $MEP_{flex}$ (p=0.005). Participants with

$MEP_{ext}$ had higher task-related fear of movement during backward bending compared to people with higher $MEP_{flex}$ (p=0.02), but no differences were present during forward bending (p=0.29). Data on pain intensity and task-related fear of movement are presented in Table 4.3 for participants with higher $MEP_{ext}$ and $MEP_{flex}$.

**Table 4.3** *Perceived back pain intensity and task-related fear of movement during MEP tasks*

| Variable | **$MEP_{ext}$** (n=21) | **$MEP_{flex}$** (n=15) | p-value |
|---|---|---|---|
| *Forward bending (pick up a pen)* | | | |
| Pain before | 1.1 ± 1.6 | 1.0 ± 1.2 | 0.87 |
| Pain after | 2.1 ± 1.9 | 4.3 ± 2.1 | **0.002** |
| Pain change | 0.9 ± 1.0 | 3.3 ± 1.5 | **< 0.001** |
| Fear of movement | 1.4 ± 2.2 | 1.6 ± 1.8 | 0.29 |
| *Backward bending (look at the ceiling)* | | | |
| Pain before | 1.1 ± 1.6 | 1.4 ± 1.1 | 0.20 |
| Pain after | 3.3 ± 1.9 | 2.4 ± 1.6 | 0.32 |
| Pain change | 2.1 ± 0.9 | 1.0 ± 1.1 | **0.005** |
| Fear of movement | 2.4 ± 2.7 | 0.6 ± 1.4 | **0.02** |

Perceived pain and task-related fear assessed using Visual Analogue Scale (0-10)

The relationship between back pain intensity and kinematics during the pain provocative tasks was assessed using correlation analyses (Figure 4.1). During forward bending, higher perceived pain was associated with lower knee ($r$=-0.37, p=0.02) and hip angle ($r$=-0.47, p=0.002), and with higher lumbar angle ($r$=0.34, p=0.03). No significant correlations were found during backward bending (p>0.19).

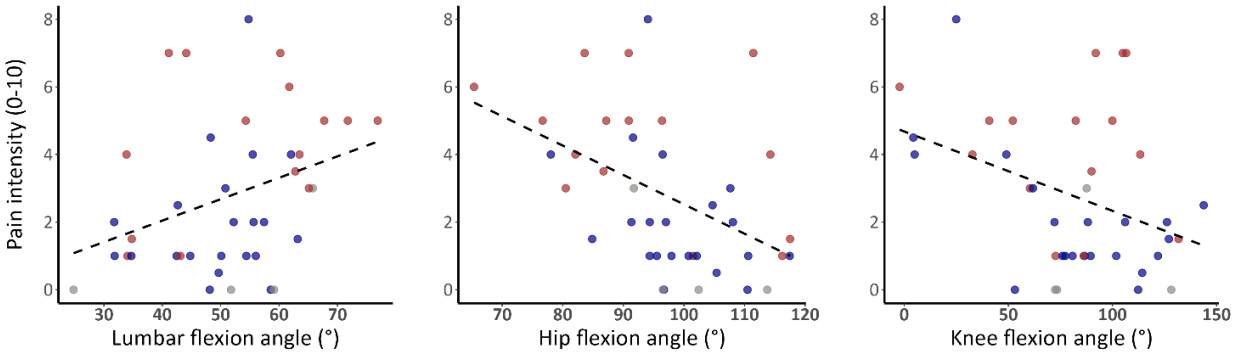


**Figure 4.1** *Correlation between pain intensity and joint angles during the 'pick up a pen' task. The value of pain intensity was the one reported at the end of the task. Lumbar, hip and knee flexion angles were measured during the peak of lumbar flexion.*

No kinematic differences between groups (p>0.48) or between participants reporting MEP in different directions (p>0.33) were identified during forward bending. However, people with NScLBP performed the backward bending task with larger trunk extension compared to CTR (p=0.036). One-way ANOVA showed a group effect (F(2,55)=3.2, p=0.048), and post-hoc test revealed higher trunk extension in people with higher $MEP_{flex}$ compared to CTR (p=0.049). No other differences were identified for the other joints between groups (p>0.137) or MEP subgroups (p>0.404). A summary of results showing comparisons between group (CTR vs cLBP) and between participants reporting MEP in different directions (CTR vs $MEP_{ext}$ vs $MEP_{flex}$) are presented in Table 4.4.

### *4.4.2 Functional tasks*

No difference in joint kinematics were observed between CTR and cLBP during the sit-to-stand task (Figure 4.2, p>0.30). However, one-way ANOVA revealed a significant group effect when cLBP participants were categorised by the pain provocative tasks (F(2,55)=5.52, p=0.007); participants with higher $MEP_{flex}$ performed the

task with higher lumbar flexion compared to participants with higher $MEP_{ext}$ (p=0.005) and CTR (p=0.05).

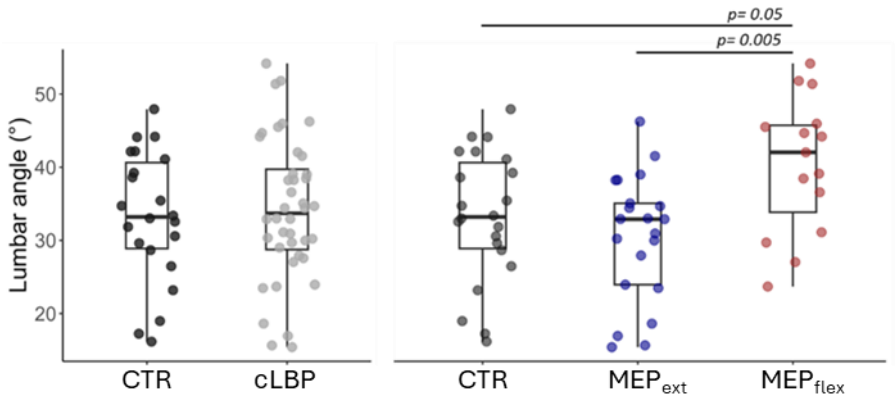


**Figure 4.2** *Differences in peak lumbar flexion between control and chronic low back pain participants during the sit-stand task.*

Neither lumbar flexion (p>0.37) nor lumbar extension (p>0.60) differed between CTR and cLBP during the pelvic tilt task. Although participants with higher $MEP_{flex}$ performed the pelvic tilt with smaller lumbar flexion, one-way ANOVA only found a trend for a statistically significant group effect (F(2,55)=3.02, p=0.057). Similar values across subgroups were observed during the posterior pelvic tilt movement (F(2,55)=0.15, p=0.86).

Compared to the CTR group, people with cLBP performed the lowering phase of the lifting task with less hip (t=2.09, p=0.043) and knee (t=2.24, p=0.031) flexion. However, no differences were found for lumbar (p=0.18) or thoracic (p=0.48) flexion. Differences in lower limb kinematics were also confirmed based on MEP responses since one-way ANOVA revealed a group effect for the hip angle (F(2,55)=3.66, p=0.03). Post-hoc comparisons showed less hip flexion in participants with higher $MEP_{flex}$

compared to CTR (p=0.024). Also, values of knee angle appeared smaller in participants with higher $MEP_{flex}$, but no group effect was present (F(2,55)=2.56, p=0.087). During the extension movement of the lifting task, people with cLBP presented less thoracic extension than CTR (t=-2.17, p=0.020). This reduction in thoracic extension was also present between subgroups (one-way ANOVA; F(2,55)=3.20, p=0.042). Post-hoc comparisons revealed that compared to CTR less thoracic extension was present in participants with higher $MEP_{flex}$ (p=0.03) but not in those with $MEP_{ext}$ (p=0.20). No other differences in joint angles between-group (p>0.30) or between participants reporting MEP in different directions (p>0.35) were found during the extension movement of lifting.

**Table 4.4** *Kinematics data (median and interquartile range) from all functional tasks divided by groups and subgroups*

| VARIABLE | CTR | LBP | | | CTR vs LBP | CTR vs $MEP_{flex}$ vs $MEP_{ext}$ | |
|---|---|---|---|---|---|---|---|
| | | ALL | $MEP_{flex}$ | $MEP_{ext}$ | *p* | *p* | *post-hoc p* |
| **Pick up a pen:** *data extracted from peak lumbar flexion* | | | | | | | |
| Lumbar flexion (°) | 49.2(18.8) | 53.3(17.6) | 60.2(22.2) | 50.8(10.9) | 0.578 | 0.46 | - |
| Hip flexion (°) | 99.3(13.4) | 96.5(15.1) | 90.9(23.6) | 97(11) | 0.548 | 0.331 | - |
| Knee flexion (°) | 77.1(29) | 86.4(44.8) | 86.2(46.2) | 86.7(50.5) | 0.482 | 0.813 | - |
| Thoracic flexion (°) | 16.1(14.1) | 16.2(10.9) | 16(6.4) | 16.4(12.2) | 0.697 | 0.886 | - |
| **Look at the ceiling:** *data extracted from peak lumbar extension* | | | | | | | |
| Lumbar extension (°) | 16.5(15.7) | 15.3(11.3) | 13.2(10.7) | 16.6(17.8) | 0.326 | 0.483 | - |
| Hip extension (°) | 3.5(6.8) | 4.2(6.1) | 5.9(7.1) | 2.8(5.5) | 0.924 | 0.564 | - |
| Knee flexion (°) | 9(11.6) | 5.4(7.4) | 6.9(7.1) | 4.7(9.5) | 0.137 | 0.404 | - |
| Thoracic extension (°) | 11.4(7.5) | 15.6(12.1) | 18.1(11.3) | 12.4(10.4) | **0.036** | **0.048** | CTR-$MEP_{flex}$: 0.049 |
| **Lifting** | | | | | | | |
| *Data extracted from peak lumbar flexion* | | | | | | | |
| Lumbar flexion (°) | 40.7(17.4) | 46.6(13.2) | 53.9(13.2) | 44.9(9.1) | 0.181 | 0.121 | - |
| Hip flexion (°) | 59(17.4) | 46.1(24) | 33.6(22.6) | 47.7(17.7) | **0.043** | **0.032** | CTR-$MEP_{flex}$: 0.02 |
| Knee flexion (°) | 29.4(26.1) | 15(25.9) | 8.1(21.1) | 17.4(30.3) | **0.031** | 0.087 | - |
| Thoracic flexion (°) | 18.4(12.5) | 19.8(10.6) | 20.2(6.9) | 17.6(9.8) | 0.477 | 0.715 | - |
| *Data extracted from peak lumbar extension* | | | | | | | |
| Lumbar extension (°) | 4.4(5) | 3.7(6.3) | 2.6(4.5) | 4.9(9.8) | 0.854 | 0.558 | - |
| Hip extension (°) | -2.5(4.1) | -1.2(3) | -0.1(3) | -1.2(3.6) | 0.302 | 0.35 | - |
| Knee flexion (°) | 4.3(6.4) | 4.1(3.6) | 4.2(3.6) | 3.9(3.6) | 0.485 | 0.814 | - |
| Thoracic extension (°) | 12.1(8.2) | 7.9(5.9) | 5.7(4.7) | 8.5(6) | **0.020** | **0.042** | CTR-$MEP_{flex}$: 0.032 |
| **Sit to stand:** *data extracted from peak lumbar flexion* | | | | | | | |
| Lumbar flexion (°) | 33.2(11.7) | 33.7(11) | 42(11.9) | 32.9(11.1) | 0.712 | **0.007** | CTR-$MEP_{flex}$: 0.05<br>$MEP_{ext}$ -$MEP_{flex}$: 0.005 |
| Hip flexion (°) | 79.0(19.3) | 77.0(12.5) | 74.7(7.4) | 77.0(11.6) | 0.516 | 0.716 | - |
| Knee flexion (°) | 85.5(9.5) | 83.0(12.2) | 85.4(15.8) | 79.7(9.4) | 0.309 | 0.347 | - |
| **Pelvic tilt** | | | | | | | |
| Lumbar *(°, peak flexion)* | 15.6(11.7) | 12.9(15.9) | 6.7(9.6) | 15.1(15.6) | 0.377 | 0.057 | - |
| Lumbar *(°, peak extension)* | 19.8(8.7) | 19.2(13.3) | 19.9(11.6) | 20.4(14.2) | 0.606 | 0.863 | - |

## 4.5 Discussion

This Chapter aimed to investigate whether individuals with NScLBP who report an increase of back pain during lumbar flexion or extension demonstrate different kinematics during functional tasks. Most of the included participants with NScLBP (90%) reported an increase of pain during repetitive spinal bending in the sagittal plane, supporting a large presence of MEP in people with NScLBP. Kinematic differences were observed across participants reporting MEP in different directions compared to healthy adults, but some of these differences were not present when data from all NScLBP participants were pooled together. Based on comparisons across participants reporting MEP in different directions and the associations between kinematics and back pain intensity, people reporting pain during forward bending showed larger lumbar flexion and smaller knee and hip flexion. These findings, along with those from *Chapter Three*, support the importance of assessing MEP both in research and clinical practice since it may provide important insights for the assessment and treatment of people with LBP.

### *4.5.1 Identification of movement-evoked low back pain in the clinical population*

This study used standardised pain provocative tasks to evaluate the presence of MEP in people with NScLBP without relying on clinical observations or theoretical models. A recent study adopted a similar approach, examining whether MEP was present and if it was unidirectional or bidirectional, but without considering what direction was pain provocative (64). They identified MEP in only 51% participants with NScLBP following repetitive spinal bending (64). In contrast, this study found that 90% experienced increased pain in at least one direction, aligning with another study where

81% of LBP patients showed MEP during functional tasks (254). Such discrepancies could arise from the distinct thresholds applied to identify people with LBP presenting MEP. For example, contrary to the previous study that used a cutoff value of pain intensity score change of 2 out of 10 (64), the present study did not utilise a specific threshold. Despite this, we observed in both directions an increase in pain intensity after spinal bending which was, on average, larger than 2 points out 10 on a numerical rating scale. Also, the presence of direction specific MEP is supported by the significant differences in perceived pain observed when performing the task in the direction with higher MEP.

Demographic characteristics, disability level, pain intensity over the previous 24 hours or week, and pain catastrophising did not differ between people reporting MEP in different directions, suggesting that these factors were not specific to pain directionality. Interestingly however, task-specific but not general fear of movement differed based on MEP direction. Specifically, fear was higher during backward bending in the subgroup experiencing higher pain in such direction of movement. Overall, these findings supported that MEP is an important clinical feature of NScLBP since present in 90% of patients.

### *4.5.2 Movement-evoked pain influences kinematic across different tasks*

This study is the first to demonstrate a correlation between higher lumbar flexion and back pain intensity following a lifting task, contrasting with previous studies. A systematic review found no evidence supporting an association between LBP and a more flexed lumbar spine during lifting movements (255). However, our findings might

differ from those of the included studies because most of them did not assess pain at the end of the task and participants performed no more than three trials. A recent study also showed no associations between lumbar kinematics and pain during 100 cycles of a lifting task (256). However, the use of different pain-related outcomes, task instruction, smaller sample size, and investigated population could explain the discrepancy with our study results. The relationship between MEP in flexion and lumbar kinematics is also supported by data from the sit-to-stand task, where greater lumbar flexion was observed in those people reporting higher pain during spinal forward bending. Interestingly, differences in lumbar kinematics were not observed when data from the LBP group were pooled together, supporting the heterogeneity of clinical presentation of people with NScLBP and the importance of considering the presence of MEP. These findings align with previous studies using the multidimensional classification system (MDCS) where people in the flexion pattern subgroup performed several functional tasks exhibiting larger lumbar flexion (61,229). In addition to lumbar kinematics, data from this study revealed an association between lower hip and knee angles with higher back pain intensity during repeated forward bending, as well as reduced hip flexion in people with MEP in flexion during lifting. These findings suggest that during lifting tasks people reporting pain during forward bending rely more on lumbar rather than lower limb movements. Although not statistically significant, it is noteworthy that the same subgroup exhibited less lumbar flexion while performing the pelvic tilt task. While speculative, this observation may suggest the presence of task-specific kinematic differences, potentially influenced by the execution of either local or global movements. Thoracic kinematics also revealed task-specific differences since

people with LBP showed larger extension while looking up at the ceiling but reduced thoracic extension during lifting. The increased thoracic extension during the pain provocative task might be a compensatory strategy to reduce the movement of the lumbar spine while achieving the task goal.

Unlike forward bending, no clear relationships were observed between MEP in extension and kinematics. Additionally, there were no significant differences between people reporting higher MEP during backward bending and the control group. This absence of kinematic differences aligns with a previous study where people with LBP in the active extension pattern performed several tasks similarly to the control group, indicating the presence of similar movement patterns (229). Several reasons might explain these findings. First, functional tasks might not sufficiently challenge extension movement. Second, tasks requiring spinal extension movements are characterised by lower ROM and less degrees of freedom. These biomechanical restrictions narrow the variety of motor strategies available to achieve the task goal, similarly to what was observed in *Chapter Three*. Based on previous studies, people with MEP in extension could exhibit larger differences in prolonged static postures since these are often reported as pain provocative, and changes in muscle activity rather than kinematics could be more relevant. Beside the ROM, people with NScLBP with MEP in extension could be more influenced by other factors since a difference in task-specific fear of movement was observed only during backward bending (61).

Overall, the findings from functional tasks requiring forward movements revealed larger lumbar flexion but smaller hip and knee flexion in people reporting MEP during repetitive forward bending. Thus, the assessments of MEP and kinematics could

enhance the understanding of the reciprocal influence between pain and movement, and partially explain clinical heterogeneity based on the presence of MEP.

### *4.5.3 Parallels with motor adaptation theories and clinical implications*

Theories on motor adaptations to pain suggest that people change how they move in a purposeful way to feel less pain (80). Since this study revealed a larger ROM in the direction of movement that was pain provocative, it plausible that people reporting pain during forward bending did not adopt strategies to limit the pain, resulting in an ongoing stimulation of tissues. This aligns with the motor control impairment classification proposed by the MDCS (61). People in this subgroup typically show a loose motor control and poor lumbo-pelvic proprioception which might affect their ability to understand the association between MEP and the performed movement, and impact on the identification of motor strategies to reduce their pain (61,225).

Given that people with higher MEP during backward bending showed no kinematic difference but exhibited higher task-specific fear of movement, it suggests that other factors, like fear of movement or muscle activity, might play a more significant role for them. In accordance with previous theories (80,87), it is arguable that people reporting higher MEP in extension changed their motor strategies to feel less pain and protect the body region after the onset of LBP, but without returning to the original motor pattern after pain had resolved. Indeed, restoring “less protective” motor strategies have been often suggested as an effective intervention for people with NScLBP showing trunk muscle guarding and fear of movement (241). Therefore, other

factors rather than ROM might be relevant for people with MEP during backward bending and this should be explored in further research.

### *4.5.4 Strengths and Limitations*

Methodological factors give larger ecological validity to findings of this Chapter compared to previous studies assessing kinematic differences between LBP subgroups. Firstly, this study investigated kinematic differences considering only MEP responses, without using subgroups based on clinical observations or physiological/psychological models. Secondly, the use of wearable sensors for kinematic assessment favours replication outside the laboratory.

This study is not without limitations. To evaluate the presence of kinematic differences based on MEP, the focus was exclusively on the spinal movement direction causing greater back pain, though some experienced pain in the opposite direction too. However, this choice enhances the power of analysis because if MEP significantly impacts kinematics, a greater effect size should be observed in individuals for whom this movement direction is more painful. Although this study considered psychological factors and task-specific fear of movement, the assessment of other factors within a multidimensional clinical profile can provide further insights on the role of MEP in people with NScLBP. Finally, this study focused on forward and backward bending only, acknowledging that people with LBP may find rotational or combined movements most painful.

## 4.6 Conclusions

Movement-evoked pain is commonly experienced in people with NScLBP, and it can represent an important factor for partially explaining clinical heterogeneity. This is supported by the identification of kinematic differences when the response to pain provocative movements is considered, but not when LBP data are pooled together and compared with controls. Specifically, larger lumbar flexion and reduced hip and knee movements were observed in people with pain provoked by forward bending. Task-related fear of movement also differed based on what direction was pain provocative, suggesting for its involvement especially in people with MEP during backward bending. Overall, the presence of kinematic differences underscores the importance of considering MEP responses to address clinical heterogeneity as this may facilitate the development of personalised interventions for people with chronic LBP.

# CHAPTER 5 – GENERAL DISCUSSION

## 5.1 Summary of findings

The aims of this thesis were to investigate how MEP experienced in the lumbar region affects how people move, and whether the identified motor adaptations to MEP are specific to the pain provocative movement. Additionally, this thesis aimed to understand whether the observed motor adaptations are a purposeful strategy to reduce pain as predicted by contemporary theories on motor adaptation to pain. To address the primary aim of this thesis, a series of studies has been conducted examining the relationship between pain and movement across different levels of causality. Specifically, this thesis provides evidence on the causal effect of pain on movement: (i) when pain is experimentally induced to directly assess its impact on movement; (ii) using a counterfactual scenario within a crossover design to assess motor adaptations when MEP is experimentally induced in opposite directions; (iii) investigating how MEP experienced during forward and backward spinal bending is related to changes in movement in people with NScLBP.

*Chapter One* presented an overview on NScLBP, and the different approaches to investigate motor adaptations to pain based on data from clinical populations and using experimental pain models. This review of the literature revealed that, despite our improved understanding of how pain affects movement over the last decades, several features of motor adaptation to pain remain unclear. First, experimental pain models revealed inconsistent results across various studies, showing different adaptations when pain is induced in the appendicular regions compared to the axial region,

highlighting the need to investigate and summarise the evidence specifically for motor adaptations to pain induced in the lumbar region. Secondly, evidence on the interaction between pain and movement is limited; this includes motor adaptations to MEP in the lumbar region when this is experienced in different directions of movement. Finally, despite the several attempts made to understand the clinical variability observed in NScLBP through subgrouping classification systems, it is still unclear whether and how motor adaptations to MEP experienced in the lumbar region are specific to the pain provocative direction. Given the higher improvement in pain and disability observed when exercises are prescribed accordingly to movement-based classifications, there is a need to investigate whether motor adaptations are specific to the pain provocative direction. Understanding this relationship could improve treatment by allowing for more personalised approaches that specifically target motor adaptations, thereby offering a more effective strategy for managing NScLBP. Thus, the gaps found in the literature motivated the need of this thesis, with the final aim of ultimately informing clinical practice. In detail, the specificity of motor adaptations to the pain provocative movement would support the importance of objectively evaluating how people with NScLBP move in the presence of MEP, and the need of personalised treatments based on the identified motor adaptations. Differently from traditional approaches using movement-based classification systems, the methodology used in this thesis fits within current data-driven approaches advocating for patient-reported and objective factors to overcome the limitations of clinician-biased classification systems.

Given the need of summarising the evidence on the effects of pain experimentally induced in the lumbar region on movement, *Chapter Two* presents the

findings of a systematic review with meta-analysis revealing kinematic and muscle activity adaptations to experimental pain. Specifically, pain experimentally induced in the lumbar region resulted in a reduction of the ROM of the lumbar spine. Also, changes in muscle activity consisted of reduced activation of the deep trunk muscles, delayed activation of the transversus abdominis, and task-dependent increased or decreased activation of the superficial lumbar muscles. Altogether, findings from *Chapter Two* supported the causal effect of experimental pain in the lumbar region on movement changes. However, most of the findings related to muscle activity were heterogenous, and MEP was induced only in one study which used movement of the arm rather than the lumbar spine to provoke pain. Therefore, the available evidence on motor adaptations to pain experimentally induced in the lumbar region were limited to tonic pain models. Such models, where pain is not consistently modulated by movement, fail to capture the interaction between pain and movement. Thus, it was not clear whether or how findings obtained from tonic pain models apply to MEP, highlighting the need to investigate the effects of MEP induced in the lumbar region.

Based on the results from *Chapter Two* providing robust evidence on the causal effect of pain on movement, and the lack of data on the kinematic adaptation to pain evoked by movement, *Chapter Three* investigated the bidirectional relationship between movement and pain. By using an experimental pain model to reproduce MEP in the lumbar region and modulated by movement in different directions, findings from *Chapter Three* revealed that motor adaptations to MEP were specific to the pain provocative direction, suggesting also that such adaptations were a purposeful strategy to limit pain. Different adaptations were observed over time, and changes in kinematics

outlasted pain, suggesting the presence of a learning process that optimise motor adaptations to become more specific to the nociceptive input. *Chapter Three* investigated the causal effect of pain on movement within a counterfactual scenario answering to the question "what would have happened if the pain provocative direction was the opposite?" providing a higher level of evidence on causality and supporting that the pain provocative direction is a main determinant of motor adaptation to pain. Taken together, evidence from experimental pain models obtained in *Chapter Two* and *Chapter Three* supports the causal effect of experimental pain on movement and align with the available findings showing a restricted lumbar ROM in the clinical population and the theory on motor adaptations to pain described in *Chapter One*. Thus, the next step for this thesis was to move from experimental to clinical evidence and investigate the effect of MEP on movement in people with NScLBP. This is essential for bridging the gap between theoretical mechanisms identified in an experimental setting and evidence coming from the clinical population, ensuring that findings are directly relevant and beneficial for patients with NScLBP.

*Chapter Four* aimed at investigating whether people with clinical LBP exhibited adaptations similar to those observed in response to experimental pain. Specifically, forty individuals with NScLBP were recruited, and then classified according to their responses to pain provocative movements (i.e., forward and backward bending). Trunk and lower limb kinematics were assessed during functional activities and compared both between these subgroups and to a control group. The main findings of this Chapter revealed that higher pain intensity immediately after repeated forward bending was associated with higher lumbar flexion and lower hip and knee flexion. Similar findings

were observed during functional tasks since people with NScLPB reporting MEP during forward bending showed larger peak of lumbar flexion during a sit-to-stand task, and lower hip flexion during lifting. Results from *Chapter Four* supported the presence of subgroup-specific differences, highlighting the importance of considering MEP response to address clinical heterogeneity and facilitate the development of personalised interventions for people with NScLBP.

Taken together, findings of this thesis provided new insights to explain motor adaptations to pain experienced in the lumbar region, with relevant clinical implications. First, pain in the lumbar region induces motor adaptations, and the direction of the pain provocative movement is a main determinant of these adaptations; this finding is consistent across studies and supported at different levels of causality. Second, motor adaptations to MEP are purposeful strategies implemented by the CNS to reduce the experience of pain. Third, data from this thesis suggest that the occurrence of MEP is a common phenomenon in NScLBP since it was reported by 90% of the participants. Finally, subgrouping participants based on MEP identifies subgroups showing kinematic differences that are not present when data from people with NScLBP are pooled together. Also, similarly to the evidence on experimental pain, reduced lumbar flexion was associated with less pain. These findings support the importance of evaluating movement strategies and how they relate to the pain provocative movement, thereby developing personalised and more effective interventions.

## 5.2 How pain and movement-evoked pain in the lumbar region affect how people move

Findings from empirical data in this thesis agree that pain in the lumbar region changes how people move, and the results align with the theory on motor adaptations to pain that predicts changes in the mechanical behaviour in response to pain, injury, or threat (80). Differently from changes in muscle activity which were heterogenous across the studies included in the systematic review presented in *Chapter Two*, the reduction in the ROM to experimental pain in the lumbar region is consistent between *Chapter Two* and *Chapter Three*. Starting from evidence of the systematic review showing a causal effect of pain on movement restriction, the counterfactual design in *Chapter Three* not only confirmed that experimental pain in the lumbar region restricts movement, but that such restriction depends on the direction of the pain provocative movement. More broadly, the biomechanical factor to which pain is associated with is a main determinant to define motor adaptations to pain. This has been also observed in previous works investigating changes in the produced torque when MEP was compared with tonic pain (137). Compared to previous evidence, pain experimentally induced in the lumbar region resulted in kinematic changes, whereas pain induced in appendicular regions did not provide consistent evidence on changes in limb kinematics (107). This supports the importance of considering the two regions separately as different neurophysiological mechanisms might be involved in the motor adaptations to pain. Additionally, the spinal region is characterised by large biomechanical redundancy, as similar adaptations can be obtained through different biomechanical solutions, leading to substantial inter-individual variability.

Based on empirical data from *Chapter Two* and *Chapter Three*, and the background from clinical populations described in *Chapter One*, one would have expected to observe a reduced lumbar ROM in the clinical population tested in *Chapter Four*; instead, people with LBP and pain during flexion exhibited larger lumbar flexion ROM during functional activities. This difference may be explained by a number of reasons, which remains speculative since a cross-sectional design does not allow to capture the temporality of events. Specifically, it is not possible to confirm whether the observed difference (i.e., higher lumbar flexion) represents a risk factor for the development of LBP because already present before the onset of LBP, or if it is an adaptation triggered by the experience of MEP. Previous evidence suggesting for the former hypothesis comes from a longitudinal cohort study showing that repetitive bending with at least 60° of lumbar flexion (similar to the value reported in the LBP flexion subgroup) is a risk factor for the development of LBP (257), therefore it is possible that the increased lumbar flexion is not an adaptation to pain, but a motor strategy that was already present before the pain occurred. This suggests that people who adapt by reducing lumbar flexion during lifting may experience less pain, which is supported by the observed correlation between lower pain intensity and reduced lumbar flexion. Another possible explanation for the discrepancy between results from experimental MEP, which demonstrated a decrease in lumbar flexion, and those from clinical LBP, indicating an increase, might be that experimental pain models assess the immediate motor response to pain. In contrast, *Chapter Four* recruited participants who, on average, have experienced NScLBP for over two years. At the time of recruitment, it is plausible that most of the people with NScLBP reporting MEP during

forward bending are those people who did not adapt by using a motor strategy able to reduce the amount of experienced pain. Similar results of larger movement in the pain-provoking direction were also obtained in previous studies using movement-based classification systems showing that people in the Flexion Pattern subgroup exhibited larger lumbar ROM during activities requiring forward bending (229). Altogether, these data align with findings from *Chapter Three* where some participants did not change their motor strategy to MEP, or in some cases even increased their lumbar flexion. Future studies are required to confirm test whether (i) the presence of acute MEP without changing the motor strategy in the pain provocative direction favours the transition from acute to chronic LBP and (ii) if promoting changes of movement in acute LBP by reducing MEP might contribute to avoid such a transition. At least for people with NScLBP, movement-based interventions focusing on the reduction of lumbar movement in the pain provocative direction revealed larger improvement in disability compared with strength and flexibility exercises (16).

Beside the clinical heterogeneity observed in people with NScLBP and partially explained by considering the response to MEP, *Chapter Two* also revealed that motor adaptations to pain in the lumbar region are task-specific. Thus, the investigated task could also represent an important factor for comparison across studies. In detail, most of the studies included in systematic reviews on NScLBP and a movement biomarker to discriminate such a population showed lower lumbar motion when lumbar flexion movements were tested during full spinal bending, and without the use of the lower limbs (94). Since in *Chapter Four* only functional activities were tested, it is plausible that the possibility of redistributing the movement to other joints lead to more

heterogenous findings, without requiring full trunk movement during flexion. Also, it is possible that different patterns of spinal movements are observed if patients with NScLBP are required to perform a task involving the lumbar spine only or a more multi-segment task like lifting. Although speculative, the reduction of lumbar flexion observed during pelvic movements in people with MEP do not exclude this option. The second movement biomarkers identified in a previous review and presented in *Chapter One* (103) is in accordance with findings of this thesis. Specifically, the alteration in lumbar/hip coordination is indirectly supported by findings in *Chapter Four* since lower hip flexion was identified during lifting when compared to a control group, and the reduced flexion was associated with higher pain intensity during repetitive forward spinal bending.

The tracking of motor adaptations over time in *Chapter Three* allowed to identify different adaptations that progressed from being multi-segment in the early stages to more localised and relevant to the painful movement. This finding revealed that motor adaptations to MEP are not static but evolve over time. However, it is unclear why this happened and different hypotheses can be considered. For example, participants changed how they move as new information on pain were obtained, or because the strategy used in the acute stage was not effective enough after considering not only the reduction in perceived pain, but also other factors like muscle activation, energy consumption, and path length, as they are all involved in the accomplishment of the task goal (238). Also, a combination of these hypotheses cannot be excluded. The evolution of adaptations over time presents important implications for the study of motor adaptations to pain since tonic experimental pain models and evidence obtained

from *Chapter Two* do not allow for such an investigation. It remains unclear whether the changes over time happen only in experimental MEP or it would also happen with tonic pain models if the nociceptive stimulus is maintained for longer and assessed at multiple time points. Similar to MEP induced with nociceptive electrical stimulation, sustained pain (e.g., NGF) results in adaptations that evolve over time. For example, a progressive reorganisation of motor cortical maps and changes in muscle activity variability were observed over several days after injection of NGF (142,236). However, with sustained pain models like DOMS and NGF, the evolution of motor adaptation from the onset of pain is unfeasible to capture. Understanding how and why people use different motor strategies over time while experiencing MEP can provide insights on patient responses to acute injuries, how these responses may influence the experience of pain in the long-term, and inform treatments. Given that pain and motor adaptations can vary within the same individual at different time of assessment, it might be necessary to tailor interventions based on the current condition of the patient. Such a personalised approach ensures that therapeutic strategies are aligned with the specific adaptation, potentially enhancing the efficacy of treatments, and potentially limiting the progression to chronic pain.

Movement-evoked pain experienced during extension resulted in smaller or no adaptations compared to MEP in flexion. Specifically, a small reduction of the peak in extension was observed in *Chapter Three*, but only over time. No adaptations were observed at other joints and the observed lumbar adaptations did not outlast pain. Similarly, the subgroup of people with NScLBP reporting higher pain during backward bending did not show any kinematic differences compared to the control group.

Different hypothesis can be formulated to explain findings in people reporting MEP in extension. Indeed, backward bending presents important biomechanical differences compared to forward bending, primarily because it usually involves a smaller ROM. Moreover, it is more difficult to redistribute the movement to other joints in tasks requiring backward bending, also because maintaining postural control during extension movements is inherently more challenging. Unlike the common action of returning from a flexed position, trunk extension from a standing position is rarely performed in daily life activities, which could make it more difficult to adopt alternative motor strategies. Similarly to findings in this thesis, previous studies using movement-based classifications found small or no kinematic differences in the Extension Pattern subgroup (229). Therefore, MEP during lumbar extension could influence other physical factors, including for example muscle activity and quality of movement, which need to be considered in future studies. In addition to physical features, people with NScLBP who experience higher pain during lumbar extension also reported increased fear of movement. This suggests that fear of movement may also be a significant factor affecting these patients.

## 5.3 Are motor adaptations a purposeful strategy to protect the region from further pain and/or injury?

Findings from the empirical data presented within this thesis support that motor adaptations to pain can represent a purposeful strategy that aim to protect the painful body region and/or reduce the experience of pain. However, different considerations are required for each individual chapter. Specifically, in *Chapter Two* most of the studies focused on the effects of tonic pain, revealing changes in muscle activity, spinal

stiffness, and kinematics that can be interpreted as protective behaviour. In *Chapter Three*, two different strategies consistent with a protective behaviour were observed. Firstly, the acute response to MEP consisted in multi-segment kinematic changes that could reduce the load on the lumbar spine by relying more on the upper arms and performing the task keeping the centre of pressure closer to the object to lift. Over time, the adaptations became more localised showing a reduction of lumbar movement in the pain provocative direction, and consequently in the perceived pain. This was well supported by a strong association between changes in kinematics during forward bending and perceived pain. Another relevant association was the one observed in *Chapter Four* between pain intensity at the end of a repetitive forward bending task and lumbar kinematics. Also in these data, people with higher pain showed higher lumbar flexion, suggesting that people could have reduced their lumbar ROM to experience less pain, similar to what was observed in *Chapter Three*. In this regard, it remains unclear whether larger movement is a predisposing factor for the development of LBP, or if it only promotes the maintenance of pain itself.

Collectively, findings across all studies support the notion that motor adaptations to pain represent a purposeful strategy to protect the body region and feel less pain. As predicted by current theories (80,87), the observed adaptations occurred at different levels of the motor system and resulted in different biomechanical behaviours at the lumbar spine, but they all underpin the same principle of protection and reduction of pain, when possible. Indeed, the level of agency of the individual can be fundamental for the observed adaptations. In other words, external constraints and the possibility to actively reduce the experience of pain might play a key role in the observed adaptations,

which have been suggested to range across a spectrum of changes at micro and macro levels, from muscle activity redistribution to movement avoidance (87). Indeed, if a movement is painful, the most obvious solution to reduce the pain would be to avoid performing the task, and, in case the movement and the task goal need to be accomplished, different motor adaptations would be observed based on the biomechanical restrictions present while performing the task. This has been also shown in previous studies inducing pain in the lower limb (85). Higher degrees of freedom would probably show gross changes, while performing a task in a constrained set up would result in more specific and subtle adaptations aiming at limit the pain and the load on the painful body area (87). Thus, the amount of biomechanical solutions able to change the experience of pain might represent a key factor on the observed motor adaptations.

Data from movements collected during the peak of lumbar extension show contrasting findings compared to those collected during peak lumbar flexion. In *Chapter Three*, despite participants reduced the movement in the direction that was pain provocative (i.e., lumbar extension), this was not associated with a reduction in perceived pain. Also, people reporting MEP during backward bending in *Chapter Four* did not show kinematic differences compared to the control group in any of the investigated tasks. In accordance with the hypothesis presented above, it is plausible that because the extension movement is characterised by smaller range of movement, alternatives to perform the movement while reducing pain are not efficient or considered as safe resulting in no changes in the motor strategy. Also, the presence of intersegmental differences at different levels of the lumbar spine cannot be excluded,

as it was demonstrated at the cervical region (127). Thus, other factors rather than the ROM could play a role when MEP in the lumbar region is experienced during extension movements.

Differently from most of the studies included in the systematic review presented in *Chapter Two*, the use of experimental MEP used in *Chapter Three* provided participants an active role in the experience of pain since changes in movement resulted in a reduction of the nociceptive stimulation. This could represent a determining factor in the persistency of the observed adaptations during pain when pain subsides. As shown in *Chapter Three*, motor adaptations outlasted pain when these allowed participants to reduce the experience of pain. In the context of a reinforcement learning paradigm, the reduction in experienced pain might represent a reward that motivates individuals to keep the new motor strategy because it is considered to be safer (237). Within a pain perception-action cycle where the individual receives a reward by adopting a new motor strategy, a learning process might be present and is supported by changes of motor adaptations over time (237). The evolution of motor adaptations that might underpin a learning process was also observed in one study included in the systematic review presented in *Chapter Two* (111). Specifically, changes in activity of deep abdominal muscles became larger over time, and, when pain subsided, such changes gradually returned to baseline values (111). However, in that case the motor adaptation was not able to reduce the nociceptive input, but protection of the lumbar region was achieved by increasing spinal stiffness through an increased activation of the external oblique muscle (111). Other experimental studies showed that the reduction of perceived pain might depend on other factors rather than just nociceptive input. For example, in

another study inducing MEP at the wrist, participants reported a reduction of pain by "taking action", even when the new motor strategy did not actually reduce the nociceptive input (144). However, they did not include a post-pain condition to assess whether motor adaptations outlasted pain. Future studies should investigate whether and how the use of a motor strategy able to reduce the experience of pain promotes the retention of motor adaptations. There is a need to understand such a phenomenon because the maintenance of adaptations observed also when pain subsides could lead to long term consequences as predicted by the theory on motor adaptations to pain (80). Specifically, a reduction of movement could result in changes in the mechanical behaviour in the spine with loading sustained on the same spinal structure (19,80). Also, reduced movement might affect the sensorimotor control of the spine because of the reduction of sensory information (240).

All chapters in this thesis considered motor adaptations and kinematic differences remotely to the painful region. Evidence from tonic pain experimentally induced in the lumbar region showed limited and contrasting findings in *Chapter Two*, and multi-segment changes mainly in the acute response to MEP in *Chapter Three*. The multi-segment changes observed in *Chapter Three* could be explained as an attempt to reduce the load from the lumbar spine, adaptations that were not kept over time, probably because they were not able to reduce the experience of pain. Over time, the absence of consistent changes remotely to the painful region can be explained by the use of different biomechanical solutions which lead to the same lumbar adaptation (i.e., reduced ROM). Kinematic differences at the lower limb have been observed in the clinical population in *Chapter Four*. Specifically, a reduction of hip and knee flexion was

observed in people with NScLBP during lifting, especially in people with higher pain during forward bending. Different to the adaptations observed in *Chapter Three*, kinematic differences observed in the clinical population could result in a higher biomechanical load and negative impact on the lumbar spine. This is partially supported by the association between lower hip and knee flexion with higher pain intensity immediately after performing a lifting task. Therefore, evaluating areas distant from the painful region may uncover adaptations that clarify the rationale behind the observed motor strategy, offering potential targets for treatment, such as by promoting movement redistribution to other joints (62,226). Also, the large inter-individual variability supports the need of personalised interventions targeting the specific adaptation.

In summary, motor adaptations to pain represent a purposeful strategy to reduce pain when this can be achieved by a new motor strategy. When pain reduction is not possible or such a motor strategy able to reduce pain is not identified, motor adaptations aim to protect and/or unload the painful area. Interestingly, when motor adaptations allow for a reduction of pain, the new motor strategy seems to be maintained in the long term. Given the negative consequences motor adaptations to pain could have on the long term, this need to be confirmed by future studies.

## 5.4 Clinical implications

Pain in the lumbar region changes how people move. This is supported by findings from experimental and clinical LBP showing a strong causal relationship between pain and movement. Hence, pain can change the mechanical behaviour of the spine with potential implications on the biomechanical loading of the spine in the long-term, even

when the original nociceptive source of pain is not present anymore. Findings from this thesis expand previous knowledge on motor adaptations to pain with results from *Chapter Three* and *Chapter Four* supporting the bidirectional relationship between movement and pain, and highlighting that motor adaptations were specific to the pain provocative direction. In other words, movement can provoke pain, and the experienced pain can specifically affect that movement that was originally pain provocative. Also, the specificity of motor adaptations suggests that movement tested during different tasks could lead to different patterns of adaptations. At least in the short-term, motor adaptations are likely to be beneficial because they are able to reduce the experience of pain. Collectively, these findings suggest important clinical implications in the assessment and management of people with NScLBP. First, they highlight the importance of the clinical assessment of MEP and movement patterns in multiple directions to identify the specific adaptations a patient has made in response to pain. Second, the observed adaptations can be beneficial in the short-term by reducing pain, but their consequences in the long term need to be considered, especially when the motor response to pain is excessive or inappropriate (81). In accordance with current theories, clinicians need to promote and restore optimal control during painful activities, enhancing useful adaptations in the short term (81). Thus, understanding the specificity of adaptations to the performed task and movement can be key to guide the development of targeted exercise programs that address the specific needs of the patient. For example, to protect the lumbar region from further pain during movement, people could adopt protective strategies aiming at the reduction of movement through increased muscle activity, reduced kinematics or movement avoidance, or a mix of all

(80,81). Exercise interventions should aim to restore full-range, and pain-free movements in accordance with personalised movement-based interventions.

Despite the observed specificity of motor adaptations to the pain provocative movement, not all participants experiencing acute MEP changed their movement to feel less pain. This aligns with the observation in *Chapter Four* where people with larger lumbar flexion also reported higher pain intensity in the direction of the pain provocative movement. Thus, the findings reported in this thesis suggest that in some people with MEP, larger ROM could be a contributing factor for the experience of pain and exercise interventions could aim to promote motor control of the lumbar region in the pain provocative directions. In this context, it would be also relevant to test individually if larger movement are actually the contributor to pain and test if pain remains even when movement is corrected. This approach already showed promising results in a recent RCT (16), and previous studies considered the pain response to movement correction to inform treatment (61,226). Although speculative, the presence of pain also when movement is corrected might suggest for the presence of nociplastic rather than a mechanical driver of pain within a nociceptive category. Based on findings from this thesis, it remains unclear why some individuals do not adapt to the pain provocative movement, even when a way to reduce pain is available. Although not investigated in this thesis, it can be speculated that some individuals might lack proprioception and are not able to perceive the relationship between pain and movement, and what movement are pain provocative or not. Previous research using movement-based classifications align with this hypothesis since poor proprioception was observed in those people with pain during lumbar flexion and exhibiting larger ROM during forward bending activities

(228,258). Other reasons to explain why some people do not adapt to the pain provocative movement might be that they have a poor motor repertoire, or that a way to redistribute the movement to other joints is not simple for them to identify.

It is possible that different interventions are required to match the specific presentation of motor patterns in relation with MEP. For example, there could be a subgroup of patients that change their movement and learn a new motor strategy to reduce the pain in the lumbar area, but without returning to the original motor pattern. Evidence from experimental pain induced in the lumbar region and previous evidence described in *Chapter One* support this view (94,259). On the other side of the spectrum, there could be patients with MEP and larger ROM during functional tasks. This aligns with the subgroup of patients with NScLBP identified in *Chapter Four* that reported pain during spinal forward bending. Taken together, these observations suggest a complex relationship between MEP and motor adaptations, supporting the need for tailored interventions that address the specific motor strategy related to MEP in each patient. Thus, understanding the variability in motor responses to MEP has the potential to inform the development of more effective rehabilitation strategies that not only focus on pain relief but also on restoring optimal movement patterns.

## 5.5 Evaluation of the quality of findings presented in this thesis

The quality of findings presented in this thesis has been assessed using a range of RoB tools. Additionally, *Chapter Two, Chapter Three* and *Chapter Four* adhere to the recommended reporting guidelines selected in accordance with the specific study

design. Altogether, these approaches ensure to draw meaningful conclusions from the obtained findings.

The systematic review with meta-analysis presented in *Chapter Two* has been evaluated against the guidelines for A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR-2) (260). When using the assessment tool to examine the systematic review, the majority of the checklist criteria were satisfied. This includes (i) the use of the PICO framework to define the inclusion criteria based on the research questions; (ii) conducting an extensive literature search across multiple databases; (iii) presenting a list of studies that were excluded along with reasons for their exclusion; (iv) the involvement of two independent reviewers in the selection of studies; (v) the use of recommended RoB tools. The source of funding of the included studies was not provided but this is unlikely to affect the quality of findings by introducing conflict of interest in the studies. Also, no statistical analyses were performed on the risk of publication bias, but this type of bias was taken into account when the quality of evidence was rated since the evidence came most of the time from small sample size studies. The quality of findings presented in *Chapter Two* is also supported by other factors. Specifically, *Chapter Two* has been published in a scientific journal so that it has been peer reviewed, with the protocol of such review published before it was conducted, and also registered in PROSPERO. Finally, the Chapter is presented following the PRISMA checklist, and the quality of the evidence was rated using the GRADE approach.

*Chapter Three* presents findings on the effects of MEP using a crossover design where all participants received two interventions in a randomised order (i.e., MEP

modulated by different). The RoB of findings has been tested using the RoB2 for crossover trials, which is the same tool used in *Chapter Two* to assess the RoB of studies having such a study design. Overall, the RoB of the conducted study is low since there are no concerns for any of the assessed domains. Specifically, RoB for the randomisation process was low since the allocation sequence was random and concealed, with no baseline imbalances in the characteristics of participants found during session 1 of the study. Although the investigators collecting the data were aware of the type of pain modulation, the participants were naïve to it and no deviations from intended intervention were reported. Also, a sufficient washout period was ensured between sessions since no differences were reported between session 1 and session 2. Regarding the third domain, outcome data were available for all participants and both sessions. Although outcome assessors were aware of the intervention participants received, it is unlikely that this knowledge influenced the assessment of outcomes, leading to a low RoB for domain four. The last domain also had a low RoB since the outcomes were assessed with the appropriate statistical analysis and the outcomes were selected and measured in accordance with the aim of the study. Finally, it is important to mention that the study has been reported in accordance with the CONSORT guidelines specific for crossover trials.

Given the different study design, the RoB of *Chapter Four* has been evaluated using the Newcastle Ottawa Scale adapted for cross-sectional studies (261). Overall, the study presented methodological strengths because the sample of people with NScLBP was moderately representative of the target population since the patients' reported outcomes were tested with validated tools and of similar values if compared with other

studies, including RCTs (16). Also, the sample size was justified with a power analysis, the statistical analyses were appropriate for the aim of the study, and no differences were found in the demographic characteristics, excluding the risk for potential confounders. The only concern on the quality of findings was the fact that the investigators were not blind to the condition of the participants. Similar to *Chapter Two* and *Chapter Three*, this Chapter was also reported following the STOBE guidelines since specific for observational studies.

## 5.6 Overall strengths and limitations

The methodologies adopted across the studies of this thesis provide several strengths to support the obtained findings. First of all, the relationship between pain and movement, and their bidirectional relationship has been investigated at all the levels of causality, including the association between MEP and movement in *Chapter Four*, the summary of evidence on the effects of experimental pain induced in the lumbar region on movement in *Chapter Two*, and the counterfactual scenario looking at what happens when pain is induced in opposite directions of movement presented in *Chapter Three*. Evidence collected across studies supported the causal effect of pain on movement and the specificity of motor adaptations to what movement is pain provocative. Secondly, innovative and consistent approaches have been used to investigate MEP. In *Chapter Three*, the experimental pain model used gave the possibility of associating pain to movement in real time and proportionally to the recorded ROM. Such a methodology reproduced the temporal characteristics of pain and provided important insights on the pattern of motor adaptations over time which cannot be investigated with other approaches because pain is not consistently

modulated by a specific movement (i.e., HSI); importantly, sustained muscle pain models (i.e., NGF; DOMS) often induce pain during both muscle activation and stretching, therefore they cannot be used to selectively induce pain during flexion or extension. The methodology presented in *Chapter Three* can be applied to different types of investigations testing the interaction between pain perception and action since the pain modulation can be associated to multiple biomechanical factors, including also EMG and forces. Additionally in the context of MEP, *Chapter Four* specifically focused on the assessment of MEP by tracking patient-reported outcomes and their relationship with movement. Finally, the wearable IMUs used in *Chapter Three* and *Chapter Four* present good reliability and validity, and represent accessible technologies that, along with the choice of selecting simple and functional tasks to assess movement, can be used in clinical settings, providing ecological validity to the obtained findings.

Despite these strengths, this thesis is not without limitations. First, evidence obtained from experimental pain models need to be considered with caution since pain experimentally induced cannot reproduce the temporal, spatial, and qualitative characteristics of clinical pain. For this reason, evidence from different experimental pain models is collected and integrated together to obtain a better view on motor adaptations to pain by leveraging the advantages provided by each pain model (e.g., qualitative or temporal characteristics of pain). Also, the correspondence between motor adaptations presented in *Chapter One* with those summarised in *Chapter Two* support the potential role of experimental pain models to investigate motor adaptations to pain. Although the investigation of MEP in this thesis represents an initial step, the

investigation of MEP requires a broader view. Specifically, other movements or combination of movements rather than just flexion and extension can be pain provocative in people with NScLBP. For example, movements of lifting associated with rotation and twisting movements can result in a high stress on the passive structures of the spine (18). Also, the investigation of MEP needs to consider not only the motor output but also how sensory information are integrated; for example, how proprioception is related to motor adaptations and how MEP could affect proprioception. Finally, the use of a cross-sectional design in *Chapter Four* limits our understanding of the observed kinematic differences. This approach does not allow to ascertain whether such differences are predisposing risk factors that contribute to the onset of LBP or if they are motor adaptations resulting from LBP.

## 5.7 Implication for future research

Based on findings from *Chapter Two*, this thesis investigated the effects of MEP on kinematics. However, other aspects remain to be investigated in future studies. For example, how movement is redistributed to other joints during tonic pain induced in the lumbar region has been poorly investigated, as well as the assessments of motor adaptations during functional tasks requiring global movements. Specifically, findings from *Chapter Three* cannot be directly compared with other experimental pain studies investigating the effects of tonic pain on kinematics during a lifting task. It would be worth to investigate if the adaptations observed in the acute phase of MEP correspond to those present when tonic pain models are used, and if such adaptations can have a protective effect on the spine by reducing the load investigated by means of

biomechanical models. Such an investigation could help to understand the different meanings of the identified motor adaptations.

*Chapter Three* provided solid foundations for further investigation. Considering that motor adaptations outlasted pain, future studies should consider whether and when people return to use the original motor strategy, and whether some other variables could explain differences across participants between those who keep the new motor strategy or return to the original one. Identifying individual factors able to explain heterogeneity is also necessary to understand why some people change their movement or not while in pain. Specifically, future studies should conduct subgroup analysis and investigate other sensorimotor variables at different levels of the motor system (e.g., corticospinal excitability, cortical function, proprioception) to understand if they could explain why some participants adapt to pain while others do not. Finally, since participants learn to move in a different way to feel less pain it is important to test if the new motor strategy also influences movement executed during different tasks. In other words, to investigate whether transfer learning mechanisms take place in this context. Taken together, the outcomes of the proposed research could inform the management of people with NScLBP and expand the theory on motor adaptations to pain. For example, understanding whether and which patients return to use the original motor strategy after pain is key in the context of the potential long-term consequences described in the theory (80). This insight could help to identify patients at risk of developing such long-term consequences. Altogether, these findings would enable the delivery of more personalised exercise interventions by explaining the heterogeneity of motor adaptations during and after the resolution of pain.

In accordance with the methodologies and findings obtained in *Chapter Two* and *Chapter Three*, future studies investigating motor adaptations to experimentally induced pain need to take into account the limitations and advantages of different pain models and how they fit to the research question that needs to be investigated. Specifically, given that the experience of clinical LBP can be either spontaneous or movement-induced (262), the selection of pain models should begin with a clear identification of the pain characteristics to be examined. Findings from this thesis also support that evidence from tonic pain do not directly apply to MEP, highlighting the necessity of independently examining motor adaptations in response to these distinct types of pain. Although tonic pain can be reproduced using different experimental models, findings from *Chapter Two* suggested that HSI is more effective in eliciting motor adaptations that closely resemble those observed in clinical LBP. This consistency in results makes HSI a better experimental model for investigating tonic pain induced in the lumbar region, underscoring its suitability for studies aiming to understand motor adaptations to spontaneous pain. Another important insight to inform future studies was that the observed adaptations were specific to the task, indicating the need to avoid generalising findings across tasks without careful examination. Additionally, the biomechanical factor associated to the pain is a main determinant to explain the adaptations. Thus, selecting this factor is fundamental and such a choice should be informed by observation of activities that are pain provocative in the clinical population.

Findings in the clinical population supported the role of MEP and demonstrated that it is largely present in people with NScLBP. Further investigations are required to

understand its role in treatment and to understand if changes in movement are related to pain reduction. Recent evidence supported this view but mainly when movement was reduced and “less protective” movement strategies were restored (242,259). Findings from *Chapter Four* however showed that in some people, larger movements were associated to higher pain so that for those people motor control exercises aiming at redistributing movement to other joints could be also strategies that need to be implemented. This might explain the contrasting findings in the literature and the need to personalise treatment based on the movement pattern of each individual. In a recent call, the role of movement has been described with the need of studies looking at the change in movement as a potential mediator of treatment to confirm its role in the management of people with NScLBP (263). In this regard, findings from *Chapter Four* cannot confirm whether the observed kinematic differences and larger lumbar flexion is a risk factor for the development of MEP or if it follows and is a consequences of pain. Although in a previous study lifting with higher lumbar flexion was a risk factor for the development of LBP (257), no studies have been conducted to investigate whether larger lumbar ROM is risk factor for the development of MEP in the same direction of movement. Longitudinal studies are required to track and assess lumbar movements over time, and to investigate how they relate to the development of LBP and its transition to chronicity. The assessment of MEP and how it is related to movement can provide also important insights to understand the underlying mechanism of pain. For example, people with NScLBP reporting MEP in a specific direction and reporting changes in pain when the motor strategy is modified might suggest for the presence of nociceptive pain. Instead, MEP reported in different movement directions and tasks,

and not influenced by changes in the performed movement might suggest for the presence of nociplastic pain, which, consequentially, will direct the focus of intervention to a cognitive and psychological domain, for example by using graded exercise and cognitive behavioural treatments.

More broadly to the context of MEP, this thesis focused on motor adaptations and the action component. However, the sensory domain is also critical, and it should be addressed in future studies. For example, the effects of MEP on pain perception and proprioception are critical to understand the intricate relationship between pain and movement. Throughout this thesis, the emphasis on kinematics was essential for providing an understanding of how pain in the lumbar region affects movement, considering an outcome that showed robust evidence from systematic reviews in the clinical population and in the response to tonic experimental pain models. Recognising that pain impacts the motor system at multiple levels, future research exploring muscle activity and corticospinal function could offer valuable insights into the comprehensive mechanisms of motor adaptations to MEP. This broader approach would significantly enhance the development of targeted treatment strategies for NScLBP.

## 5.8 Conclusions

This thesis investigated the relationship between MEP in the lumbar region and motor adaptations with a focus on kinematics. Findings revealed that pain in the lumbar region changes movement, and that the observed motor adaptations were specific to the direction of the pain provocative movement. Additionally, motor adaptations to acute MEP were consistent with a purposeful strategy to reduce pain as predicted by

contemporary theories of motor adaptations to pain. This thesis aligns with previous research highlighting the heterogeneity of motor adaptations to pain and identifies pain directionality as a potential factor to partially explain such heterogeneity. Collectively, these findings support the importance of evaluating movement strategies and how they relate to the pain provocative movement, offering further insights for the development of personalised and more effective interventions.

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# APPENDICES

**Appendix 1 –** Literature search and databases screened for the systematic review in *Chapter Two*

**Appendix 2 –** Collated reported in the systematic review presented in *Chapter Two*

**Appendix 3 –** Table of characteristics extracted from included studies in the systematic review presented in *Chapter Two*

**Appendix 4 –** PRISMA Checklist for *Chapter Two*

**Appendix 5 –** Confirmation letter with ethical approval for study in *Chapter Three* (ERN_19-1018)

**Appendix 6 –** CONSORT Checklist for *Chapter Three*

**Appendix 7 –** Confirmation letter with ethical approval for study in *Chapter Four* (ERN_21-1772)

**Appendix 8 –** STROBE Checklist for *Chapter Four*

## **Appendix 1 -** *Literature search and databases screened for the systematic review in Chapter Two*

Main concepts: ((“EXP PAIN” or “EXP PAIN INTERVENTION”) and (“LOW BACK” or “BACK PAIN”)

**MEDLINE, Ovid interface (31/01/22) = 2709**

1. ((Experiment* adj5 pain) or (experimentally-induced adj4 pain) or (pain-induced or 'experimental induced' or 'experimentally induced') or (induced adj3 pain) or 'induced LBP' or (noxious adj3 stimul*) or (nociceptive adj3 stimul*) or (pain* adj3 stimul*)).mp

2. ((('hypertonic saline' or capsaicin or glutamate or 'laser evoked potential' or 'laser evoked potentials' or 'nerve growth factor') and pain) or (electric* adj2 pain*) or (electric* adj2 stimul*) or (mechanic* adj2 pain*) or (mechanic* adj2 stimul*) or (thermal* adj2 pain*) or (thermal* adj2 stimul*) or (chemical* adj2 pain*) or (chemical* adj2 stimul*) or (cutaneous adj2 pain*) or (cutaneous adj2 stimul*)).mp or Saline Solution, Hypertonic/ or Electric Stimulation/

3. Back Pain/ or ('back pain' or 'back ache' or backache*).mp. or exp Low Back Pain/ or ('low back pain' or 'lower back pain' or lumbago or LBP or 'lumbar pain' or 'lumbar spine' or 'low back' or 'lower back').mp

4. 1 or 2

5. 3 and 4

**EMBASE, Ovid interface (31/01/22) = 4668**

1. ((Experiment* adj3 pain) or (experimentally-induced adj3 pain) or (pain-induced or 'experimental induced' or 'experimentally induced') or (induced adj3 pain) or 'induced LBP' or (noxious adj3 stimul*) or (nociceptive adj3 stimul*) or (pain* adj3 stimul*)).mp

2. ((('hypertonic saline' or capsaicin or glutamate or 'laser evoked potential' or 'laser evoked potentials' or 'nerve growth factor') and pain) or (electric* adj1 pain*) or (electric* adj1 stimul*) or (mechanic* adj1 pain*) or (mechanic* adj1 stimul*) or (thermal* adj1 pain*) or (thermal* adj1 stimul*) or (chemical* adj1 pain*) or (chemical* adj1 stimul*) or (cutaneous adj1 pain*) or (cutaneous adj1 stimul*)).mp or Saline Solution, Hypertonic/ or Electric Stimulation/

3. Back Pain/ or ('back pain' or 'back ache' or backache*).mp. or exp Low Back Pain/ or ('low back pain' or 'lower back pain' or lumbago or LBP or 'lumbar pain' or 'lumbar spine' or 'low back' or 'lower back').mp

4. 1 or 2

5. 3 and 4

**CINAHL, EBSCO interface (31/01/22) = 1962**

((experiment* N5 pain) OR (experimentally-induced N4 pain) OR pain-induced OR “experimental induced” OR “experimentally induced” OR (induced N3 pain) OR “induced LBP” OR (noxious N3 stimul*) OR (nociceptive N3 stimul*) OR (pain* N3 stimul*) OR ((“hypertonic saline” OR capsaicin OR glutamate OR “laser evoked potential” OR “laser evoked potentials” OR “nerve growth factor”) AND pain) OR (electric* N2 pain*) OR (electric* N2 stimul*) OR (mechanic* N2 pain*) OR (mechanic* N2 stimul*) OR (thermal* N2 pain*) OR (thermal* N2 stimul*) OR (chemical* N2 pain*) OR (chemical* N2 stimul*) OR (cutaneous N2 pain*) OR (cutaneous N2 stimul*)) [TX all text]

AND

(“back pain” OR “back ache” OR backache* OR “low back pain” OR “lower back pain” OR lumbago OR LBP OR “lumbar pain” OR “lumbar spine” OR “low back” OR “lower back” OR (MH “low back pain+”) OR (MH “back pain+”)) [TX all text]

**ZETOC (31/01/22) = 2108**

experimental* AND “back pain” = 971

“hypertonic saline” AND “back pain” = 46

capsaicin AND “back pain” = 40

electrical* AND “back pain” = 333

thermal* AND “back pain” = 227

chemical* AND “back pain” = 177

cutaneous AND “back pain” = 212

“nerve growth factor” AND “back pain” = 102

**PubMed (31/01/22) = 1164**

((“experimental pain”[tw] OR “experimentally-induced pain”[tw] OR “experimentally induced”[tw] OR “pain induced”[tw] OR “induced pain”[tw] OR “induced back pain”[tw] OR “induced low back pain”[tw] OR “experimental low back pain”[tw] OR “experimental back pain”[tw] OR “experimental muscle pain”[tw] OR “experimental LBP”[tw] OR “induced LBP”[tw] OR “noxious stimulation”[tw] OR “noxious stimuli”[tw] OR “nociceptive stimulation”[tw] OR “nociceptive stimuli”[tw] OR “noxious stimulus”[tw] OR “nociceptive stimulus”[tw] OR “pain stimulus”[tw] OR “pain stimulation”[tw] OR “pain stimuli”[tw] OR “painful stimulation”[tw] OR “painful stimuli”[tw] OR “painful stimulus”[tw])

OR

(“saline injection”[tw] OR “hypertonic saline”[tw] OR “buffered acidic”[tw] OR “acidic saline”[tw] OR capsaicin[tw] OR "capsaicin"[mesh] OR glutamate[tw] OR “laser evoked potential”[tw] OR “laser evoked potentials”[tw] OR “nerve growth factor”[tw] OR “electrical stimulation”[tw] OR “electrical pain”[tw] OR “electrical stimulus”[tw] OR “electrical stimuli”[tw] OR “thermal stimulation”[tw] OR “thermal stimuli”[tw] OR “thermal stimulus”[tw] OR “thermal pain”[tw] OR “chemical pain”[tw] OR “chemical stimulation”[tw] OR “chemical stimulus”[tw] OR “chemical stimuli”[tw] OR “cutaneous stimulation”[tw] OR “cutaneous stimuli”[tw] OR “cutaneous stimulus”[tw] OR “heat pain”[tw] OR "Saline Solution, Hypertonic"[mesh] OR "Electric Stimulation"[mesh]))

AND

(“back pain”[tw] OR “low back pain”[tw] OR backache[tw] OR backaches[tw] OR LBP[tw] OR lumbago[tw] OR “lumbar pain”[tw] OR “back ache”[tw] OR “lumbar spine”[tw] OR “back pain, low”[mesh])

**Web Of Science (31/01/22) = 2408**

TI/AB=((experiment* NEAR/1 pain) OR (experimentally-induced NEAR/1 pain) OR pain-induced OR “experimental induced” OR “experimentally induced” OR (induced NEAR/1 pain) OR “induced LBP” OR (noxious NEAR/1 stimul*) OR (nociceptive NEAR/1 stimul*) OR (pain* NEAR/1 stimul*) OR ((“hypertonic saline” OR capsaicin OR glutamate OR “laser evoked potential” OR “laser evoked potentials” OR “nerve growth factor”) NEAR/5 pain) OR (electric* NEAR/1 pain*) OR (electric* NEAR/1 stimul*) OR (mechanic* NEAR/1 pain*) OR (mechanic* NEAR/1 stimul*) OR (thermal* NEAR/1 pain*) OR (thermal* NEAR/1 stimul*) OR (chemical* NEAR/1 pain*) OR (chemical* NEAR/1 stimul*) OR (cutaneous NEAR/1 pain*) OR (cutaneous NEAR/1 stimul*))

AND

TI/AB=(“back pain” OR “back ache” OR backache* OR “low back pain” OR “lower back pain” OR lumbago OR LBP OR “lumbar pain” OR “lumbar spine” OR “low back” OR “lower back”)

**Appendix 2 -** *Collated reported in the systematic review presented in Chapter Two*

| |
|---|
| Dickx N, Cagnie B, Achten E, Vandemaele P, Parlevliet T, Danneels L. **Changes in lumbar muscle activity because of induced muscle pain evaluated by muscle functional magnetic resonance imaging.** Spine (Phila Pa 1976). 2008 Dec 15;33(26):E983-9. doi: 10.1097/BRS.0b013e31818917d0. |
| Dickx N, Cagnie B, Achten E, Vandemaele P, Parlevliet T, Danneels L. Differentiation between deep and superficial fibers of the lumbar multifidus by magnetic resonance imaging. Eur Spine J. 2010 Jan;19(1):122-8. doi: 10.1007/s00586-009-1171-x. |

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| van den Hoorn W, Hodges PW, van Dieën JH, Hug F. **Effect of acute noxious stimulation to the leg or back on muscle synergies during walking.** J Neurophysiol. 2015 Jan 1;113(1):244-54. doi: 10.1152/jn.00557.2014. |
| van den Hoorn W, Hug F, Hodges PW, Bruijn SM, van Dieën JH. Effects of noxious stimulation to the back or calf muscles on gait stability. J Biomech. 2015 Nov 26;48(15):4109-4115. doi: 10.1016/j.jbiomech.2015.10.013. |

| |
|---|
| Henchoz Y, Tétreau C, Abboud J, Piché M, Descarreaux M. **Effects of noxious stimulation and pain expectations on neuromuscular control of the spine in patients with chronic low back pain.** Spine J. 2013 Oct;13(10):1263-72. doi: 10.1016/j.spinee.2013.07.452. |
| Tétreau C, Dubois JD, Piché M, Descarreaux M. Modulation of pain-induced neuromuscular trunk responses by pain expectations: a single group study. J Manipulative Physiol Ther. 2012 Oct;35(8):636-44. doi: 10.1016/j.jmpt.2012.06.008 |
| Henchoz Y, Tétreau C, Abboud J, Piché M and Descarreaux M. Effects of Pain Expectations on Neuromuscular Control of the Spine in Patients with Chronic Low Back Pain and Healthy Participants. Arthritis and Rheumatism. 2012;10, S1122 |

| |
|---|
| Moseley GL, Nicholas MK, Hodges PW. **Pain differs from non-painful attention-demanding or stressful tasks in its effect on postural control patterns of trunk muscles**. Exp Brain Res. 2004 May;156(1):64-71. doi: 10.1007/s00221-003-1766-0. |
| Moseley GL, Hodges PW. Attention demand, anxiety and acute pain cause differential effects on postural activation of the abdominal muscles in humans. Society for Neuroscience Abstracts.2001;27(1):801 |

| |
|---|
| Moseley GL, Hodges PW. **Are the changes in postural control associated with low back pain caused by pain interference?** Clin J Pain. 2005 Jul-Aug;21(4):323-9. doi: 10.1097/01.ajp.0000131414.84596.99. |
| Moseley GL, Hodges PW. Reduced variability of postural strategy prevents normalization of motor changes induced by back pain: a risk factor for chronic trouble? Behav Neurosci. 2006 Apr;120(2):474-476. doi: 10.1037/0735-7044.120.2.474. |
| Hodges PW, Moseley GL, Gabrielsson A, Gandevia SC. Experimental muscle pain changes feedforward postural responses of the trunk muscles. Exp Brain Res. 2003 Jul;151(2):262-71. doi: 10.1007/s00221-003-1457-x. |
| Hodges, P. W., Moseley, G. L., Gabrielsson, A., Gandevia, S. C. Acute experimental pain changes postural recruitment of the trunk muscles in pain-free humans. Society for Neuroscience Abstracts. 2001;27(1):801 |

**Appendix 3 -** *Table of characteristics extracted from included studies in the systematic review presented in Chapter Two*

| | |
|---|---|
| Identification features of the report | Authors<br>Title<br>Year<br>Source (e.g. journal article, conference abstract) |
| Population | Sample size<br>Age<br>Gender<br>Height, weight, body mass index<br>Randomisation details and arm group characteristics (crossover design only) |
| Intervention | Experimental pain model/s adopted<br>Intervention characteristics (e.g. type, dosage, method)<br>Body region stimulated (anatomical structure and location, unilateral or bilateral stimulation)<br>Average and highest level of pain experienced (VAS or NRS)<br>Duration of pain symptoms<br>Qualitative description of pain (e.g. McGill Pain Questionnaire)<br>Perceived location and distribution of pain symptoms (including referred pain)<br>Co-interventions<br>Potential confounders to the intervention effect (NRSI only)<br>Deviations from intended intervention<br>Time window between interventions |
| Comparator | No intervention (baseline condition) or control intervention<br>Typology of control intervention<br>Level of pain induced with the control intervention (minimal versus not at all)<br>Duration of pain symptoms (if experienced)<br>Co-interventions<br>Assessment of the POST-PAIN condition<br>Time window between PAIN and POST-PAIN condition |
| Outcomes | Outcome domain<br>Outcome measure<br>Measurement tool<br>Body region/muscle investigated (including all spinal regions and limbs)<br>Task |
| Design | Randomised trial (crossover) or NRSI (repeated measure)<br>Time point assessments, including their order and time in between (e.g. wash-out period) |

## **Appendix 4 -** *PRISMA Checklist for Chapter Two*

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | 47 |
| **ABSTRACT** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | 48 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | 49-50 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | 51 |
| **METHODS** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | 51-53 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | 53-54 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Appendix 1 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | 54-55 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | 55 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Appendix 3 |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Appendix 3 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | 55-56 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | 56-59 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | 56-59 |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | 56-59 |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | 56-59 |

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | 56-59 |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | 56-59 |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | 56-59 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | 60 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | 60 |
| **RESULTS** | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | 60-62 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | 61 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | 62-68 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | 69-70 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | 71-85 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | 71-85 |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | 71-85 |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | 71-85 |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | 71-85 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | 86-87 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | 86-87 |
| **DISCUSSION** | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | 90-98 |
| | 23b | Discuss any limitations of the evidence included in the review. | 90-98 |
| | 23c | Discuss any limitations of the review processes used. | 90-98 |

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| | 23d | Discuss implications of the results for practice, policy, and future research. | 90-98 |
| **OTHER INFORMATION** | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | 51 |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | 51 |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | NA |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | NA |
| Competing interests | 26 | Declare any competing interests of review authors. | NA |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | 47 |

*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

**Appendix 5 -** *Confirmation letter with ethical approval for study in Chapter Three (ERN_19-1018)*

Dear Dr Gallina

**Re: "Task-relevant painful electrical stimulation"**
**Application for Ethical Review ERN_19-1018**

Thank you for your application for ethical review for the above project, which was reviewed by the Science, Technology, Engineering and Mathematics Ethical Review Committee.

On behalf of the Committee, I confirm that this study now has full ethical approval.

I would like to remind you that any substantive changes to the nature of the study as described in the Application for Ethical Review, and/or any adverse events occurring during the study should be promptly brought to the Committee's attention by the Principal Investigator and may necessitate further ethical review.

Please also ensure that the relevant requirements within the University's Code of Practice for Research and the information and guidance provided on the University's ethics webpages (available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Links-and-Resources.aspx ) are adhered to and referred to in any future applications for ethical review. It is now a requirement on the revised application form (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx ) to confirm that this guidance has been consulted and is understood, and that it has been taken into account when completing your application for ethical review.

Please be aware that whilst Health and Safety (H&S) issues may be considered during the ethical review process, you are still required to follow the University's guidance on H&S and to ensure that H&S risk assessments have been carried out as appropriate. For further information about this, please contact your School H&S representative or the University's H&S Unit at healthandsafety@contacts.bham.ac.uk.

Kind regards,

**Ms Sam Waldron** (she/her)
Research Ethics Officer
Research Support Group

## **Appendix 6 -** *CONSORT Checklist for Chapter Three*

Table S1. CONSORT Checklist for randomised crossover trial

| **Section/topic** | **Item N** | **Description** | **Page N** |
|---|---|---|---|
| Title | 1a | Identification as a randomised crossover trial in the title | 99 |
| Abstract | 1b | Specify a crossover design and report all information outlined in table 2 | 99 |
| Introduction: | | | |
| Background | 2a | Scientific background and explanation of rationale | 100-102 |
| Objectives | 2b | Specific objectives or hypotheses | 102 |
| Methods: | | | |
| Trial design | 3a | Rationale for a crossover design. Description of the design features including allocation ratio, especially the number and duration of periods, duration of washout period, and consideration of carry over effect | 103-104 |
| Change from protocol | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | NA |
| Participants | 4a | Eligibility criteria for participants | 104 |
| Setting and location | 4b | Settings and locations where the data were collected | 104 |
| Interventions | 5 | The interventions with sufficient details to allow replication, including how and when they were actually administered | 105-107 |
| Outcomes | 6a | Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed | 109-111 |
| Changes to outcomes | 6b | Any changes to trial outcomes after the trial commenced, with reasons | NA |
| Sample size | 7a | How sample size was determined, accounting for within participant variability | 104 |
| Interim analyses and stopping guidelines | 7b | When applicable, explanation of any interim analyses and stopping guidelines | NA |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 103 |
| Sequence generation | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 103 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | NA |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who | 103 |

| | | | |
|---|---|---|---|
| | | assigned participants to the sequence of interventions | |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how | 106-107 |
| Similarity of interventions | 11b | If relevant, description of the similarity of interventions | NA |
| Statical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes which are appropriate for crossover design (that is, based on within participant comparison) | 112-113 |
| Additional analyses | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | NA |
| Results: | | | |
| Participant flow | 13a | The numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome, separately for each sequence and period | 104 |
| Losses and exclusions | 13b | No of participants excluded at each stage, with reasons, separately for each sequence and period | 104 |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | 104 |
| Trial end | 14b | Why the trial ended or was stopped | NA |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics by sequence and period | 104 |
| Numbers analysed | 16 | Number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | 115 |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results including estimated effect size and its precision (such as 95% confidence interval) should be based on within participant comparisons. In addition, results for each intervention in each period are recommended | 115-121 |
| Binary outcomes | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | NA |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory | NA |
| Harms | 19 | Describe all important harms or untended effects in a way that accounts for the design (for specific guidance, see CONSORT for harms) | NA |
| Discussions: | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and if relevant, multiplicity of analyses. Consider potential carry over effects | 129 |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | 128-129 |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | 123-128 |

| | | | |
|---|---|---|---|
| Other information: | | | |
| Registration | 23 | Registration number and name of trial registry | NA |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | NA |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | NA |

**Appendix 7 -** *Confirmation letter with ethical approval for study in Chapter Four (ERN_21-1772)*

Dear Dr Gallina,

**Re: "The influence of movement-evoked pain on neuromuscular control in people with chronic low back pain"**
**Application for Ethical Review ERN_ 21-1772**

Thank you for your application for ethical review for the above project, which was reviewed by the Science, Technology, Engineering and Mathematics Ethical Review Committee.

On behalf of the Committee, I confirm that this study now has full ethical approval.

I would like to remind you that any substantive changes to the nature of the study as described in the Application for Ethical Review, and/or any adverse events occurring during the study should be promptly brought to the Committee's attention by the Principal Investigator and may necessitate further ethical review.

Please also ensure that the relevant requirements within the University's Code of Practice for Research and the information and guidance provided on the University's ethics webpages (available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Links-and-Resources.aspx ) are adhered to and referred to in any future applications for ethical review. It is now a requirement on the revised application form (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx ) to confirm that this guidance has been consulted and is understood, and that it has been taken into account when completing your application for ethical review.

Please be aware that whilst Health and Safety (H&S) issues may be considered during the ethical review process, you are still required to follow the University's guidance on H&S and to ensure that H&S risk assessments have been carried out as appropriate. For further information about this, please contact your School H&S representative or the University's H&S Unit at healthandsafety@contacts.bham.ac.uk.

Kind regards

**Mrs Susan Cottam**
Research Ethics Manager
Research Support Group
University of Birmingham

## **Appendix 8 -** *STROBE Checklist for Chapter Four*

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation | Page N |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 131 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 131 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 132-134 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 134 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 135 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 135 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 135-136 |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 136-139 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 140-141 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 137-139 |
| Study size | 10 | Explain how the study size was arrived at | 135 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 139-140 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 140-141 |
| | | (*b*) Describe any methods used to examine subgroups and | 140-141 |

| | | | |
|---|---|---|---|
| | | interactions | |
| | | (*c*) Explain how missing data were addressed | NA |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | NA |
| | | (*e*) Describe any sensitivity analyses | NA |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 135 |
| | | (b) Give reasons for non-participation at each stage | 136 |
| | | (c) Consider use of a flow diagram | NA |
| Descriptive data | 14* | (a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders | 142 |
| | | (b) Indicate number of participants with missing data for each variable of interest | NA |
| | | (c) *Cohort study*—Summarise follow-up time (e.g., average and total amount) | NA |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | NA |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | NA |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | 142-146 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 142-146 |
| | | (*b*) Report category boundaries when continuous variables were categorized | NA |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | NA |
| Other analyses | 17 | Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses | 142-146 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 148-151 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 153 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering | 152 |

| | | | |
|---|---|---|---|
| | | objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 152-153 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | NA |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.