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**BY**
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DISSERTATION SUBMITTED 2016

AALBORG UNIVERSITY
DENMARK

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# CV

Christian Ariel Mista was born in Puerto Belgrano, Argentina in 1983. In 2010 he obtained his degree as bioengineer at the Faculty of Engineering of the National University of Entre Ríos, Argentina. His main areas of research are biomedical signal processing with focus on surface electromyography and force in the study of pain.

# PREFACE

This Ph.D. thesis summarizes the work carried out while working from 2010 to 2013 at the Center for Sensory–Motor Interaction, Aalborg University. A stay abroad of two month was carried out at the University Rovira i Virgili and Hospital Joan XXIII (Spain), as part of a collaboration with Aalborg University.

The present Ph.D. thesis aims to add valuable knowledge about motor adaptations to muscle pain in humans. In order to obtain new insight into the motor adaptation to pain, advanced techniques are required in the assessment of the motor output, as for example spatial activation of the muscle or three-dimensional force variability. Learning about pain mechanisms facilitates the improvement of pain relief treatments in acute and chronic pain conditions.

This thesis is divided into four chapters. The first chapter presents the relevance of studying pain mechanisms and the aims of the project. The second chapter explore the required background knowledge on muscle activity and force variability. The third chapter presents the modulations of the motor control obtained using an acute experimental pain model. The fourth chapter describes motor changes during a persistent pain. Finally, the thesis is ended with a brief conclusion.

# ENGLISH SUMMARY

Pain is a strong stimulus that typically reorganizes the motor control. Existing pain theories predict changes within muscle activity and between muscles when performing a painful motor task. Muscle adaptations result in decreased motor control performance, reflected by changes in the motor output, such as increased variability during isometric contractions. These motor adaptations provide short-term benefits, but present potential detrimental consequences in the long-term due to overloading of non-painful structures. Thus, the study of motor reorganization during acute and persistent pain is crucial to understand the motor changes when translating from acute pain to chronic pain conditions. This knowledge might facilitate the improvement of pain relief treatments.

The present dissertation intends to describe the relation between three-dimensional isometric force recordings and surface electromyographic (EMG) activity during acute and persistent muscle pain. To do so, two pain models with distinct characteristics (intensity and time profile of pain) were used. To accomplish the previously stated goal, three studies were carried out. In study 1, the relation between EMG and force was analysed by quantifying the spatial activity of the main muscle involved in the motor task, as well as auxiliary muscles, in a pain-free condition. In study 2 and 3, acute experimental pain was induced in biceps brachii and extensor carpi radialis brevis muscles, in order to quantify changes in the motor control during isometric elbow flexion and wrist extension, respectively. In the study 3, nerve growth factor (NGF) was injected into the extensor carpi radialis brevis muscle to investigate whether the motor adaptation are altered during soreness and persistent movement-evoked pain over time.

The overall results from the studies showed the relevance of the auxiliary muscle activity in the motor adaptation to acute and persistent pain. Additionally, study 2 and 3 showed that the force variability was increased in the less restrictive motor tasks when inducing acute experimental muscle pain. However, increasing the restriction on the motor task resulted in lack of motor control changes, which implies that pain adaptations are task-dependent. Moreover, acute pain leads to greater variability and changes of direction of the force, whereas persistent movement-evoked pain is related to a force direction that differed from the pain-free state, but with no difference in variability. These differences may imply an initial “search” for a beneficial solution mediated by increased variation, and a later “consolidation” to the new motor alternative. In conclusion, it was shown that motor adaptations to pain are task and time-dependent. Therapies to musculoskeletal pain condition could be accompanied with functional performance assessments, such as force and net force direction analysis, in order to restore the optimal control for achieving a motor task.

# DANSK RESUME

Smerte er et kraftigt stimulus, der ofte reorganisere motorisk kontrol. Nuværende smerteteorier forudsiger adaptationer i muskel aktivitet, både i den enkelte muskel samt muskler imellem, under udførslen af en smertefuld opgave. Muskel adaptationer resulterer i nedsat motorisk kontrol, hvilket reflekteres i et ændret motorisk output som f.eks. en øget variabilitet under isometriske kontraktioner. Nogle teorier angiver at disse motoriske adaptationer giver en kortvarig fordel mens det potentielt kan være skadeligt i det lange løb. Med udgangspunkt i dette er det yderst vigtigt, at undersøge den motoriske reorganisering under akutte og vedvarende smerter for, at forstå de forandringer der finder sted i overgangen fra akut til kronisk smerte. En sådan viden kan måske endda være med til at optimere smertebehandling.

Denne afhandling sigter mod at beskrive relationen mellem tredimensionelle kraft målinger og overflade EMG aktivitet under akutte og vedvarende muskelsmerter. Med dette for øje, er der anvendt to smertemodeller med forskellig karakteristika i forhold til smerte intensitet og tidsprofil. For at kunne beskrive den tidligere nævnte relation, er der gennemført tre studier. I studie 1 blev relationen mellem EMG og den spatiale aktivitet i den vigtigste muskel, samt hjælpe muskler analyseret og kvantificeret under en smertefri motorisk opgave. I studie 2 og 3 blev der induceret en akut eksperimentel smerte i m.biceps brachii og m.extensor carpi radialis brevis, for at kunne kvantificere forandringer i motorisk kontrol under en isometrisk albue fleksion samt under en håndleds fleksion. Ud over den akutte smerte, blev der i studie 3 givet en NGF injektion i m.extensor carpi radialis brevis for, at undersøge effekten af vedvarende smerte hos raske deltagere. Herefter blev motoriske forandringer hos folk med lateral epikondyalgia undersøgt og sammenhold med resultaterne fra NGF modellen.

Det overordnede resultat fra studierne viser betydningen af hjælpe musklerne under den motorsiek adaptation i overgangen fra akut til vedvarende smerte. Ydermere viste studie 2 og 3, at kraft stabiliteten var nedsat ved akutte eksperimentel muskelsmerte under en mindre indskrænket motorisk opgave. Dog viste studie 2, at ved at indskrænke den motoriske opgave, så fandt man ikke disse forandringer, hvilket kunne tyde på at adaptationer til smerte er afhængig af opgaven der udføres. I modsætning til dette viste resultaterne fra studie 3, at kraft variabiliteten ikke blev påvirket af vedvarende ømhed mens kombinationen af tangentielle kræfter blev signifikant ændret med tiden. Hos patienter med kronisk smerte blev en lignende adfærd observeret, når disse blev sammenholdt med resultaterne fra NGF modellen. Konklusionen er, at motoriske adaptationer under smerter har vist sig at være både opgave og tids afhængige. Behandling af muskuloskeletal smertetilstande kan

akkompagneres af funktionelle præstationsmålinger, så som kraft og kraft retnings analyser, for at kunne estimere fremgangen i et rehabiliterings forløb for en patient.

# ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to my supervisor, Professor Thomas Graven-Nielsen, whose expertise, understanding, patience, and guidance has made my PhD project a thoughtful and rewarding journey. I deeply appreciate his support and confidence in me, and his friendly and enthusiastic character, that pushed me to keep working on my research career.

It would have been impossible to perform the studies on which this thesis is based without the contribution of all the people involved in the experiments, from those who helped with the idea and design of the protocols, to those who voluntary participated in the studies. I would also like to thank to Steffan W. Christensen and Thorvaldur S. Palsson for carrying out the injection in my studies and great discussions, to Sauro Salomoni and Rogerio Hirata for helping me with the setup and the discussion about how to improve the data analysis. I would also specially like to acknowledge Sonia Monterde for her kindness and help in my stay in Spain. I extend my sincere gratitude to the co-authors of my papers for their valuable contributions, Michael Bergin, Kelly Tucker, and Paul Hodges. I would also like to thank to all the administrative and technical staff at SMI for creating such a lovely work environment.

I am thankful with my Argentinian friends in Aalborg, who were truly friends for me during all this time. In particular, I want to thank Jose and Marta for treating me like part of their family. I would also like to express my deeply grateful and appreciation to my family for supporting me in all my new initiatives. They were always encouraging me with their best wishes. I would like to thank my girlfriend Silvana, who was always there cheering me up and stood by me despite the distance.

Thanks to all who directly or indirectly contributed to make this experience possible.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| **BB** | **Biceps Brachii** |
| CoP | Centre of pressure |
| CPD | Centroid position difference |
| CV | Coefficient of variation |
| ECRB | Extensor Carpi Radialis Brevis |
| EMG | Electromyography |
| HD-EMG | High density electromyography |
| MU | Motor unit |
| NGF | Nerve growth factor |
| SD | Standard deviation |
| SampEn | Sample Entropy |
| VAS | Visual analogue scale |

# CHAPTER 1. INTRODUCTION

Pain alters the motor pattern used to achieve a motor task. Under the effects of pain, patients change the way in which they perform a motor task, reflecting adaptive or protective mechanisms to avoid noxious stimulus (1). For a long time, researchers have been exploring these pain evoked motor adaptations, assessing behavioural changes in the strategies to perform a motor task (2–6). Since pathological settings can be associated with diverse processes that result in the final dysfunction of the system, the influence of all these confounding factors interferes with the individual assessment of the pain mechanisms. In order to reduce complexity, human experimental pain models have been widely used in healthy volunteers to investigate the effect of pain on the motor control (7). The advantage of these models is that they reduce the confounding factors, because the stimulus causing pain is known, facilitating the assessment of pain effects.

Advanced tools are required to evaluate the motor adaptations during pain. Progress in medical technology has contributed to the development of such tools, enabling the quantification of alteration in the motor system when performing a painful motor task. In particular, two recent techniques have been useful to investigate the motor adaptations. First, the spatial surface electromyography (EMG) which records muscle activity over different near locations (8), reflecting global redistribution of the motor units (MU) activity. This spatiotemporal information of the myoelectric activity shows adaptations within a muscle during an isometric force task (9,10). Second, force variability in multiple directions can be assessed using high resolution three-dimensional force recordings. Several studies have highlighted the relevance of the tangential force variability in pain-free motor control experiments (11–13), and even some of them found increased force variability in isometric contractions during acute experimental muscle pain (5,14). The combination of these two techniques, spatial EMG and three-dimensional force recordings, may facilitate the identification of fine-tuned motor adaptations during acute and persistent muscle pain.

Muscle activity and force variability are altered during acute pain (5,15–17). However, most of the induced pain by acute experimental models is transient and it is unrelated to the movement of painful structures (7). Motor adaptations have showed to be complex and apparently present changes over time, although it remains unclear which features of the motor adaptations are refined when pain persists over time. When inducing delay onset muscle soreness (DOMS), an exercise-induced pain model based on eccentric contractions, force precision is briefly reduced after contractions while movement-evoked pain is persistent over days (18,19), reflecting that motor adaptations due to pain may change over time. However, the major disadvantage of DOMS model is that muscle fibres are

damaged after eccentric exercises, and this effect may have an impact on the motor adaptations (20).

One possibility to induce persistent pain without affecting the contractile properties of the muscle fibres is to use intramuscular injection of nerve growth factor (NGF). NGF does not induce spontaneous pain, but elicits soreness and movement-evoked pain for several days (21–23). Intramuscular administration of NGF can provide additional information about the effects of pain in chronic settings, and therefore can potentially clarify the mechanisms present in the transition from acute to chronic pain.

## 1.1. AIMS OF THE PH.D. PROJECT

The aim of the present Ph.D. project was to investigate motor adaptations induced by experimental muscle pain, assessing spatial distribution of the muscle activity and three-dimensional force variability during isometric motor tasks.

The three main research questions addressed in this project were:

1. How is the relation between spatial EMG activity and force output during a contraction in pain-free condition?

2. How is the motor control altered during experimental acute muscle pain?

3. How are the motor adaptations changed over time during a persistent muscle pain stimulus?

This Ph.D. thesis is based on 3 peer-reviewed articles.

S1- **Mista, CA**; Salomoni, SE; Graven-Nielsen, T. Spatial reorganisation of muscle activity correlates with change in tangential force variability during isometric contractions. Journal of electromyography and kinesiology. 2014 24(1) pp37-45.

S2- **Mista, CA**; Christensen, SW; Graven-Nielsen, T. Modulation of motor variability related to experimental muscle pain during elbow-flexion contractions. Human Movement Science. 2014. 2015 39(1) pp222–235.

S3- **Mista, CA**; Bergin, M; Hirata, R; Christensen, SW; Tucker, K; Hodges, P; Graven-Nielsen, T. Differential effects of prolonged movement-evoked pain and acute muscle pain on the force control strategy during isometric contractions. Journal of Pain. Submitted.

## 1.2. DISSERTATION OUTLINE

The research question about the relationship between myoelectric activity and three-dimensional force variability is addressed in the S1, S2, and S3. The effects of experimental acute muscle pain on the motor control is explored in the S2. Alteration of motor adaptations during persistent movement-evoked muscle pain and acute pain were assessed in the S3. Figure 1.1 summarizes the overall connection between the studies.

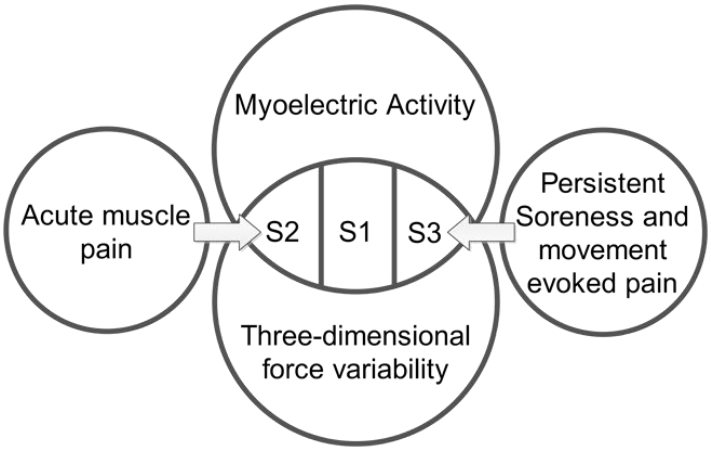


*Figure 1.1- Dissertation outline*

# CHAPTER 2. FORCE AND EMG

## 2.1. FORCE RECORDING

Force is the primary outcome of the contraction of a single or several muscles. When performing a voluntary contraction, the pattern of muscle activation is commanded and coordinated by the central motor control system. Thus, force performance can be considered as a tool that facilitates an indirect assessment of the motor control system. Changes observed in force output can be depicted as modulation of the motor control, potentially related to adaptive mechanisms or decreased force performance during pain (1,5,14,24–26).

Two major indexes of the force have been widely used to describe motor performance during an isometric contraction: magnitude of the force variability and direction of the net force. The first index shows the amount of change in the force magnitude over time, also known as force variability, and the second index quantifies the resultant direction of the force, reflecting the preferred combination of tangential and task-related force used to fulfil a motor task.

### 2.1.1. FORCE VARIABILITY

Force variability is an intrinsic feature of the motor control, generally referred as noise component of the force (27). Schmidt et al. (1979) showed a direct relationship between movement speed and force variability, i.e., increasing movement speed results in increasing force variability. In addition, the force variability presents a linear relationship with the force level in isometric motor tasks (27–29). Comparison of the force variability between different motor tasks can be challenging, since several factors may influence the force variability, including structure of the muscle (27), force feedback information (30–33), subject age (34), among others.

The force variability can be quantified by linear and nonlinear methods. Linear indexes show the “size” of the variability generally (amount of variability), whereas nonlinear indexes reflect the “regularity/complexity” (structure of the variability). Among linear indexes, standard deviation (SD) (S2, S3), which has a linear relation with the mean force, and coefficient of variation (CV = SD/mean force) (S1), which reflects relative variability, are the most used methods for assessing force variability due to their simplicity. Changes of SD and CV of the task-related force across level of contractions are exemplified in figure 2.1a-b.

The force in tangential directions frequently presents mean values close to zero in tangential force directions, resulting in high CV indexes. Hence, in all studies (S1,

S2, S3), tangential force variability was assessed using the total excursion of the centre of pressure (CoP) (5,25). The excursion of the CoP quantifies lateral shifts of the quasi-static net force, which reflects the total length of the CoP path in a given time period (35) and represents an indirect quantity of the tangential force variability (5,25,36) (Fig. 2.1c). In addition, a nonlinear index, sample entropy (SampEn) was included to quantify structure of the force variability (S2) (Fig. 2.1d). SampEn has been a relevant tool for assessing the complexity of the force variability (37–39).

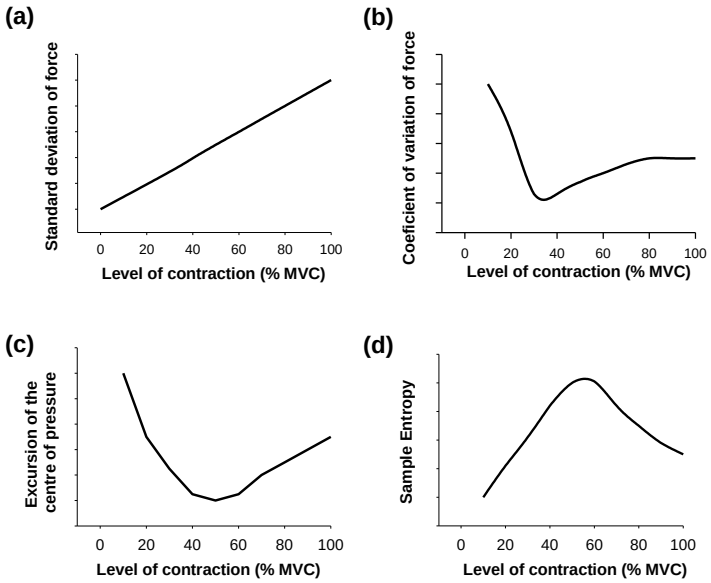


*Figure 2.1- Illustration of (a) standard deviation, (b) coefficient of variation of task-related force, (c) total excursion of the centre of pressure of tangential forces, (d) sample entropy of the task-related force across level of contractions (% MVC).*

## 2.1.2. NET FORCE DIRECTION

The force direction results from individual contribution of multiple muscles combined to produce a net force. Altered force directions imply changes of the muscle coordination or increase/decrease activity of one particular muscle (26). Modulation of force direction has been quantified generally by mean of tangential angles (5,26). In S2, and S3, a new index is proposed to assess force direction based on a two-dimensional histogram of the tangential force components. The histograms were developed using a 5-by-5, equally-spaced grid to represent the range of the force in the Fy and Fx direction. The coordinates of the centroid

position were calculated at baseline, and subtracted from follow-up trials. The absolute difference was calculated in Fy and Fx directions and referred as centroid position difference (CPDy and CPDx, respectively). A CPD value deviating from zero reflects changes in the combination of tangential forces and thereby a new direction of the net force in the tangential plane between two conditions (Fig. 2.2).

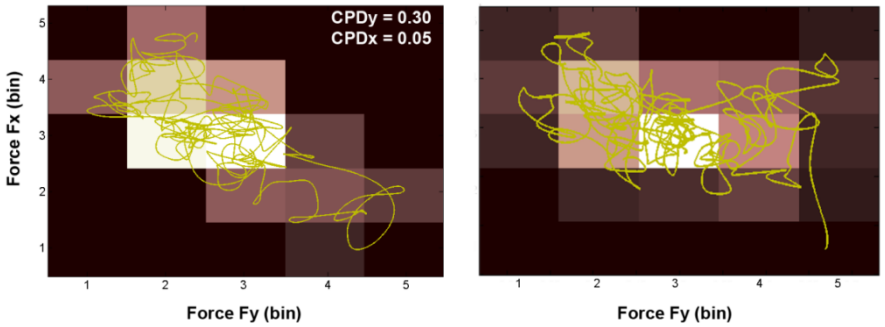


*Figure 2.2- Representative two-dimensional histograms of the tangential forces (Fx-Fy) between two trials. Each histogram is a 5-by-5, equally-spaced grid to represent the range of the force in the Fy and Fx direction. The absolute differences between the centroids of the histograms are subtracted for each force direction, and refer as Centroid Position Difference (CPDx and CPDy).*

## 2.2. MYOELECTRIC ACTIVITY

The EMG activity is recorded using two techniques: intramuscular and surface. Intramuscular EMG is an invasive technique, which requires the insertion of needle electrodes into the muscle. Not only potential risks of infection are present using this technique, but also only few motor units are recorded (40). In contrast, surface EMG, which is a non-invasive technique, quantify the integrated global activity of motor unit populations (41) although this method is prone to present noise contamination and crosstalk (42). Surface EMG was used in all the studies (S1, S2, S3).

Bipolar surface EMG signals were collected from relevant muscles during elbow flexion (S1, S2) and wrist extension (S3). In addition to bipolar recordings, spatial information of the EMG activity was quantified by recording activity from multiple near locations over the main muscle involved in motor task (S1, S2, S3). This method is usually known as High Density EMG (HD-EMG) and assessed the spatiotemporal information of muscle activity, evidencing reorganization within a muscle over time during isometric motor task (43–46).

## 2.3. EXPERIMENTAL SETUP

An advanced experimental setup was developed in order to record force and EMG signals from isometric elbow flexion (S1, S2) and wrist extension (S3). The setup combines high resolution force recordings (3 force directions and 3 torques) with surface HD-EMG from primary muscles and surface bipolar EMG from relevant auxiliary muscles (Fig. 2.3).

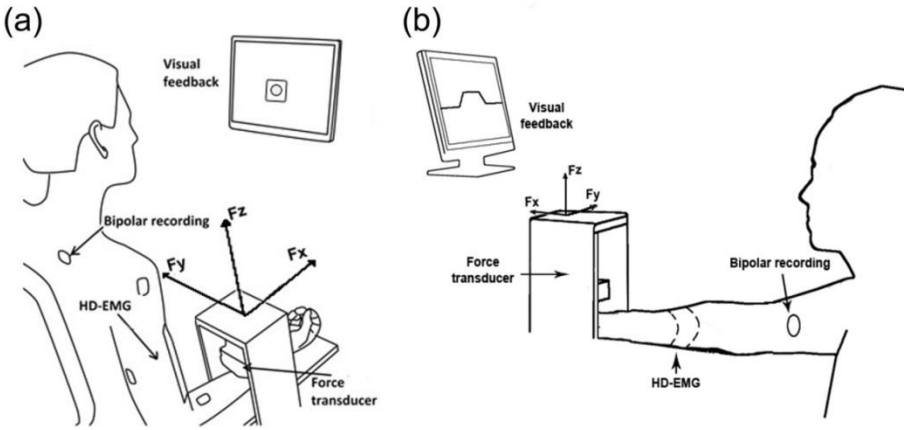


*Figure 2.3- Schematic description of the experimental setup. Isometric forces and torques are recorded using a six-axis force transducer from (a) elbow flexion [S1, S2] and (b) wrist extension [S3]. In (a), a grid of surface electrodes is placed on muscle biceps brachii and bipolar EMG electrodes on triceps brachii, deltoid, trapezius medialis, and brachioradialis muscle. In (b), grid of surface electrodes are placed on the extensor carpi radialis brevis and bipolar EMG electrodes on flexor carpi radialis, and biceps brachii muscle.*

Visual feedback of the force plays a key role in motor control performance during isometric force tasks (30,47). In the present work, real-time force visual feedback was provided to subjects when performing the isometric contractions. Two types of visual feedback were used: in S1 and S2, visual feedback showed real-time force in all directions at the same time; in S3, task-related force was represented on an oscilloscope screen. Feedback of all force directions increased the force restriction in more than one direction (details in section 3).

## 2.4. LINK BETWEEN FORCE VARIABILITY AND EMG

The relationship between the force output and the EMG activity during isometric contractions has been investigated applying linear correlation (48). This method is the most used due to their simplicity, but shows unsatisfactory performance when comparing force and EMG in steady contractions (48–50). As an alternative, non-linear approaches can be used to describe the relation between the signals. In S1, an

advanced technique was proposed to compare the force variability and the EMG, by analysing the signals from perspective of information theory. The technique is referred as Normalised Mutual Information (NMI) and is gaining more popularity due to its flexibility. NMI quantifies the inherent dependence between two signals whereas the conventional linear correlation is based on linear dependences (51). Some reports describes NMI as a suitable method when the relationship between signals is complex (51), as in the case of muscle activity and force variability.

Steady forces are originated by summation of the contribution of multiple muscles acting in one direction, although the individual contribution of each muscle fibre to the force variability remains unclear (52). During sustained contractions, the primary, antagonist, and stabiliser muscles increased their activity monotonically in order to maintain the same force output (S1). NMI showed that the information between muscles (primary and auxiliary) and task-related force were globally decreased (about 10%) after 24 s compared with the first seconds of the steady contractions. These results reflect that force variability is affected by the summation of additional auxiliary muscles when contractions are prolonged over time (Fig. 2.4).

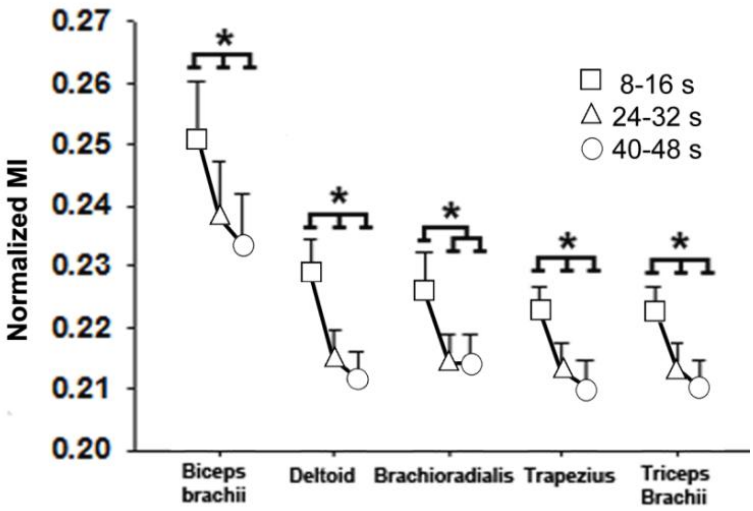


*Figure 2.4- Mean (±SEM, N=14) NMI between task-related force and EMG signals for different epochs (8-16, 24-32, 40-48 s) during sustained isometric elbow flexion. Information between relevant muscles and force variability present a global decreased during prolonged steady contractions (* P<0.05). New analysis based on data from S1.*

The information between force variability-EMG was heterogeneously distributed over different parts of the muscle during the sustained contractions, quantified by heterogeneous NMI maps. This is in accordance with previous studies that showed

localized activation of the muscle in confined regions depending on the motor task performed (49,53).

The root-mean-square (RMS) EMG amplitude and the NMI centroids position showed different excursion over the sustained contractions. In other words, the NMI centroids (that represent the distribution of the information) diverged from the excursion of the muscle activity centroid. This finding showed that muscle adaptations not necessarily affect force variability during prolonged contractions, as increased activity of some muscle fibres may not impact on the force variation (Fig. 2.5). There are several explanations for the difference between the centroid excursions. One possibility is that muscle coactivation could compensate for muscles contributing to unwanted directions without affecting the force variability (54). Localized effects of muscle fatigue could also change the EMG signals in different regions (45), affecting the relationship between EMG-force. Another possibility is that slight changes in the direction of the net force occur during the sustained contractions, and may result in recruitment of new motor units (26).

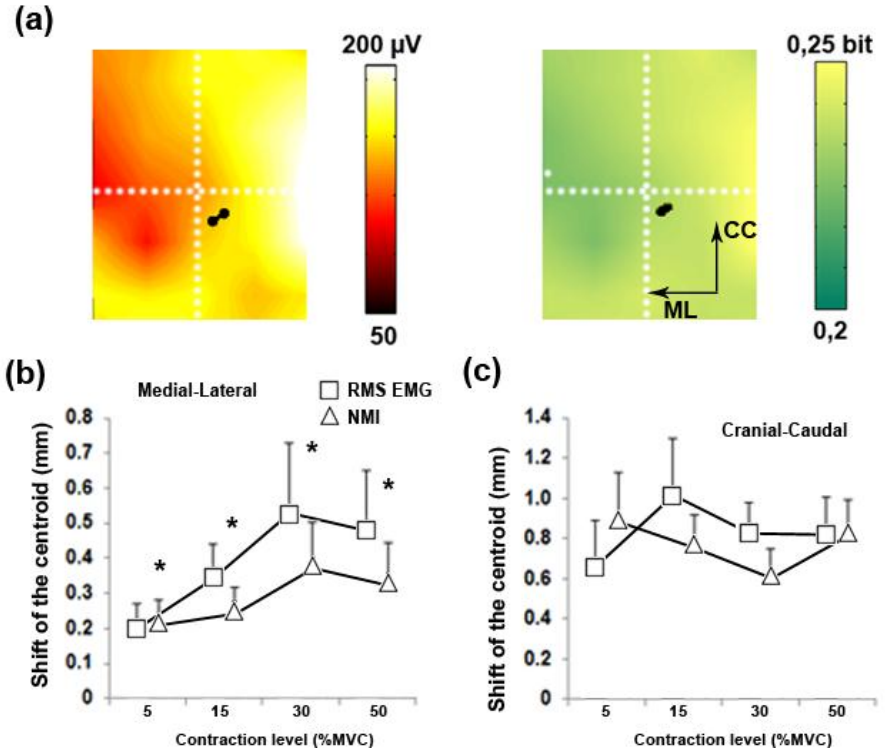


*Figure 2.5- Excursion of the centre of gravity of RMS EMG and NMI force-EMG maps based on data from S1. (a) Example of RMS EMG (red-yellow) and NMI task-related force (green-yellow) in the last period of the sustained contraction. The shifts of the centroid position across time are indicated by black circle and the difference between circles marked by a black line. (b) Distance between centroids (Mean ±SEM, N=14) in the medial-lateral (ML) and (c) in the cranial-caudal (CC) direction. RMS EMG centroid show greater centroids shift compared with the NMI centroids, implying that increased in muscle activity is not link with changes in force variability in sustained contractions (* P<0.05).*

Increased muscle activity from auxiliary muscle concurred with greater tangential force variability at 30% of the maximal voluntary contraction (MVC), without significant changes in the primary mover activity (S1). As aforementioned, auxiliary muscle activity likely accounts for the tangential force variability (55,56). Co-activation of auxiliary muscle may also counteract internal forces protecting the joint from potential damage (54).

The results from study S1 show that the investigation of the physiological mechanisms that control the force steadiness can be challenging in tasks involving multiple muscles, and even more complex when the contractions are sustained for long periods. The difference between muscle activation and its contribution to the

task-related force variability plays a main role in the modulation of the tangential force variability. The divergence of the EMG and the NMI map centroids over time are potentially compensated by increased activity of the auxiliary muscles, and it is mainly the auxiliary muscles that account for most of the tangential force variability (55,56).

# CHAPTER 3. EXPERIMENTAL ACUTE MUSCLE PAIN

Pain is a complex phenomenon, and so is the response of the human body to pain. Plenty of evidence has shown that patients suffering from pain present difficulties to perform accurate contractions (24,57,58). The functional limitation of pain is unquestionable, yet the assessment of the pain mechanisms is still complex in pathological conditions. Musculoskeletal pain has been linked to diverse processes resulting in the motor dysfunction. Several experimental pain models have emerged to mimic pain conditions in healthy volunteers, reducing the intervening factors and facilitating the study of pain mechanisms (7,59). Existing pain models use several techniques to induce pain, including mechanical painful stimulation (60,61), exercise-induced muscle pain (62–65), or intramuscular injection of algesic substances (S2,S3,7,66–68). Among the algesic substances, hypertonic saline is a widely used model to elicit muscle pain. The saline-induced pain model causes a robust excitation of group III and IV afferent fibres to evoked pain (59), and last for around 8-12 minutes with quality similar to the pain reported by acute pain patients (7).

## 3.1. IMPACT OF EXPERIMENTAL ACUTE PAIN ON THE FORCE

Saline-induced muscle pain has been widely used to study pain adaptations in movement during acute pain. Previous studies assessed the impact of pain on the motor control specifically during isometric motor tasks. For instance, saline-induced muscle pain in the biceps brachii muscle resulted in increased variability in isometric elbow flexion compared with pain-free trials (S2,5,69). Likewise, increased force variability during pain has been observed in different isometric motor tasks, including shoulder abduction (14), wrist extension (S2,3), dorsiflexion and plantar flexion (5). Several mechanisms may explain changes in force variability during nociceptive stimulation, some of which are associated with the neural drive, as for example motor unit synchronicity (65,69) and increased variability of the common drive (70). In addition to the altered neural drive, experimental muscle pain has been shown to interfere with the processing of the proprioceptive information (71). It has been showed that muscle spindle afferent increased their fire rate variability, disrupting the relationship between muscle length and afferent output during pain (72). Experimental acute muscle pain on the lower limb (tibialis anterior and soleus muscle) disturbs the process of proprioception information from the ankle joint only during high pain, although sensibility might change from joint to joint (73).

All the aforementioned pain effects contribute to reduce the force control. The motor system needs to counteract these alterations in order to achieve a required motor task by changing the motor strategy, minimizing the force error and the force variability. In this regard, the available information (visual and proprioceptive feedback loops) plays a critical role in the force control, allowing subjects to adjust the amplitude of their movement (74). Lack of pain effects has been observed using high precision visual feedbacks in different motor tasks (16,75). Likewise, the inclusion of tangential force directions (three-dimensional force feedback) in the visual feedback improved the motor performance (S2). Subjects were forced to correct the force output in all directions restricting the movement, and resulting in lack of pain effects on the force output (Fig. 3.1a-b). Not only the SD and complexity of the task-related force was unaffected by pain, but also the CoP of the tangential forces during the motor task (Fig. 3.1b). In contrast, a less restrictive motor task (visual feedback of only the task-related force) leads to changes in the force variability in elbow flexion (S2) and wrist extension (S3) (Fig. 3.1a-c and Fig. 3.2a,c). In accordance with these results, the inclusion of the tangential force information shown to be an alternative source of information to overcome the nociceptive effects on the force variability, since subjects could voluntary adjust their motor strategy.

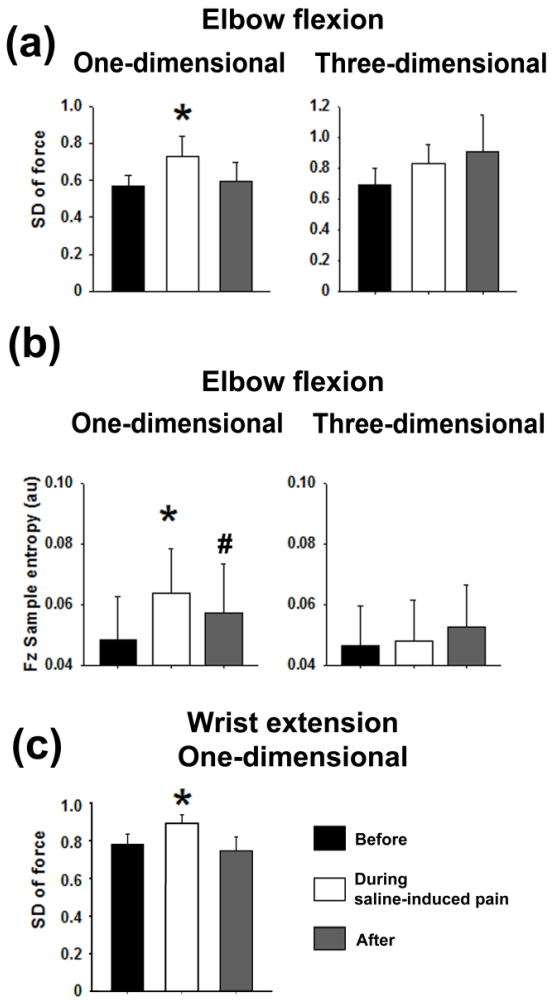


*Figure 3.1- (a) Mean (±SEM, N = 12) standard deviation of task-related force averaged across the level of contractions at baseline, during and after saline-induced muscle pain in biceps brachii [S2]. (b) Mean (±SEM, N = 12) sample entropy of task-related force averaged across the level of contractions at baseline, during and after saline-induced muscle pain [S2]. (c) Mean (±SEM, N = 26) standard deviation of wrist extension at 10% MVC before, during, and after saline induced muscle pain in the extensor carpi radialis brevis (ECRB) [S3]. Significantly higher compared with baseline and post pain trials (*, NK: $P < .05$). Significantly higher compared with baseline trial (#, NK: $P < .05$).*

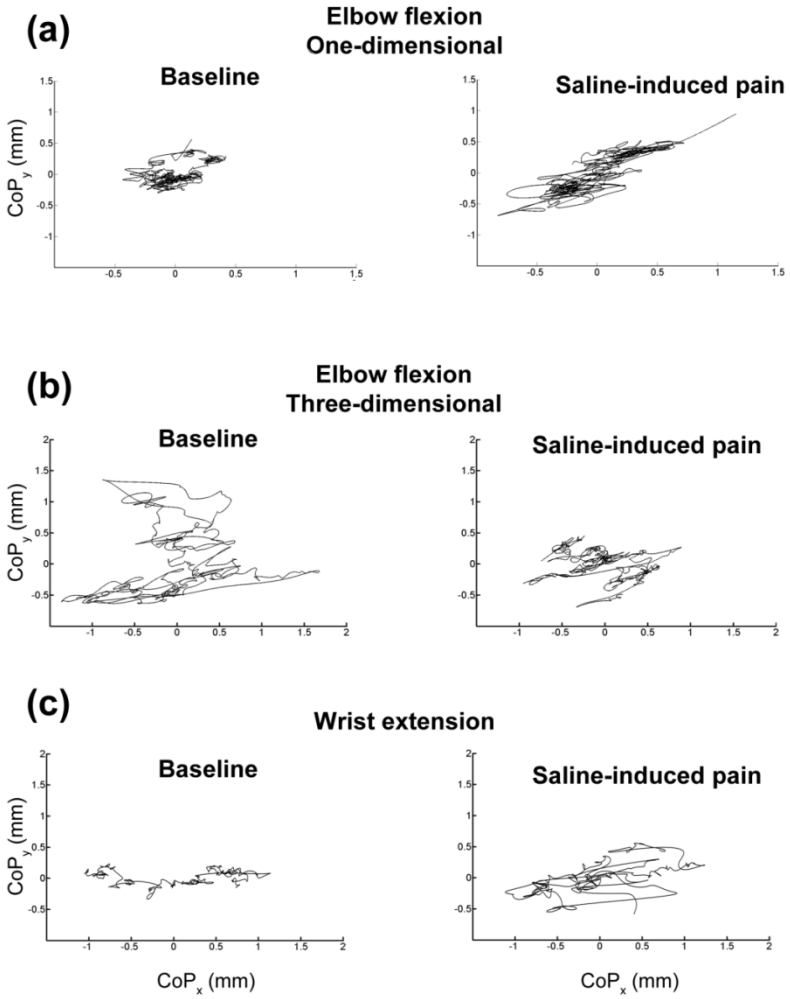


*Figure 3.2- Representative example of excursion of the CoP of tangential forces before and during saline-induced pain in (a,b) elbow flexion [S2] and (c) wrist extension [S3]. The 'x' and 'y' subscripts represent the anterior-posterior and medial-lateral force direction, respectively. During elbow flexion using the one-dimensional feedback, total excursion of the CoP was increased compared with the baseline. CoP was increased in wrist extension during pain compare with the baseline.*

In addition to the altered force variability, changes in the net force direction during matched isometric knee extension has been found during saline-induced infrapatellar fat pad pain (26). This modulation on the force direction has been associated with changes of MU recruitment strategy when performing a painful task (26,76). Changing the MU recruitment strategy contributes to the redistribution of

the load within and between muscles, diminishing pain during the motor tasks and preventing further damage of the painful area (1).

In S2 and S3 the combination of tangential forces were quantified by introducing a new index: the centroid position difference (CPD). This index measures the degree of rearrangement of tangential forces when performing a force task (contrasted with a reference trial), reflecting changes of the direction of the net force on the tangential plane. The CPD index shows degree of change between two conditions, without assuming the direction of the changes. This feature is useful to analyse pain effects, since variable patterns of adaptation are generally found between subjects and tasks during pain (5,24,77). The heterogeneous responses are likely associated with the changes at multiple sites of the motor pathway (1). Therefore, some indexes may not be able to discriminate motor changes due to the variability of the motor adaptations, and it may be inaccurate to attribute stereotype effects of pain on the motor system (1,78).

During painful elbow flexion, increased CPD values were found in the less restrictive task (one-dimensional) during pain compared with post-pain condition, whereas there were no significant changes when including the tangential forces in the visual feedback (S2). These results showed that voluntary adjustment of the combination of tangential force depends on the information available when performing a motor task (Fig.3.3). In addition, CPD showed to be greater when inducing experimental acute pain in the ECRB muscle with/without pre-sensitized using intramuscular NGF injections (in detail in chapter 4) compared with before and after saline-induced pain (S3). In general, it is assumed that the motor system employs the optimal strategy (in terms of metabolic cost) to perform a motor task (78). Therefore, even though departure from the painless strategy may be inefficient and have potential detrimental consequences in the long-term (overloading scenarios) (1), the motor system seems to prioritize the reduction of pain and damage in the short-term in most of the cases.

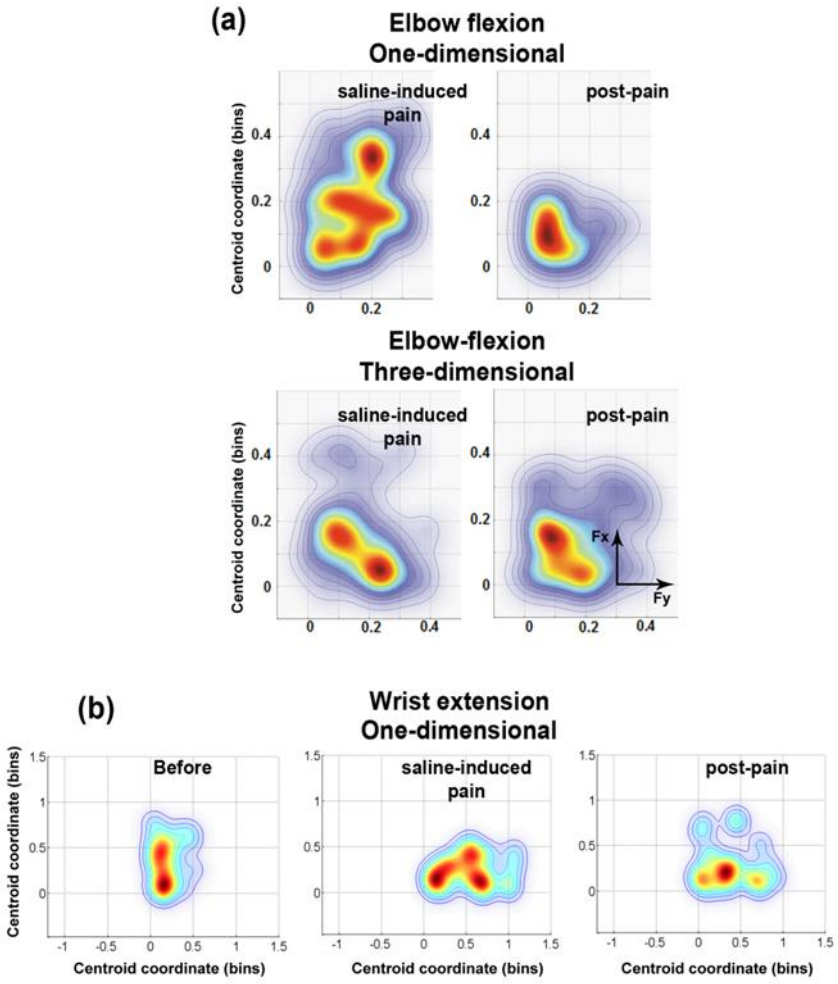


*Figure 3.3- Distribution of the CPD of the tangential force (bins) across subjects during saline-induced muscle pain in (a) elbow flexion and (b) wrist extension. In (a), real-time visual feedback of the task related force (one-dimensional) was provided to the subjects when executing the motor task, whereas task-related and tangential force were displayed in the three-dimensional task. Increased CPD were found in the elbow flexion during the less restrictive motor task ($P < 0.01$). In (b), before trial was calculated by contrasting baseline day-0 and baseline day-2 (before saline-induced pain). Greater CPD values were found during saline-induced pain compared with before and post-pain ($P < 0.001$). The results reflect changes in the combination of tangential forces (changing the direction of the net force) when performing a motor task during saline-induced pain.*

## 3.2. MUSCLE ACTIVITY AND ADAPTATIONS TO PAIN

Muscle activity is increased or decreased within and between muscles during painful submaximal contractions (2,6,9,10,15). Altered muscle activity due to pain results in redistribution of the load across muscles and joints, serving as a protective mechanism in the short time against further pain and tissue damage (1,78). Moreover, decreased voluntary MVC has been found during pain, without changes in the conduction membrane properties or neuromuscular transmission, suggesting a strong central inhibition (42,79,80). In fact, excitability of both cortical and spinal motoneuron is reduced during saline-induced muscle pain (81).

### 3.2.1. SPATIAL DISTRIBUTION OF MUSCLE ACTIVITY DURING PAIN

In study S2 and S3, saline-induced muscle pain was induced in the muscle biceps brachii (BB) and in the muscle extensor carpi radialis brevis (ECRB), respectively. The pattern of the BB and ECRB muscle activity was not significantly affected by the experimental muscle pain (Fig. 3.4), contrasting with previous findings in muscle trapezius (9,10). Using surface and intramuscular EMG, it was suggested that redistribution of the activity within a muscle caused by pain might not be a generalized strategy of the motor system for all muscles (82), and different neuromuscular mechanisms could explain these discrepant results. First, the population of active motor units could be altered during muscle pain without significant impact on the surface EMG (76). Second, high inter-subject variability could hinder the identification of stereotypical patterns for some muscles, since all subjects may change motor pattern but not all in the same direction. This could be associated with the changes in multiples levels along the motor pathway (1). Therefore, the study of spatial reorganization within a muscle requires advanced algorithms that take into account the variable response found between subjects.

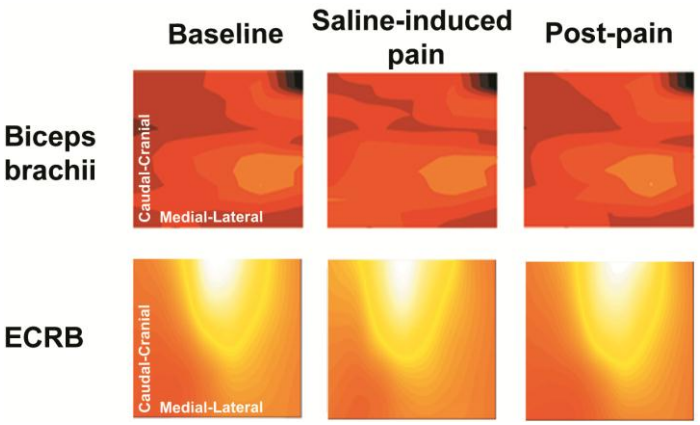


*Figure 3.4- Representative example of the RMS EMG maps obtained from the muscle biceps brachii [S2] and muscle extensor carpi radialis brevis, at baseline, during and post saline-induced muscle pain by hypertonic saline.*

### 3.2.2. ACCESSORY MUSCLE ACTIVITY DURING PAIN

Accessory muscles have been shown to play a key role during a pain-free motor task. These muscles increased their activity without contributing to the external torques in sustained contractions (S1,54,83). This increased activity could be aimed to balance relative contribution of muscles that acts on unwanted directions (83), or it may counteract internal forces and protect the joint from unbalanced forces and potential damage (54).

The pain adaptation theory predicts a decreased activity of the muscles associated with painful voluntary movement, whereas antagonist muscles increase their activity (84). A certain number of experimental results supports this theory (2,6), but others findings are contradictory with these principles. For instance, pain adaptations are less pronounced or even not detected when high precision motor task are required (S2,4,16,75), and lack of relaxation is found in acute low-back pain during full forward-bending (85). A recent theory, supported by clinical and experimental results, proposes that pain adaptations are non-stereotyped responses (1). This theory predicts a high variability in the response to pain observed between subjects and tasks, and suggests that the motor changes have short-term benefits, although these changes may have potential negative consequences in the long-term due to sustained redistribution and increment of loads across structures.

Altered neuromuscular control can be described quantifying the complexity of the EMG signals (Sample Entropy [SampEn]). The SampEn index provides information about dynamic changes of the signal. Increased complexity of EMG from triceps and deltoid muscles has been found during saline-induced pain in the

BB muscle, when performing isometric submaximal elbow-flexion. The increased complexity was close to 6% but only during the visual feedback that provided information of the tangential forces (S2), suggesting that altered neuromuscular control during acute experimental pain depends on the requirements of the task. Increased complexity has been also found in painful condition such as patellofemoral pain (86) and low-back pain (87).

Altered muscle activity during pain has been generally described as a protective mechanism in the short-term (1). Nevertheless, increased activity of trapezius muscle observed during saline-induced pain in BB muscle (S2), does not present any mechanical or metabolic advantage (15,88). This increased muscle activity was independent of the constraints of the required motor task, so this adaptation seems to not be connected with elbow flexion force control (S2), and most likely aimed at reducing shoulder movements and protecting the joint from further injuries (1). Increased muscle activity as a mechanism to reduced movement was found in recurrent low-back pain patients, increasing the trunk muscle activity, limiting the range of motion and increasing the stability of the spine (1,89). However, increasing the muscle activity may result in a situation in which the load is increased across non-painful structures of the motor system for long periods of time causing further problems in the future (1,17).

# CHAPTER 4. SUSTAINED SORENESS AND PERSISTENT MUSCLE PAIN

Musculoskeletal pain is associated with multiple adaptions in movement control. The motor adaptations are complex and presumably present changes over time (90). Most of the pain models have transient pain and are inconsistently affected by movement, consequently the study of the motor adaptations are confined by the transience of the induced pain (7,91). How the motor adaptation evolved during persistent pain has received little attention, mainly due to the lack of suitable persistent pain models. There are clear differences in motor control when comparing chronic pain patients to acute pain conditions or experimental acute pain. For instance, patients suffering subacromial impingement syndrome have shown reduced force steadiness during concentric contractions (24), whereas the force steadiness was unaffected when inducing experimental shoulder pain in healthy subjects (14). Therefore, the study of the motor adaptation during persistent pain is crucial to understand the changes observed during the transition from acute to chronic pain conditions.

One possibility to induced soreness and persistent movement-evoked pain is based on repetitive active lengthening of the muscle (7,92). The soreness and pain have been associated with ultrastructural damage of muscle fibres after the eccentric exercises (93). The mechanisms behind the movement-evoked pain after eccentric exercise remain unclear, although algesic agents including nerve growth factor (NGF) are released, and these agents may account for the soreness and movement-evoked pain (94). As an alternative, recent studies used intramuscular injection of nerve growth factor (NGF) to induce movement-evoked pain for several days (21,23,91,95). The advantage of the NGF model is that pain duration is persistent and pain is evoked during movement, contraction, and stretch of the injected muscle without damaging the muscle fibres (21,91). Healthy subjects receiving intramuscular injection of NGF reported movement-evoked pain that peaked 48-72 hours after injection and lasted for almost 10 days (91,95), which facilitates the exploration of the time-course of motor adaptations.

## 4.1. IMPACT OF PERSISTENT PAIN ON MOTOR CONTROL

The effects of persistent movement-evoked pain (NGF) on the motor control were addressed for the first time in S3. In contrast with acute experimental pain, force steadiness and MVC was not significantly affected by intramuscular administration of NGF across sessions (Fig. 4.1). Similar results has been observed when inducing DOMS by eccentric exercises (19,34,96), although MVC remained reduced 24-48 hs after the eccentric exercises (61,97). The inconsistency between NGF and

DOMS could be related to dissimilar mechanisms behind each model. Exercise-induced soreness has been associated with ultrastructural damage of the muscle fibre and release of algesic substance, while NGF directly excites/sensitizes the nociceptive afferents (98).

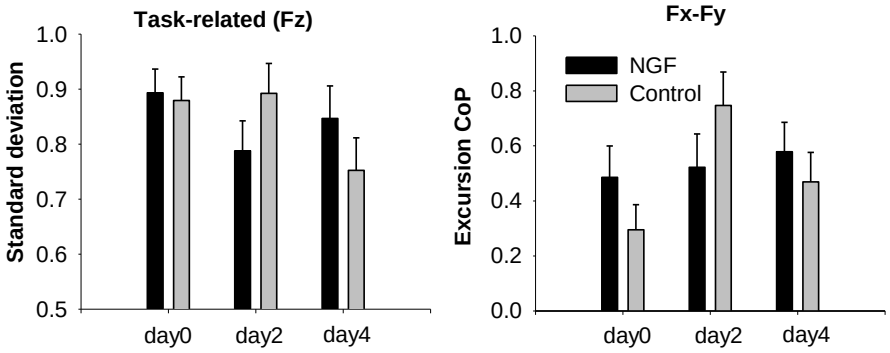


*Figure 4.1- Normalized mean (±SEM, N=13) standard deviation (SD) of task–related force and total excursion of the centre of pressure for tangential forces (CoP) during persistent movement-evoked pain.*

Interestingly, subjects injected with NGF changed the direction of the net force in the tangential plane (revealed by higher values of CPD) when performing the motor task after 2 and 4 days of persistent movement-evoked pain (Fig 4.2) (S3). In other words, participants who received NGF continued to display protective behaviours even when persistent pain decreased significantly. There are several reasons to explain this phenomenon. One possibility is that solely the anticipation to experience pain could sustain the protective adaptations for longer periods of time (99), or this could be related to the fact that pain cessation not necessarily represents a starting point of return to the painless pattern (1,77). Alternatively, this could be interpreted as part of different elements of learning a motor strategy from the contemporary motor control prospective, explained in details in the following section.

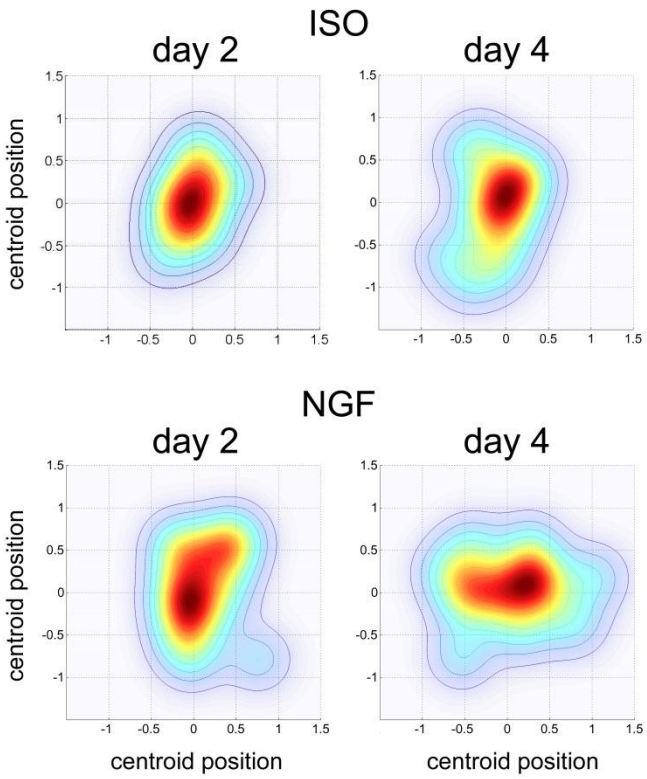


*Figure 4.2- Normalized CPD distribution of tangential forces (Fx and Fy) across participants during isometric wrist extension at day 2 (before saline-induced pain) and day 4. CPD values reflect changes in the combination of tangential forces between two conditions. Greater CPD values show changes in the tangential forces and consequently different direction of the net force in the tangential plane. NGF group showed greater CPD values compared with the control group (ISO) across days in the Fy direction (P<0.05). NGF group gradually deviate from the painless motor strategy across days.*

### 4.1.1. SEARCH AND CONSOLIDATION OF A NEW MOTOR STRATEGY DURING PAIN

Adapt to changes is an essential characteristic of the motor control. The central nervous system used internal representations of the body dynamics in order to achieve accurate movements, and these representations required to be continuously updated to new conditions (100). Under influence of pain, the motor system needs to refine the motor strategy in order to find the safest alternative to perform a movement (1,101). Acute muscle pain, as showed in BB (2) and ECRB (S3), increased the variability and changes the direction of the net force, whereas persistent pain, induced by injection of NGF in ECRB (S3), involved force in a new

tangential direction without affecting the force variability. These findings likely denote a search and then resolution to a new, potentially more beneficial solution.

The role of force variability in isometric contraction during muscle pain has been fairly controversial. Increased force variability may have different interpretations depending on the direction of the force. In the tangential force direction, the force variability could represents a search for less painful/threatening directions, protecting the painful structures in the acute phase of pain (1). In the task-related force direction, increased force variability is not likely to represents a search for a new strategy (as the aim is to maintain a constant level of force). Instead, it can be interpreted as a failure to reproduce the pain-free pattern, related to the purposeful variability in the tangential force direction or result from pain secondary to distraction (102), decreased proprioception (71), or altered synchronization/recruitment of different population of motor units (76,103,104).

The execution of a motor task depends on different processes including perception and cognition (105). Saline-induced pain induced large areas of pain disrupting the proprioceptive acuity (73), and causing force changes that are compensated when increasing the visual feedback information (S2). Thus, the exploration for a new motor strategy seems to be discontinued when imposing high restrictions to the contraction.

Time-course of saline-induced pain provided insufficient time to consolidate a motor adaptation, since the painless pattern is restore short time after pain cessation (S2, S3). In this regard, the search and consolidation of the motor strategy require some processing time. Spatial extent of cortical activation are increased in healthy subjects when learning an untrained motor task over the course of weeks (106) and then decreases with further training. Learn and consolidate a new strategy to achieve a painful motor task might require training time.

The consolidation of a motor strategy implies acquiring a novel or modifying a well-established motor strategy (107). The learning of a motor strategy involves supplementary motor cortical areas (associated with the programing of the motor sequences). These areas may be associated with the first stages of the persistent pain, rather than the primary motor cortex (connected to the execution of the motor tasks) (108). The involvement of supplementary motor cortical areas may explain why reduced function of the arm is observed after 2 days of movement-evoked pain (induced by NGF (S3)), but 2 days before any reorganization of the primary motor cortex - reported using NGF as persistent pain model (109). Thus, the major changes at the beginning of persistent pain might be related to cognitive process of searching and consolidating a motor adaptation.

It is worth mentioning that some aspects of pain, such as stress or fear, may change the motor behaviour (110). The resolution of pain not necessary imply a returning

point to the pain-free motor strategy (77). Moreover, saline-induced muscle pain superimposed in a pre-sensitized muscle (induced by NGF) results in a new search for a beneficial motor strategy (S3), observed by increased force variability and altered tangential force combinations. In other words, a change in the nociceptive input results in a new search for a motor adaptation independently of the previous status of the system.

# CHAPTER 5. CONCLUSIONS

The results from study S1 showed that the relation between the spatial muscle activity and the force output is complex in motor tasks involving multiple muscles, and becomes increasingly complicate when the contraction time is extended. Auxiliary muscle activity played a key role in all the studies, and in particular in the motor adaptations to acute and persistent pain. Neither acute nor persistent pain altered the spatial activity of the arm muscles (BB or ECRB) during isometric contractions.

Unquestionably, pain represents a major adversity to the motor system. In studies S2 and S3, acute experimental pain increased the force variability (task-related and tangential), although pain effects were not found under high restrictive contractions in study S2, reflecting that pain adaptations are task-dependent. Increased force variability could aim at searching for the most beneficial/ less threatening motor pattern when conditions are changing, such as in case of muscle pain. Acute pain resulted in variability and changes the direction of the net force (S2, S3), whereas persistent pain, involved force in a new tangential direction without affecting the force variability. These results imply an initial search of the motor strategy, which is succeeded by a consolidation of a new motor strategy during persistent pain.

Overall, the results showed the relevance of assessing the tangential force components, since minor changes of the net force direction result in redistribution across muscle and joints. This is in accordance with the current pain adaptation theories, which established that changes in the loads across structures may be beneficial in the short-term, but could have detrimental consequence in the long-term - due to scenarios where non-painful structures are overloaded.

The study of motor adaptations during acute and in particular persistent pain may facilitate the motor changes observed when translating from acute pain to chronic pain conditions. The benefits of training based on correcting the force variability or the force direction targeting at supraspinal level requires more investigation, and negative aspects such as overloading non-painful structures should be carefully considered.

# TABLE SUMMARY

| Table 1. Overview on the relationship between force and superficial EMG in humans | | | |
|---|---|---|---|
| **Reference** | **Motor task** | **Parameter** | **Main finding** |
| Falla and Farina (2007) | Shoulder elevation task at 20% MVC during 6 min, and another trial of the same task interrupted every 30 s increasing the force at 25% MVC. | Coordinates of the centroid of the EMG root mean square map from trapezius muscle. | Periodic increase in force contributes to larger spatial muscle activity reorganization and reduced fatigue compared to constant contractions. |
| Falletin et al (1993) | Isometric endurance elbow flexion at 10% and 40% of the MVC. | Endurance time.<br>Number of motor unit spikes. | Central nervous system uses different MU recruitment strategies for low and high level static contractions. |
| Farina at al. (2008) | Abduct both arm at 90 degree with elbw fully extended | Coordinates of the centre of gravity of the root mean square and median frequency EMG maps.<br>Entropy of the EMG maps. | Spatial reorganization of the activity maps are correlated to the endurance time when a static contraction is maintained. |
| Gallina et al. (2011) | Fatigue task: alternating period of 5s between 0 to 50% MVC.<br>Task: Isometric plantar flexion at the 50% of the MVC | Plantar flexion torque.<br>Spatial changes of the root mean square and the median frequency of the EMG. | Fatigue manifestations are confined to localized regions of the medial gastrocnemius muscle. |
| Hedayatpour et al. (2006) | Fatigue task: Knee extension at 40% and 80% of the MVC until exhaustion.<br>Task: Knee extension at 40% and 80% of the MVC for 2 s. | Spatial EMG average rectified value, mean power spectral frequency, and conduction velocity. | EMG variables over time depend on the location over the muscle.<br>Non-uniform recovery of electrophysical membrane properties are found within a muscle. |

| Table 1. Overview on the relationship between force and superficial EMG in humans | | | |
|---|---|---|---|
| **Reference** | **Motor task** | **Parameter** | **Main finding** |
| Holtermann et al. (2005) | Sinusoidal shape isometric elbow flexion (0-80% MVC). | Force and spatial surface EMG from biceps brachii muscle. | MUs are not randomly distributed, but present distinct regions in the biceps brachii muscle. |
| Holtermann et al. (2008) | Isometric elbow flexion at 25% of MVC until exhaustion. | Root mean square of EMG analyzed medial and laterally from biceps brachii | Dynamic sharing load between the heads of the biceps brachii, which is negatively correlated to the exhaustion time. |
| Poortvliet et al (2013) | Isometric knee extension in position-control and force-control force task. | Time endurance. EMG from vastus lateralis, vastus medialis, tensor fascia latae, biceps femoris, and semitendinosus. | Position-control task present reduced time failure compared with force-control task. Increased prime mover, proximal, and antagonistic muscle activity is found for position-control task. |
| Potvin and Brown (2003) | Isometric elbow flexion. | EMG recordings were high-pass filtered and correlated to force output. | Force estimation is maximized when removing 90 to 99% of the power spectrum. |
| Rudroff et al (2007) | Isometric endurance elbow flexion at 20% of MVC in two different posture of the arm | Time endurance.<br>EMG activity from short and long head of the biceps brachii, brachioradialis, triceps brachii, anterior and posterior head of the deltoid muscle. | Increasing EMG activity from accessory muscles is correlated to brief time to failure in sustained contractions. |

| Table 1. Overview on the relationship between force and superficial EMG in humans | | | |
|---|---|---|---|
| **Reference** | **Motor task** | **Parameter** | **Main finding** |
| Staudenmann at al. (2008) | plantar flexion, plantar flexion combined with rotation around the longitudinal axis of the leg, and plantar flexion combined with rotation around the foot at 30 % of the MVC | Spatial EMG activity decomposed using principal component analysis. Isometric force. | Coactivation in different localization of the muscle depends on the motor task. The localization presents high variability between subjects. |
| Svendsen and Madeleine (2010) | Isometric elbow flexion at 10-90 %MVC with 10 % increment for 5 s, at 5-50 %MVC (30 s ramp), and at 20%MVC until task failure. | Gender difference analysis assessing force steadiness, structure of the force, and endurance time. | Males present higher values of amount and structure of force variability compared to females. |
| Theeuwen et al (1994) | Increasing isometric forces up to 50 N in different directions. | EMG activity and force in different directions | EMG activity presents a proportional relation between the preferred direction of the muscle and the direction of the net force direction. |

| Table 2. Overview on the interaction between pain and motor control | | | | |
|---|---|---|---|---|
| **Reference** | **Pain** | **Motor task** | **Parameter** | **Main finding** |
| Bandholm et al (2008) | Saline-induced muscle pain in supraspinatus muscle. | Isometric and dynamic shoulder abduction force at 20%, 27.5%, and 35% MVC. | Force steadiness, intramuscular EMG from the supraspinatus and infraspinatus muscle, and surface EMG from middle deltoid, upper and lower trapezius, latissimus dorsi and serrtus anterior. | Shoulder-abduction force steadiness is reduced during pain.<br>Activity of middle deltoid is increased during isometric contraction and pain.<br>Activity of infraspinatus is increased during concentric contraction and pain. |
| Birch et al (2000) | Saline-induced muscle pain in the extensor carpi ulnaris muscle. | Task requiring use a computer mouse with high and low levels of precision. | Task performance variables (time, velocity, and cursor movement). Surface EMG from extensor carpi ulnaris, flexor carpi radialis, and trapezius muscle. | There is no influence of pain in the performance variables.<br>The extensor carpi ulnaris shows reduced activity during pain for the low level precision task. |
| Ervilha et al (2004) | Mild and moderate saline-induced muscle pain in the biceps brachii (0.5 ml and 1.5 ml hypertonic, respectively). | Elbow flexion with external loads from 0 to 10 kg. | Elbow joint position, VAS, and surface EMG was recorded from biceps brachii, triceps brachii, brachioradialis, and trapezius muscle. | Mild and moderate saline-induced pain reduces agonistic, antagonistic, and synergistic EMG activities affect the movement kinematics. |

| Table 2. Overview on the interaction between pain and motor control | | | | |
|---|---|---|---|---|
| **Reference** | **Pain** | **Motor task** | **Parameter** | **Main finding** |
| Ervilha et al (2005) | Saline-induced pain in biceps and triceps brachii muscle | Cyclic elbow flexion/extension movement at maximum speed. | Angular position and integrated EMG from upper trapezius, biceps brachii, and brachioradialis muscle. | Acceleration is decreased throughout the exercise, although kinematic parameters are not altered by pain.<br>The control strategy of muscle activity presents a complex reorganization, not only in the main muscles but also in the synergistic muscles. Trapezius muscle activity is increased during biceps brachii pain. |
| Falla et al (2008) | Saline-induced muscle pain in the cranial and caudal region of the trapezius muscle. | Hold both arms in 90° of abduction for 60 s. | Centroid of the RMS map of the EMG activity. | Spatial activation of the trapezius muscle is redistributed independently of the site of the noxious stimulus. |
| Farina et al (2004) | Saline-induced muscle pain in tibialis anterior muscle. | Isometric dorsiflexion at 10% MVC for 20 s. | Force steadiness, motor unit firing rate and muscle fibre conduction velocity measured from the tibialis anterior simultaneously | There is no change in the force steadiness neither the muscle fibre conduction velocity during pain.<br>Muscle pain is negatively correlated to the motor unit firing rate. |

| Table 2. Overview on the interaction between pain and motor control | | | | |
|---|---|---|---|---|
| **Reference** | **Pain** | **Motor task** | **Parameter** | **Main finding** |
| Hodges et al (2008) | Saline-induced muscle pain in the lateral gastrocnemius. | Plantar-flexion until record 1 to 4 MU on each muscle. | Intramuscular and surface EMG recordings from lateral and medial gastrocnemius and soleus muscle. | Motor unit firing rate is reduced not only in the main muscle but also in synergistic muscles of the force task during pain. Synergistic muscles do not compensate the reduction in force of the painful muscle. |
| Madeleine et al (2006) | Saline-induced pain in the trapezius muscle. | Hold both arms at 90° abduction for 90 s, corresponding to the 15-20% for the MVC of the trapezius muscle. | Spatial surface EMG activity from trapezius muscle. Centroid of the RMS and the mean power spectrum frequency of the EMG. | Trapezius muscle activity is dynamically reorganized during transient muscle pain. |
| Ervilha et al (2004) | Mild and moderate saline-induced muscle pain in the biceps brachii (0.5 ml and 1.5 ml hypertonic, respectively). | Elbow felxion with external loads from 0 to 10 kg. | Elbow joint position, VAS, and surface EMG was recorded from biceps brachii, triceps brachii, brachioradialis, and trapezius muscle. | Mild and moderate saline-induced pain reduces agonistic, antagonistic, and synergistic EMG activities affecting the movement kinematics. |

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|---|---|---|---|---|
| **Reference** | **Pain** | **Motor task** | **Parameter** | **Main finding** |
| Ervilha et al (2005) | Saline-induced pain in biceps and triceps brachii muscle | Cyclic elbow flexion/extension movement at maximum speed. | Angular position and integrated EMG from upper trapezius, biceps brachii, and brachioradialis muscle. | Acceleration is decreased throughout the exercise, although kinematic parameters are not altered by pain.<br>The control strategy of muscle activity presents a complex reorganization, not only in the main muscles but also in the synergistic muscles. Trapezius muscle activity is increased during biceps brachii pain. |
| Graven-Nielsen et al (1997) | Saline-induced muscle pain in the tibialis anterior or the gastrocnemius muscle. | Isometric dorsiflexion. MVC every 15 s in 4 s epochs for 10 min (40 contractions).<br>Time decay of isometric dorsiflexion from 80% to 30% of the MVC.<br>Walk on a treadmill. | Torque, EMG (root mean square and median frequency), and VAS. | Pain decreases MVC level and reduces endurance time in the submaximal contractions.<br>Muscle pain changes the coordination between muscles in the walk task. |

| Table 2. Overview on the interaction between pain and motor control | | | | |
|---|---|---|---|---|
| **Reference** | **Pain** | **Motor task** | **Parameter** | **Main finding** |
| Hug et al (2013) | Saline-induced muscle pain in the medial and distal part of the soleus muscle. | Isometric ankle plantarflexion. | Intramuscular and surface EMG was recorded from gastrocnemius medialis, gastrocnemius lateralis, and four different regions of soleus muscle. | Muscle activity is not reorganized in a simple systematic manner with respect to pain location. |
| Madeleine et al (2006) | Saline-induced pain in the trapezius muscle. | Hold both arms at 90° abduction for 90 s, corresponding to the 15-20% for the MVC of the trapezius muscle. | Spatial surface EMG activity from trapezius muscle. Centroid of the RMS and the mean power spectrum frequency of the EMG. | Short-term dynamic reorganization of the trapezius activity during transient muscle pain. |
| Salomoni and Graven-Nielsen (2012) | Saline-induced muscle pain in the tibialis anterior, brachioradialis, vastus medialis, gastronemius medialis. | Dorsiflexion, elbow flexion, knee extension, and plantarflexion at 2.5% to 70% of the MVC | Force in three directions and torques. Surface EMG from agonistic and antagonistic muscle for each force task. | There are no significant effects on the muscle activity.<br>Force steadiness is affected in the task-related and the tangential force directions during pain. |
| Schulte et al (2013) | Saline-induced muscle pain in the biceps brachii muscle. | Isometric elbow flexion at the 40% of MVC. | RMS and median frequency of EMG from biceps brachii, brachioradialis, deltoid, and trapezius muscle. | There are no significant changes in the biceps brachii activity or endurance of the elbow flexor.<br>Trapezius muscle activity is increased during biceps brachii pain. |

| Table 3. Overview on the interaction between persistent/clinical pain and motor control | | | | |
|---|---|---|---|---|
| **Reference** | **Pain** | **Motor task** | **Parameter** | **Main finding** |
| Arndersen et al (2008) | Soreness and movement-evoked pain induced by injection of NGF in the tibialis anterior. | | Pressure pain thresholds. | NGF causes a time-dependent enlargement of hyperalgesic region that peak at 24 hrs after injection. |
| Bandholm et al (2007) | Patients with subacromial impingement syndrome. | Isometric and isokinetic submaximal shoulder-abduction force steadiness at 20%, 27.5%, and 35% of the maximal shoulder abductor torque, and maximal shoulder muscle strength. | Shoulder abduction force steadiness.<br>EMG activity from supraspinatus, infraspinatus, lower trapezius, serratus anterior, anterior deltoid, middle deltoid, latissimus dorsi, and upper trapezius muscle. | Shoulder-abduction force steadiness is only mildly impaired in the patients.<br>Maximal shoulder muscle strength and maximal muscle activity is not reduced in the patients. |
| Descarreaux et al (2004) | Low back pain patients. | 50% and 75% of the maximal trunk flexion and extension. | Time to peak force, time to peak force variability, peak force variability, and absolute error in peak force.<br>Patients were subgroup according to the time to achieve the force levels (short vs long). | Controls and patients ‘short’ patient group show faster time to peak force than 'long' patient group.<br>Accuracy of low back pain patient is similar to control group. |

| Table 3. Overview on the interaction between persistent/clinical pain and motor control | | | | |
|---|---|---|---|---|
| **Reference** | **Pain** | **Motor task** | **Parameter** | **Main finding** |
| Hodges et al (2009) | Recurrent low back pain patients. | Trunk perturbations in the front and back directions. | Trunk stiffness, mass and damping using a linear second-order system to model the trunk. | Trunk stiffness is greater but lower damping in patients compared with healthy controls.<br>Increased stiffness may protect spinal structures. |
| Schabrun et al ( 2015) | Soreness and movement-evoked pain induced by injection of NGF into right extensor carpi radialis brevis | Transcranial magnetic stimulation targeting the extensor carpi radialis brevis muscle. Maximal voluntary grip force. | Pressure pain thresholds, maximal grip effort, EMG from extensor carpis radialis brevis. | NGF induces increasing hyperalgesia.<br>Grip force is reduced in day 4 and 14 in participant that received NGF.<br>Primary motor cortical is altered in the transition of acute to sustained muscle soreness. |
| Slater et al (2005) | Patients with lateral epicondylalgia.<br>Healthy with delay onset muscle soreness.<br>Saline-induced pain at extensor carpi radialis brevis for both groups. | Maximal grip and maximal wrist extension force. | Pressure pain thresholds. | Lateral epicondylalgia patients present longer pain duration, more widespread pain, a greater number of referred pain areas and pressure hyperalgesia compared with the control. The patients and control show reduced maximal force in the affected arm. |

| Table 3. Overview on the interaction between persistent/clinical pain and motor control | | | | |
|---|---|---|---|---|
| **Reference** | **Pain** | **Motor task** | **Parameter** | **Main finding** |
| Willigenburg et al (2012) | Low back pain patients. | Self-chosen upright trunk posture task using two targets increasing the demanded precision. Lumbar muscle vibration to reduce proprioception. | Precision and accuracy of trunk control and EMG ratio between muscles of the trunk. | Vibration in the lumbar region decreases the precision for both groups. Patients control as accurately and precise as healthy group when increasing the precision in the visual feedback. Pain patients may be less able to detect slow drift in posture. |

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