Three-Dimensional Force Variability: Assessment of Impairments in Motor Control during Fatigue and Pain

Three-Dimensional Force Variability: Assessment of Impairments in Motor Control during Fatigue and Pain

PhD Thesis by

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List of abbreviations

CoP: Centre of pressure
CNS: Central Nervous System
CV: Coefficient of Variation
EMG: Electromyography
MU: Motor Unit
MVC: Maximal Voluntary Contraction
SD: Standard Deviation
VAS: Visual Analogue Scale

Additional abbreviations used in table 1 and table 2

1-RM: One-repetition maximum
ADM: m. *abductor digiti minimi*
ARV: Absolute rectified value
BB: m. *biceps brachii*
EO: m. *external oblique*
ES: m. *erector spinae*
GRF: Ground reaction force
IO: m. *internal oblique*
ISI: Inter-spike interval
LE: m. *lumbar erector spinae*
MEP: Motor evoked potential
MUL: m. *multifidus*
NRS: Numeric rating scale
PPT: Pressure pain threshold
RMS: Root mean square
MDF: Median power frequency
MNF: Mean power frequency
RA: m. *rectus abdominis*
RF: m. *rectus femoris*
SCM: m. *sternocleidomastoideus*
SDN: Signal-dependent noise
TE: m. *toracic erector spinae*
VM: m. *vastus medialis*
VL: m. *vastus lateralis*

Preface

This Ph.D. thesis is based on three studies performed at the Center for Sensory-Motor Interaction (SMI), Pain and Motor Control Laboratory, Department of Health Science and Technology, Aalborg University, Denmark, from 2009 to 2012.

Study I

Salomoni S.E., Graven-Nielsen T., Muscle fatigue increases the amplitude of fluctuations of tangential forces during isometric contractions, Human Movement Science (2012), In Press.

Study II

Salomoni S.E., Graven-Nielsen T., Experimental muscle pain increases variability of multidirectional forces during isometric contractions, European Journal of Applied Physiology (2012), In Press.

Study III

Salomoni S.E., Ejaz A., Laursen A.C., Graven-Nielsen T., Experimental knee pain increases variability of three-dimensional force components during isometric contractions, Submitted.

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Summary

Variability is an inherent characteristic of human force output which is mainly governed by motor unit recruitment and modulation of discharge rates. Impairments in the motor control system associated with fatigue and pain affect the mechanical properties of muscle contractions, increasing force variability and hindering the ability of individuals to generate and control fine forces during daily activities. In fact, high levels of force variability have been associated with decreased motor skills and increased risk of falls. These effects are particularly relevant considering the large prevalence of chronic pain disorders. Using experimental pain models, it is possible to assess the effects of pain in healthy individuals, avoiding other potentially confounder mechanisms involved in chronic conditions, such as structural damage, inflammation, and fear-avoidance.

In the present work, a novel setup was developed to assess, in healthy subjects, the effects of muscle fatigue (Study I), experimental muscle pain (Study II), and experimental knee joint pain (Study III) on the generation and variability of force during static contractions. A high resolution six-axis sensor, yielding three dimensional components of force and moment, was mounted into custom setups, allowing the assessment of the force output during contractions of different muscle groups: Trunk extensors (Study I), elbow flexors, plantarflexors, dorsiflexors (Studies I and II), and knee extensors (Studies I, II, and III). Contractions were performed over a wide range of target forces (2.5% – 80% of maximal voluntary force) while the activity of agonist and antagonist muscles was measured using bipolar surface electrodes.

The standard deviation of the three force components increased monotonically with increasing force levels, demonstrating a relation of signal-dependent noise in the three directions. When assessed by a normalized parameter, the coefficient of variation (standard deviation/mean) of the normal, task-related force component exhibited a cubic polynomial relationship across force levels, with maximal values at low target forces, and a plateau at high forces. However, the coefficient of variation could not be used to assess the variability of tangential force components, since low force magnitudes resulted in inconsistently high coefficients of variation. Using the output of the multi-axis sensor, variability of tangential force components was indirectly assessed by the total excursion of the centre of pressure, which represents the lateral displacements of quasi-static forces, also resulting in a cubic polynomial relation with increasing force levels. Compared across muscle

groups, the dorsiflexors exhibited the highest variability in task-related force, while the knee extensors showed the highest tangential force variability.

In Study I, muscle activity increased during fatigue compared with baseline recordings for all the tasks assessed. This increase was associated with increased variability of task-related and tangential force components during contractions at target forces lower than 50% of maximal voluntary force. As a fatigued muscle requires increased input to produce a given force, larger motor units are recruited, resulting in increased fluctuations. Since multiple muscles contribute to force generation on different directions of action, the resultant force vector is not kept mono-directional during the contractions, and increased variability is observed not only in task-related, but also tangential force components.

The force output was also affected by experimental pain, which was elicited using injections of hypertonic saline into a main agonist muscle (Study II) and into the infrapatellar fat pad (Study III). Although the mean force magnitude and mean force angle were not significantly affected, pain elicited a larger range of angle of the resultant force vector, indicating increased force displacements during painful compared with non-painful contractions. Moreover, pain resulted in higher variability of task-related and tangential force components, particularly at low force levels. While changes in the force output ultimately originate from changes in muscle activation, only marginal changes were observed in the mean level of muscle activity, suggesting that multiple pain adaptations balanced the magnitude of surface electromyographic signals. In fact, since pain reduces motor unit discharge rates, the increase in force variability probably reflects a compensatory reorganization of motor unit activity in order to sustain the required force output. The relative impact of changes in motor unit behaviour is greater in a small motoneuron pool, thus low force levels were particularly affected.

The detrimental effects of fatigue and pain on force variability impair task precision and contribute to the decreased performance in functional tasks commonly observed in patients with chronic pain. Although conservative recommendations for the management of chronic pain conditions emphasize muscle strengthening, steadiness training, which can be associated with analgesic treatment, may act as an important cofactor for the improvement of functional performance, improving the efficiency of rehabilitation programs for these patients.

Dansk sammenfatning

Variabilitet er en naturlig del af den kraftudvikling, som er styret ved rekrutteringen af motoriske enheder samt ved modulering af fyringsrater for disse. Ændringer i det motoriske kontrolsystem ved udtrætning og smerte påvirker de mekaniske egenskaber for muskelkontraktion, ved at øge kraft variabilitet og hindre den enkelte persons mulighed for at generere og kontrollere finmotoriske bevægelser under almindelige daglige aktiviteter. Faktisk er det foreslået at høje niveauer af kraftvariabilitet er forbundet med reduceret motorisk kontrol og øget faldrisiko. Denne effekt er specielt relevant i relation til den høje prævalens af kroniske smertefulde lidelser. Ved at bruge eksperimentelle smertemodeller er det muligt at vurdere effekten af smerte på raske individer og dermed undgå andre faktorer, såsom strukturelle forandringer, inflammation og fear-avoidance, der er til stede i forskellige kroniske lidelser og som kan indvirke på resultaterne.

I dette projekt er der udviklet en ny teknik til at vurdere hvordan raske personer påvirkes af muskel udtrætning (Studie I), eksperimentel muskelsmerte (Studie II), og eksperimentel knæledssmerter (Studie III) i forhold til generering og variabilitet af kraft under en statisk kontraktion. En højresolutions, seks-akses sensor blev brugt i en specialdesignet forsøgsopstilling, til at give tredimensionel information om moment og kraft under kontraktioner. Dette muliggjorde måling af kraftudvikling under kontraktioner i forskellige muskelgrupper: Ekstensor muskler på truncus (Studie I), albue fleksorer, plantarfleksorer, dorsifleksorer (Studie I og III), og knæ ekstensorer (Studie I, II og III). Muskelkontraktioner blev udført ved flere forskellige intensiteter (2,5 % - 80 % af maksimal voluntær kontraktion) mens muskelaktivitet af agonister og antagonister blev målt ved elektromyografi med bipolar overfladeelektroder.

Standard deviationen af de tre kraft komponenter steg kontinuerligt som følge af den stigende kraftintensitet og viste dermed en signalafhængig støj i de tre retninger. Vurderet med normaliserede parametre blev koefficienten for variation (standard-deviation/middel-værdi) for den normale opgaveafhængige kraftkomponent udtrykt som en kubisk polynomisk sammenhæng over kraftniveauer med maksimale værdier ved lav kraftintensitet og et plateau ved høj kraftintensitet. Dog kunne koefficienten for variation ikke benyttes til at vurdere variabiliteten af tangentielle kraftkomponenter, da den lave kraftudvikling resulterede i urealistiske høje værdier. Ved at bruge den multi-aksielle sensor kunne variabiliteten af tangentielle kraft komponenter indirekte vurderes ud fra den

totale bevægelse af center-trykpunktet (CoP), der repræsentere sideforskydningen forårsaget af semi-statiske kræfter, hvilket også blev udtrykket som en kubisk polynomisk sammenhæng ved stigende kraftintensitet. Ved sammenligning af de forskellige muskelgrupper viste dorsifleksorerne den højeste variabilitet på den opgaverelaterede kraft mens knæekstensorene viste den største variabilitet i den tangentielle kraft.

I Studie I steg muskel aktiviteten under udtrætning sammenlignet med baseline målinger for alle typer af kontraktioner. Denne øgede aktivitet blev fulgt af en stigning i variabiliteten af den opgaverelateret kraft og tangentiel kraftkomponenter under en kontraktion med mindre end 50 % maksimal voluntær kraft. Da en udtrættet muskel skal bruge flere fyringer for at generere en given kraft blev der rekrutteret større motoriske enheder, hvilket resulterede i større variabilitet. Eftersom flere muskler bidrager til udviklingen af kraft i en given retning, er kraftvektorerne heller ikke kun i en retning under en kontraktion og en øget variabilitet findes, ikke kun i den opgaverelaterede kraftkomponent, men også i de tangentielle kraftkomponenter. Kraftudviklingen blev ligeledes påvirket af eksperimentel smerte, der blev induceret ved injektion af hypertont saltvand i en agonist muskel (Study II) og i den infrapatellare fedtpude (Study III). Til trods for at gennemsnits kraften og kraftvinkelen ikke var signifikant påvirket, fremkaldte smerter en større variation af de resulterende kraftvektorer. Dette indikerer en kraftforskydning under en smertefuld kontraktion sammenlignet med en ikke smertefuld kontraktion. Ydermere resulterede smerter i en højere variabilitet af den opgaveafhængige og tangentielle kraftkomponenter, specielt ved lave kraftniveauer. Overordnet sker variabiliteten i kraftudviklingen som følge af forandringer i muskelaktivering og kun marginale forandringer blev observeret i middelværdien af muskelaktivitet, hvilket indikere at multiple smerteadaptationer udlignede størrelsen på de elektromyografiske signaler målt med overfladeelektroder. Da smerte reducere fyringsraten af de motoriske enheder kan den øgede variabilitet tolkes som en kompenserende strategi for at kunne opretholde den krævede kraftudvikling. Den relative påvirkning af de motoriske enheder er større ved mindre grupper af aktive motoriske enheder, hvorfor de lavere kraftniveauer i særlig grad bliver påvirket.

Den skadelige virkning af udtrætning og smerte på kraftvariabilitet svækkede præcisionen i generationen af kraft og bidrog til en reduceret evne til at udføre en funktionel opgave. Tilsvarende er ofte observeret i patienter med kroniske smerter. Selv om konservative behandlingsstrategier for folk med kroniske smertetilstande understreger vigtigheden af styrketræning, kan specifik træning, evt. i kombination med smertestillende behandling, vise sig at være en vigtig bidragende faktor til forbedringen af funktionelle opgaver og derved forbedre effektiviteten af genoptræningen for denne patientgruppe.

Chapter 1.

Introduction

It is well known that conditions such as fatigue and pain affect motor performance (Arendt-Nielsen et al. 1996; Sterling et al. 2001; Babault et al. 2006). For example, fatigue in the lower limbs causes impairments in postural stability (Salavati et al. 2007; Paillard 2012) and pain affects muscle coordination during stair ascending (Hortobágyi et al. 2004; Hodges et al. 2009).

The precise assessment of adaptations in motor strategy by means of electromyographic (EMG) signals requires the decomposition of the signals into its constituent motor unit (MU) action potentials. This is classically performed using intramuscular EMG, comprising the contributions of a relatively small number of active MUs which are close to the recording site (Stålberg 1980). In addition, this technique is limited to contractions at low force levels and it is difficult to detect the same MUs over repeated recordings (Holobar et al. 2009).

On the other hand, force signals reflect the collective activity of all the muscles involved in a given task and impose no restraints to the level of muscle contraction. Moreover, since the production of force is one of the final outcomes of any voluntary contraction, certain parameters of the force signals are associated with functional performance and adaptive control mechanisms. Increased force variability has been associated with decreased motor skills (Harris and Wolpert 1998) and increased risk of falls (Carville et al. 2007), suggesting a strong correlation between force variability and impairments in the motor control system. In fact, it has been shown that the magnitude of force variability increases during muscle fatigue conditions and during musculoskeletal pain disorders compared with control conditions (Hortobágyi et al. 2004; Missenard et al. 2009).

1.1 FORCE STEADINESS

Variability is an inherent characteristic of human motor output (Stein et al. 2005). As a result, the force exerted when an individual performs a steady contraction is not constant but rather it fluctuates about an average value (Galganski et al. 1993; Löscher and Gallasch 1993; Slifkin and Newell 1999; Tracy et al. 2002; Enoka et al. 2003). The term force steadiness refers to the ability to perform muscle contractions with minimum fluctuations. It may be quantified by the amount of fluctuations in force or acceleration during standardized tasks, which is mainly governed by the recruitment strategy and discharge behaviour of the motoneuron pool (Taylor et al. 2003; Tracy et al. 2007). High motor output variability can hinder the ability to achieve a desired force and to perform accurate tasks and movements (Harris and Wolpert 1998), and the lack of control of fine forces may cause functional impairments during activities of daily living (Hortobágyi et al. 2004; Seynnes et al. 2005; Pua et al. 2010). For example, high force variability in the lower limbs has been associated with increased postural instability (Kouzaki and Shinohara 2010). Conversely, there is strong evidence that steadiness training using low-force exercises leads to a concomitant improvement in hand dexterity (Kornatz et al. 2005). Besides, the amount of variability in multidirectional force and movement plays an important role in the development of work-related musculoskeletal disorders, especially during repeated fatiguing tasks (Sjøgaard and Søgaard 1998; Madeleine 2010).

Many factors are known to influence the steadiness of force, including the architecture of the muscle group performing the task (Lieber and Friden 2000; Hamilton et al. 2004; Tracy et al. 2007), contraction type (Laidlaw et al. 2000; Laidlaw et al. 2002; Mottram et al. 2005a; Baudry et al. 2009), contraction intensity and duration (Laidlaw et al. 2000; Jones et al. 2002; Tracy and Enoka 2002), and size and intermittency of the feedback provided (Jones 2000; Slifkin et al. 2000; Tracy 2007a; Prodoehl and Vaillancourt 2010).

In addition to exogenous constraints related to the task, the variability of the force output depends also on the conditions of the individual performing the contraction, such as age (Deutsch and Newell 2001; Enoka et al. 2003; Sosnoff and Newell 2006), physical condition (Yan 1999; Hortobágyi et al. 2001; Ranganathan et al. 2001), fatigue (Semmler et al. 2007; Missenard et al. 2009; Singh et al. 2010; Study I), pain (Del Santo et al. 2007; Henriksen et al. 2011a; Study II; Study III), and musculoskeletal disorders (Hortobágyi et al. 2004; Descarreaux et al. 2005; Bandholm et al. 2006; Muceli et al. 2011).

1.2 MUSCLE FATIGUE AND MOTOR CONTROL INTERACTIONS

Although the term fatigue is commonly used during exercises and daily activities, it consists of a complex phenomenon which has been described as a motor deficit, an increase in the perceived effort necessary to exert a desired force, an exhaustion

of contractile function, among others (Enoka and Stuart 1992; Enoka and Duchateau 2008). In the past few decades, most investigators adopted a more focused definition of muscle fatigue as an exercise-induced reduction in the ability of muscle to produce force or power whether or not the task can be sustained (Bigland-Ritchie and Woods 1984; Søgaard et al. 2006). In this definition, a distinction is made between muscle fatigue and the moment of task-failure, and fatigue is considered to gradually develop soon after the onset of the physical activity.

The fatigue-induced reduction of motor output originates from central and peripheral mechanisms (Stephens and Taylor 1972; Bigland-Ritchie et al. 1986a; Babault et al. 2006). Central mechanisms involve a decrease in voluntary activation to the muscles (Bigland-Ritchie et al. 1986a), including reduced excitation of spinal motoneurons (Butler et al. 2003), suboptimal output from the motor cortex (Gandevia 2001; Søgaard et al. 2006; Milanovic et al. 2011), and motoneuron inhibition caused by activity from group III and IV muscle afferents (Rotto and Kaufman 1988; Luc Darques et al. 1998). Peripheral mechanisms involve a decrease in the contractile strength of the muscle fibres or in the transmission of action potentials (Krnjevic and Miledi 1959; Lamb 2009) involving increased intracellular concentration of metabolites (Westerblad et al. 1998) and impaired excitation-contraction coupling (Lamb 2009).

Despite fatigue, the central nervous system (CNS) is able to sustain a certain submaximal force output mainly by recruiting additional MUs and increasing firing rates of the active MUs (Gandevia 2001). The increased drive to motoneurons usually results in increased EMG activity (Edwards and Lippold 1956; Löscher et al. 1996; Carpentier et al. 2001) and increased force variability, which has been observed during prolonged fatiguing contractions (Garland et al. 1994; Hunter et al. 2003; Johnson et al. 2004; Mottram et al. 2005b) as well as during intermittent contractions after fatiguing exercise (Lavender and Nosaka 2006; Semmler et al. 2007; Dartnall et al. 2008; Missenard et al. 2008).

Table 1 presents an overview of investigations on the effects of muscle fatigue in the variability of the force output. The articles in table 1 were selected in January 2012 based on an extensive search in the PubMed database using the expressions “force variability”, “force steadiness” or “force fluctuations” in association with “muscle fatigue”, “muscular fatigue” or “fatigue exercise”. In addition, reference lists from the retrieved articles and reviews were examined. No constraints were imposed in relation to date of publication. For the sake of keeping a consistent scope across the selected articles and avoiding an excessively long table, studies based on the analysis of kinematic data were excluded. Moreover, although some authors refer to force fluctuations as “tremor”, force fluctuations and physiological tremor are not the same (Saxton et al. 1995; Lavender and Nosaka 2006), and investigations of physiological tremor were also excluded.

1.3 PAIN AND MOTOR CONTROL INTERACTIONS

Pain is commonly experienced in routine activities and sports. Indeed, a large number of investigators have observed interactions between pain and both voluntary and reflex motor function (Arendt-Nielsen et al. 1996; Graven-Nielsen et al. 1997a; Madeleine et al. 1999; Svensson et al. 1999; Graven-Nielsen et al. 2002; Ervilha et al. 2005; Hodges et al. 2009; Samani et al. 2009; Henriksen et al. 2010). Besides, pain is the cardinal symptom in several musculoskeletal disorders, causing physical disability and functional limitations in adult population, thus constituting a major socio-economical burden (Woolf and Pfleger 2003).

The perception of pain is mediated by the activation of nociceptive afferent fibres from group III and IV (Mense et al. 2001; Arendt-Nielsen and Graven-Nielsen 2008). This activity elicits adaptations in motor control such as reduced maximal voluntary force (Graven-Nielsen et al. 2002; Henriksen et al. 2011b), reduced MU firing rates (Sohn et al. 2000; Farina et al. 2004; Hodges et al. 2008), and changes in motor unit recruitment (Tucker et al. 2009; Hodges and Tucker 2011), resulting in impaired muscle coordination (Graven-Nielsen et al. 1997a; Ervilha et al. 2005; Madeleine et al. 2006; Hodges et al. 2009).

Investigations using experimental pain models have demonstrated that the muscle membrane properties are not significantly affected by pain (Farina et al. 2004; Farina et al. 2005a; Farina et al. 2005b). Therefore, it is believed that the decrease in muscle function and neuromuscular control is caused by central inhibition of multiple reflex pathways (Schomburg et al. 1999; Graven-Nielsen et al. 2002). This is consistent with reports of decreased excitability of spinal and cortical motoneurons during experimental muscle pain conditions compared with control (Rossi and Decchi 1997; Le Pera et al. 2001).

During painful submaximal contractions, muscle activity is redistributed within and between muscles in order to compensate for a decrease in MU firing rates (Madeleine et al. 2006; Falla et al. 2007a; Tucker et al. 2009; Tucker and Hodges 2009). As a result, the control of fine muscle force is impaired, and increased force fluctuations are observed during experimental and chronic pain conditions compared with control (Hortobágyi et al. 2004; Bandholm et al. 2008; Farina et al. 2011; Muceli et al. 2011). Moreover, pain-induced redistribution of muscle activity may alter the direction of the resultant force vector (Danion et al. 2002; Kutch et al. 2008; Tucker and Hodges 2010). However, investigations of force variability during painful contractions have been limited to assessments in one direction. In fact, multi-dimensional assessments of force fluctuations have only been employed during baseline conditions and sustained fatiguing contractions of the upper limb (Hunter et al. 2002; Mottram et al. 2005a; Hong et al. 2007; Kutch et al. 2008; Svendsen and Madeleine 2010); hence it is unclear if the three components of force fluctuations are similarly affected by pain. This investigation may provide new insight on how pain adaptations in muscle activity affect the stability of three-dimensional forces during musculoskeletal disorders.

Table 2 provides an overview of investigations on the effects of experimental and chronic pain in the variability of the force output. The articles in table 2 were selected in January 2012 from an extensive search in the PubMed database using the expressions “force variability”, “force steadiness” or “force fluctuations” in association with “experimental pain”, “chronic pain”, “muscle pain” or “osteoarthritis”. In addition, reference lists of the retrieved articles and reviews were examined. Similarly to table 1, no constraints were imposed in relation to date of publication, and exclusion criteria included assessments based on kinematic data and physiological tremor.

1.4 AIM OF THE PH.D. PROJECT

The aim of this Ph.D. project was to investigate, in healthy individuals, the effect of muscle fatigue, experimental muscle pain and experimental knee joint pain on the variability of three-dimensional force output (figure 1.1). Since multiple factors are known to influence force variability, different muscle groups were assessed at a wide range of force levels in order to provide a consistent characterization of the adaptations in motor control.

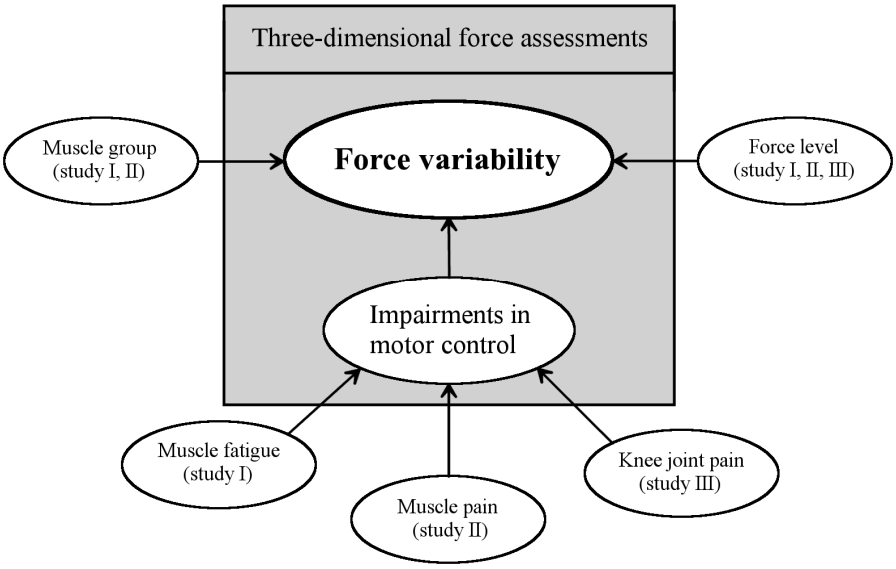

Figure 1.1 Outline of the main focus of the present Ph.D. project, highlighting the mechanisms assessed in each study.

Chapter 2.

Force variability and motor performance

The variability inherently present in the motor output can be interpreted as noise limiting precision and accuracy of force and movement (Schmidt et al. 1979; Meyer et al. 1988). Using this concept, modelling studies using optimal control theory have suggested that the central nervous system chooses motor strategy based on minimization of noise during task planning and execution (Todorov and Jordan 2002; Tanaka et al. 2006; Bays and Wolpert 2007). These studies have identified important characteristics of human motor control such as the scaling of force variability according to the level of force, a relation often termed signal-dependent noise, which corroborates with reports that variability of motor error increases with the magnitude of movement or velocity, as described by Fitt's law (Fitts 1954).

2.1 VARIABILITY AND FORCE LEVEL: SIGNAL-DEPENDENT NOISE

The concept of signal-dependent noise is based on empirical observations that the standard deviation (SD) of neuronal firing increases proportionally with the mean signal level (Clamann 1969; Matthews 1996). Similarly, the SD of force increases monotonically with increasing target forces (Sutton and Sykes 1967; Schmidt et al. 1979; Slifkin and Newell 1999; Taylor et al. 2003; Study I; Study II). During voluntary contractions, increments in muscle force are controlled by recruitment of additional MUs and modulation of the discharge rate of the active units (Person and Kudina 1972; Milner-Brown et al. 1973; Thomas et al. 1991). Recruitment follows the size principle (Henneman et al. 1965), i.e. smaller MUs are recruited

first, continuously progressing to larger units as the force increases. The larger, newly recruited MUs have lower firing rates and hence generate unfused twitches, increasing force variability (Jones et al. 2002; Stein et al. 2005; Faisal et al. 2008; Missenard et al. 2009). As force progresses, most MUs in the motoneuron pool are recruited, and modulation of discharge rate coding further increases force variability (Jones et al. 2002; Taylor et al. 2003; Moritz et al. 2005; Missenard et al. 2009).

In contrast, during contractions elicited by neuromuscular electrical stimulation, the SD of force remains relatively constant across force levels (Jones et al. 2002; Missenard et al. 2009). This happens because MU recruitment does not follow the size principle but rather depends mostly on the distance from the stimulating electrodes (Singh et al. 2000), and the discharge rates are always in synchrony with the provided stimuli, i.e. there is no discharge rate code modulation. Therefore, the monotonic increase in variability as a function of muscle force observed during voluntary contractions does not originate from peripheral neuromuscular noise. Instead, it is a natural by-product of the physiological organization of the motor unit pool, including distribution of MU recruitment thresholds, range of MU forces within a pool and orderly recruitment of MUs (Jones et al. 2002; Faisal et al. 2008; Missenard et al. 2009).

The magnitude of force variability can be assessed using normalized parameters such as the coefficient of variation (CV = SD/mean) of force, representing the amount of variability relative to the level of force exerted. Although the SD of force is sometimes assumed to have a perfectly linear relation with the mean force (Sutton and Sykes 1967; Fuglevand et al. 1993), the CV of force is not invariant across target forces. In fact, a cubic polynomial relationship between the CV of force and the mean force level has been repeatedly reported both experimentally and using computer simulations (Jones et al. 2002; Taylor et al. 2003; Hamilton et al. 2004; Tracy et al. 2007; Semmler et al. 2007; Study I; Study II; Study III). High values of the CV of force are observed at low force levels, as few MUs are active and small changes in recruitment or discharge rate elicit a proportionally large effect (Enoka et al. 1999; Laidlaw et al. 2000; Jones et al. 2002). As muscle force increases, so does the size of the motoneuron pool, reducing the relative increment in whole muscle force attributed to a single MU (Fuglevand et al. 1993) and the CV of force reaches minimum values around 30% of maximal voluntary contraction (MVC) force (Taylor et al. 2003). At higher forces, the force output is less dependent on MU recruitment and more dependent on variations in discharge rate of the MU population, resulting in slower force development and a plateau in the CV of force (Ferrucci et al. 1997; Christou et al. 2002).

However, the CV of force alone is not suitable to assess three-dimensional force variability. In particular, when an individual is required to match a certain force in the normal, task-related direction, tangential force components may exhibit mean values close to zero, resulting in inconsistently high CV of force (e.g. Figure 2.1). One alternative is the assessment of parameters of the centre of

pressure (CoP), which represents the point of application of the resultant normal force acting on a surface, thus reflecting lateral displacements of quasi-static forces (Seigle et al. 2009). Although CoP measures are traditionally applied to postural control analysis, the use of miniature high-resolution multi-axis force sensors allows the assessment of the CoP variability to indirectly measure tangential force variability during static contractions of individual body segments (Zhang et al. 2010; Zhang et al. 2011). Supporting this approach, a strong correlation has been shown between muscle lateral displacements measured with a laser sensor and force fluctuations during isometric contractions (Yoshitake et al. 2008).

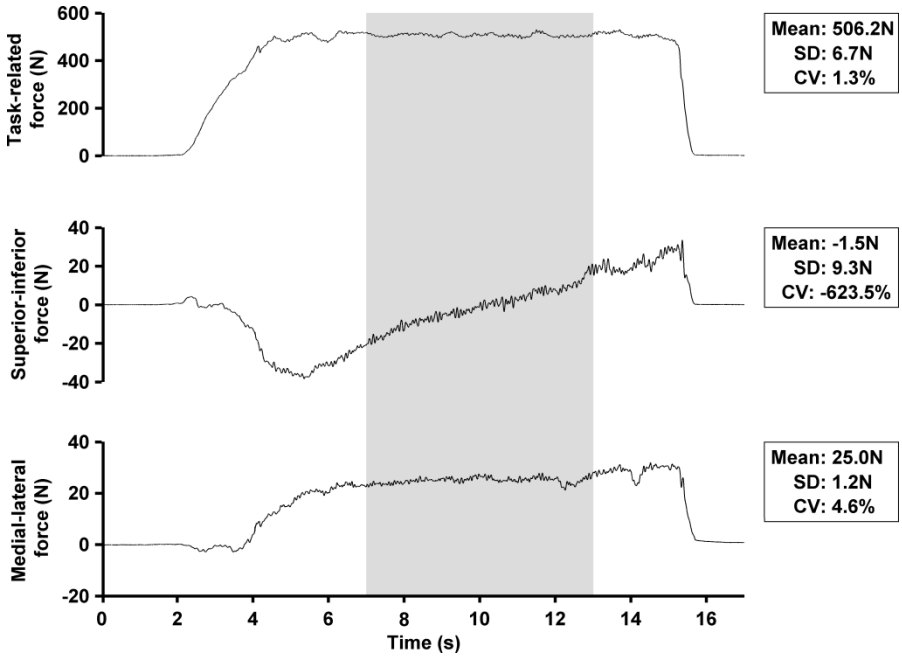

Figure 2.1 Three-dimensional force signals recorded during isometric knee extension at 80% of MVC force (data from Study III). The shaded area represents the time window used to extract the mean, SD and CV of force. The parameters extracted from the superior–inferior force component illustrate that low values of mean force may result in inconsistently high CV of force. In order to avoid this issue, the variability of tangential force components was assessed indirectly in Studies I, II and III using the total excursion of the CoP, which represents the lateral displacements of normal forces within a time interval (Prieto et al. 1996).

2.2 MOTOR UNIT CONTROL PROPERTIES

Among the mechanisms involved in discharge rate coding, MU synchronization and discharge rate variability have been suggested to play particularly important roles in the modulation of force variability (Yao et al. 2000; Taylor et al. 2002; Lowery and Erim 2005; Moritz et al. 2005). Computer simulations have demonstrated that MU synchronization can increase force variability (Yao et al. 2000; Taylor et al. 2003), which has been experimentally observed after eccentric exercise of the *biceps brachii* muscle (Dartnall et al. 2008). However, the magnitude of fluctuations can differ between individuals despite similar levels of MU synchronization (Semmler et al. 2000b; Kornatz et al. 2004). Similarly, although simulation and experimental studies have identified discharge rate variability as a key contributor to force fluctuations (Laidlaw et al. 2000; Enoka et al. 2003; Moritz et al. 2005), greater force fluctuations have been observed in older compared with younger adults despite no differences in the CV of discharge rate (Semmler et al. 2000b).

Recent studies using principal component analysis to assess MU firing rates have found a high correlation between force signals and low-frequency oscillations of the neural drive (Negro et al. 2009; Farina et al. 2011). These findings support the idea that force output variability is regulated by the *common drive* to the motoneuron pool (De Luca et al. 1982a; De Luca and Erim 1994). Due to the electrical properties of the motoneurons, low-frequency components of the common drive are reflected in the motor output while high-frequency components are largely attenuated (Partridge 1965; Mannard and Stein 1973). Hence, the presence of high-frequency components related to synaptic noise and motoneuron post-spike after-hyperpolarisation in the motoneuron firing rates (Matthews 1996) could partially explain the weak association between force variability and firing rate variability reported in some studies (Semmler et al. 2000b; Mottram et al. 2005b; Negro et al. 2009).

Furthermore, it has been suggested that force variability depends on the number of MUs innervating a muscle, so that stronger muscles produce lower CV of force compared with weaker muscles (Hamilton et al. 2004; Tracy 2007b). Although this relation is valid when comparing muscle groups with a large difference in maximal voluntary force such as plantar- and dorsiflexors (Tracy 2007b), the results are inconsistent when other muscle groups are compared (Tracy et al. 2007; Salomoni and Graven-Nielsen 2011). In fact, simulation models have shown that the number of MUs within a muscle has little effect on the coefficient of variation of force (Fuglevand et al. 1993; Taylor et al. 2002; Enoka et al. 2003).

2.3 DESCRIPTION OF EXPERIMENTAL SETUP

Changes in muscle activity and muscle coordination associated with impairments in the motor control system may cause directional deviations in the resultant force

vector (Kutch et al. 2008; Tucker and Hodges 2010). In the present work, a novel setup was developed to record and assess the effects of fatigue and pain in the generation and stability of three-dimensional forces during static contractions. A high resolution six-axis sensor was used to perform the recordings (figure 2.2), yielding three force signals and three angular moment signals.

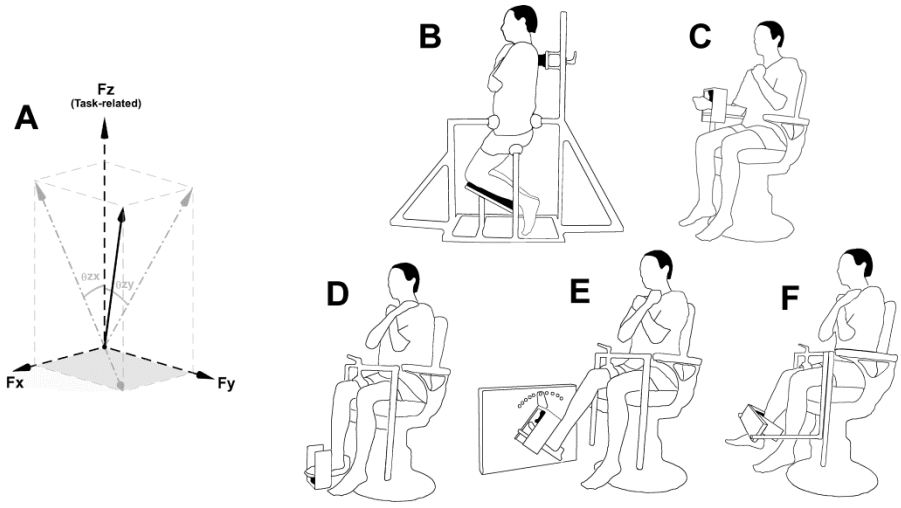

Figure 2.2 (A) Schematic representation of the three-dimensional force output of the sensor used in Studies I, II and III in relation to its surface. The sensor, displayed as a black box, was mounted to custom setups, allowing the assessment of forces during isometric contractions of the (B) trunk extensors, (C) elbow flexors, (D) plantarflexors, (E) dorsiflexors, and (F) knee extensors.

As shown in figure 2.2, the sensor was mounted into custom setups in order to assess the forces exerted by different muscle groups: Trunk extensors (Study I), elbow flexors, plantarflexors, dorsiflexors (Studies I and II), and knee extensors (Studies I, II, and III). These contractions were chosen because they involve muscle groups with different architectural and neuromuscular properties such as number of agonist and antagonist muscles, motor unit number, muscle fibre composition, muscle size and strength, and corticospinal input (Tracy et al. 2007; Tracy 2007b), which might distinctly influence multidirectional force variability. Through all acquisitions, muscle activity was recorded from the relevant agonist and antagonist muscles using bipolar surface EMG electrodes.

During experimental procedures, participants were required to perform sustained isometric contractions (12 – 13 seconds) at a wide range of target forces (2.5% – 80% MVC). In Study I, visual feedback of the normal, task-related force component was provided for the subjects on an oscilloscope screen. In an attempt

to improve the quality of the visual feedback and the ease of configuration, a graphical user interface was developed and used in Studies II and III, providing real-time feedback of the task-related force component on a computer screen (figure 2.3).

Using three-dimensional force recordings, parameters of magnitude and angular direction were assessed in Studies I, II and III, such as the mean force angle and the range of force angle. The variability of the force signals was estimated using the standard deviation and the normalized coefficient of variation of force. Moreover, the total excursion of the centre of pressure time series was calculated, representing tangential displacements of the resultant force.

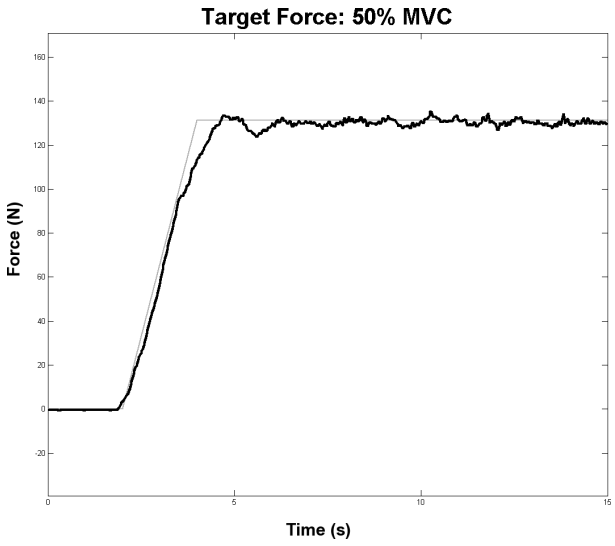

Figure 2.3 Example of the feedback provided for subjects in Studies II and III on a computer screen. A static ramp-and-hold feedback (shown in gray) was shown together with the real-time representation of the normal, task-related force component (shown in black).

Chapter 3.

Muscle fatigue and force variability

Muscle fatigue causes a reduction in the capacity to generate muscle force or power (Stephens and Taylor 1972; Bigland-Ritchie et al. 1986a; Babault et al. 2006). During maximal voluntary contractions, fatigue reduces muscle activity with a subsequent decrease in the force outcome (Bigland-Ritchie et al. 1983). During submaximal contractions, a constant force output can be sustained with increased intensity of central command, achieved by recruitment of additional MUs, increased discharge rates and MU substitution (Gandevia 2001). As a fatigued muscle requires increased input to produce a given force, larger MUs are recruited, resulting in increased force fluctuations (see table 1 for an overview of previous findings). However, few studies have investigated the effects of fatigue using multi-directional assessments of force variability. Limited to sustained isometric elbow flexions, these results have shown that the amplitude of force fluctuations in task-related and tangential directions increase progressively until task failure (Hunter et al. 2002; Hunter et al. 2003; Mottram et al. 2005a; Svendsen and Madeleine 2010).

In Study I, three-dimensional force variability was assessed during intermittent isometric contractions (12s, 2.5% – 80% MVC) of different muscle groups: trunk extensors, elbow flexors, plantarflexors, dorsiflexors, and knee extensors. The contractions were performed before and after a fatigue-inducing task consisting of three repetitions of sustained isometric contractions at 60% MVC force until exhaustion (Figure 3.1). The SD of task-related and tangential forces increased monotonically with increasing target force for all muscle groups during contractions performed both before and after the fatigue task. Fatigue caused a general increase in agonist muscle activation compared with baseline, but only marginal changes in antagonist muscle activity, resulting in further increase of

normalized force variability in task-related and tangential components during contractions at 2.5% – 30% MVC, with no significant effects at higher forces. Compared across muscle groups, the dorsiflexors exhibited the highest CV of task-related force, while the knee extensors showed the largest excursions of the CoP.

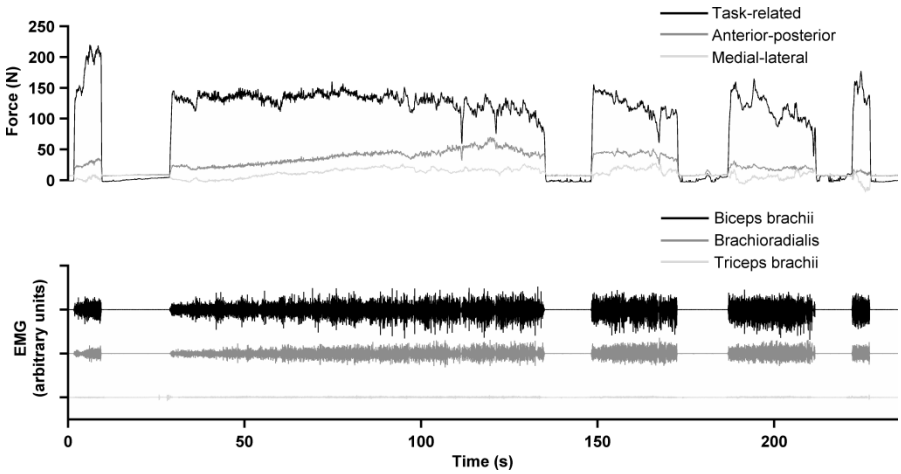

Figure 3.1 Representative force and EMG recordings performed during fatigue protocol performed with the elbow flexors (Study I). The fatigue task consisted of three consecutive isometric contractions at 60% MVC force until exhaustion. MVC trials were performed before and after the fatigue task in order to assess the decrease in voluntary force.

The increase in SD of force with increasing force levels is related to the orderly recruitment of MUs: In order to increase muscle force, larger MUs are recruited (Henneman et al. 1965), which produce larger and unfused twitches, resulting in increased force fluctuations (Jones et al. 2002). Since the resultant force represents the spatial summation of activity from different muscles, each contributing to fluctuations on its own direction of action (Herrmann and Flanders 1998; Kutch et al. 2008), the exerted force is not kept purely mono-directional during the contraction, and increased variability is observed not only in task-related, but also tangential force components (Hong et al. 2007; Svendsen and Madeleine 2010). Consistent with these arguments, previous studies reported varying degrees of coordination of index finger muscles in relation to different directions and magnitudes of endpoint forces (Kutch et al. 2008) and heterogeneity of activation within the *triceps surae* muscle in relation to force direction (Staudenmann et al. 2009). Moreover, positive correlations between the SD of EMG and the SD of force were observed in Study I, supporting the idea that changes in muscle coordination such as load sharing and alternation of activity

between muscles during the sustained task may influence motor performance (Kouzaki et al. 2002; Kouzaki et al. 2004).

It has been shown that fatigue increases activity of agonist muscles (Lippold et al. 1960; Bigland-Ritchie et al. 1986b; Sacco et al. 1998; Ciubotariu et al. 2004). In Study I, increased agonist muscle activity during fatigue was associated with increased force variability in task-related and tangential directions compared with baseline assessments. Missenard et al. (2009) reported that force variability is not significantly affected by fatigue when (1) contractions are elicited by neuromuscular electrical stimulations or (2) the increase in muscle activity is controlled by imposing participants to match the same EMG magnitude (for target forces > 13% MVC). These results indicate that peripheral factors do not contribute directly to the increase in force variability during fatigue, and that increased muscle activity is the critical factor responsible for increased force variability at moderate and high force levels. At low forces, other central mechanisms associated with fatigue have a proportionally stronger effect in force variability (Taylor et al. 2003; Semmler et al. 2007) such as increased MU firing rate variability (Enoka et al. 1989), higher gain of the Ia-afferent reflex loop (Cresswell and Löscher 2000), and activity from group III and IV afferents (Garland et al. 1988). Moreover, impaired co-contraction of synergist and antagonist muscles may reduce stiffness, further contributing to increased force variability during fatigue, particularly in muscle groups with considerable redundancy in force generation such as the trunk extensors (Sparto et al. 1997; Reeves et al. 2008; Hall et al. 2009).

The results of Study I showed no clear associations between MVC force and the CV of force. Although the dorsiflexors exhibited the highest CV of force among the muscle groups assessed, the highest total excursion of the CoP was observed during knee extensions, indicating that high fluctuations in the task-related force component do not necessarily imply in high fluctuations of tangential forces. These findings are in line with previous observations that muscle strength is not a good predictor of the magnitude of force fluctuations (Taylor et al. 2002; Tracy et al. 2007). Since load sharing and alternation of activity during sustained contractions can modulate force variability (Kouzaki et al. 2002; Kouzaki et al. 2004), it is likely that the involvement of multiple synergist muscles in a given contraction contributes to higher fluctuations of tangential forces., e.g. in the knee extensor muscles.

In summary, muscle fatigue resulted in higher fluctuations of task-related and tangential forces due to increased muscle activity, particularly at low force levels. The results support that increased muscle activity is the main factor responsible for the increase in force fluctuations, most likely mediated by central mechanisms. The detrimental effects of fatigue on force steadiness affect task precision and may contribute to the development of chronic pain disorders, particularly during tasks characterized by repeated fatiguing contractions.

Chapter 4.

Nociception and sensory-motor interactions

Nociceptive information is conveyed into the central nervous system by thin myelinated (group III or Aδ) and unmyelinated (group IV or C) afferent fibres, which terminate in widely distributed free nerve endings in the skin, muscles, joints, and viscera (Heppelmann et al. 1990; Graven-Nielsen and Mense 2001). These fibres are connected to second order neurons mainly in laminae I and V of the dorsal horn (Pomeranz et al. 1968; Cervero et al. 1976; Nyberg and Blomqvist 1984; Mense and Craig 1988) and in subnucleus caudalis in the brain stem (Shigenaga et al. 1988; Sessle 2000). Second order axons project to the thalamic nuclei via the spinothalamic or trigeminothalamic tracts (Foreman et al. 1979; Kniffki and Mizumura 1983; Craig and Kniffki 1985) and further to the somatosensory cortex (Lamour et al. 1983; Kenshalo et al. 1988).

A large number of experimental models have been proposed in the literature to activate nociceptive afferent fibres in order to elicit and assess the effects of pain in animals and humans (Graven-Nielsen 2006). Human models include endogenous techniques such as ischemic occlusion (Lewis 1932) and delayed onset muscle soreness (Newham et al. 1983; Jones et al. 1986); and also exogenous techniques such as electrical stimulation (Brucini et al. 1981; Laursen et al. 1997) and injection of algesic substances (e.g. capsaicin, bradykinin, and hypertonic saline) (Graven-Nielsen et al. 1997b; Graven-Nielsen and Mense 2001). In particular, intramuscular injections of hypertonic saline, which cause a robust excitation of group III and IV afferent fibres, have been extensively used to assess basic mechanisms of nociception as well as sensory and motor adaptations as the quality

of the induced pain is comparable to acute clinical pain (Svensson et al. 1995; Graven-Nielsen et al. 1997c; Graven-Nielsen and Arendt-Nielsen 2010).

Nociceptive pathways are connected via interneurons to alpha-motoneurons at the spinal cord level, hence modulating motor control strategies. The interaction between sensory input and motor output has a strong clinical relevance, and different theories have been proposed to explain the effects of pain in muscle activity. The "*vicious cycle*" proposed by Travell et al. (1942) hypothesizes that pain causes muscle hyperactivity, inducing ischemia and accumulation of metabolites (Roland 1986), thus perpetuating pain sensation. A number of mechanisms underlying the increase in muscle activity have been proposed, including increased sensitivity of muscle spindles via activation of gamma motoneurons from group III and IV afferents (Johansson and Sojka 1991). Some results from animal studies and clinical observations partially support this theory (Flor et al. 1983; Wall and Woolf 1984; Yu et al. 1995; Cairns et al. 1998), but investigations using experimental pain models in humans have shown only transient increase in muscle activity, with no long-lasting effects (Svensson et al. 1998), while many other studies reported unchanged or decreased muscle activity during pain (Graven-Nielsen et al. 1997a; Farina et al. 2005a; Kawczynski et al. 2007).

The "*pain adaptation model*", on the contrary, proposes that pain elicits inhibition of agonist muscles and excitation of antagonist muscles, resulting in reduced movement amplitude and velocity (Lund et al. 1991). A vast number of experimental results support this theory (Svensson et al. 1996; Graven-Nielsen et al. 1997a; Hodges et al. 2003; Farina et al. 2005a; Falla et al. 2007b), but other studies reported increased agonist muscle activation (Del Santo et al. 2007), decreased activity of antagonist muscles (Ervilha et al. 2004), or no changes in either agonist or antagonist muscles (Birch et al. 2000) during painful compared with non-painful conditions.

Recently, Hodges and Tucker proposed a new pain adaptation theory based on clinical and experimental observations, suggesting that pain causes a heterogeneous and non-stereotyped reorganization of the motoneuron pool which cannot be explained by simple changes in muscle excitability but involves adaptations at multiple levels of the motor system (Hodges and Tucker 2011; Hodges 2011). It is suggested that, instead of the homogeneous muscle inhibition predicted by the pain adaptation model, the central nervous system is able to maintain a certain level of force during pain by reducing MU firing rates (Sohn et al. 2000; Farina et al. 2004) in addition to a spatial redistribution of activity within and between muscles (Madeleine et al. 2006; Falla et al. 2007a; Tucker and Hodges 2009; Tucker and Hodges 2010), which might be mediated by an unequal balance of excitatory and inhibitory inputs from nociceptive afferents (Kniffki et al. 1979; Hodges and Tucker 2011).

4.1 EXPERIMENTAL MUSCULOSKELETAL PAIN AND FORCE VARIABILITY

Few studies have investigated the impact of pain in force variability using experimental pain models, and the results available suggest site-dependent effects (for an overview of experimental and clinical findings, see table 2). Increased CV of force was reported during isometric contractions of hand and arm muscles during muscle pain compared with control conditions, which was attributed to higher synchronization and variability of synaptic input to the motoneurons (Del Santo et al. 2007; Farina et al. 2011). During isometric shoulder abduction, experimental pain in m. *supraspinatus* elicited increased SD (but not CV) of force, although no significant changes were found during isotonic tasks (Bandholm et al. 2008). In the lower limb, Farina et al. (2004) reported no effects of m. *tibialis anterior* pain in the CV of force during isometric dorsiflexion, while Henriksen et al. (2011a) observed changes in the frequency content (but not the magnitude) of force fluctuations during one-legged plantar and dorsiflexions following experimental Achilles tendon pain. While the aforementioned studies were limited to contractions at moderate force levels (10% – 35% MVC), investigations employing delayed onset muscle soreness, a well-known endogenous pain model, have shown greater impairments during contractions below 10% MVC force (Semmler et al. 2007).

In Study II, the effects of experimental muscle pain on the generation and steadiness of multidirectional (task-related and tangential) forces were assessed during sustained isometric contractions (13 s, 2.5% – 70% MVC) of the elbow flexors, plantarflexors, dorsiflexors, and knee extensors. Intramuscular injections of hypertonic saline (1.0 ml, 5.8%) were applied in healthy individuals to elicit pain into a main agonist muscle of each muscle group. In Study III, isometric knee extensor forces (13s, 2.5% – 80% MVC) were assessed in healthy volunteers using an experimental model of knee joint pain (Bennell et al. 2004). This model consists of injections of hypertonic saline into the infrapatellar fat pad, which is a pain-sensitive structure due to high presence of nociceptive nerve fibres (Dye et al. 1998; Bohnsack et al. 2005) and is considered a contributing source of anterior knee pain in patients with knee osteoarthritis (Hill et al. 2007; Clockaerts et al. 2010). In both experiments, subjects performed series of isometric contractions before, immediately following, and after the effects of a painful (hypertonic saline) and a placebo control (isotonic saline, 1.0 ml, 0.9%) injections while pain intensity was continuously recorded using an electronic visual analogue scale (VAS).

For all the tasks assessed, VAS scores of pain were higher following injections of hypertonic compared with isotonic saline (Figure 4.1). Pain did not affect significantly the mean force amplitude or the mean force angle for any of the tasks, except for a marginal decrease in the mean task-related force at 80% MVC knee extensions compared with non-painful conditions in Study III. A wider range of angle of the resultant force was observed during painful compared with non-painful contractions of the plantarflexors (Study II) and knee extensors (Studies II and III), particularly at low force levels. The variability of task-related force

increased during pain compared with baseline among all tasks. The total excursions of the CoP also increased consistently during experimental muscle pain for elbow flexions, knee extensions and dorsiflexions, but plantarflexions were significantly affected only at 2.5% MVC. In Study III, experimental knee pain elicited higher tangential force variability only at low force levels, as revealed by increased range of force angles and increased total excursion of the CoP (figure 4.2). No significant differences in muscle activity were observed across trials in Study II. In Study III, the mean EMG activity of m. *vastus medialis* decreased during pain only at 80% MVC force, followed by an increase after the effects of hypertonic saline (post-pain) also at 80% MVC force.

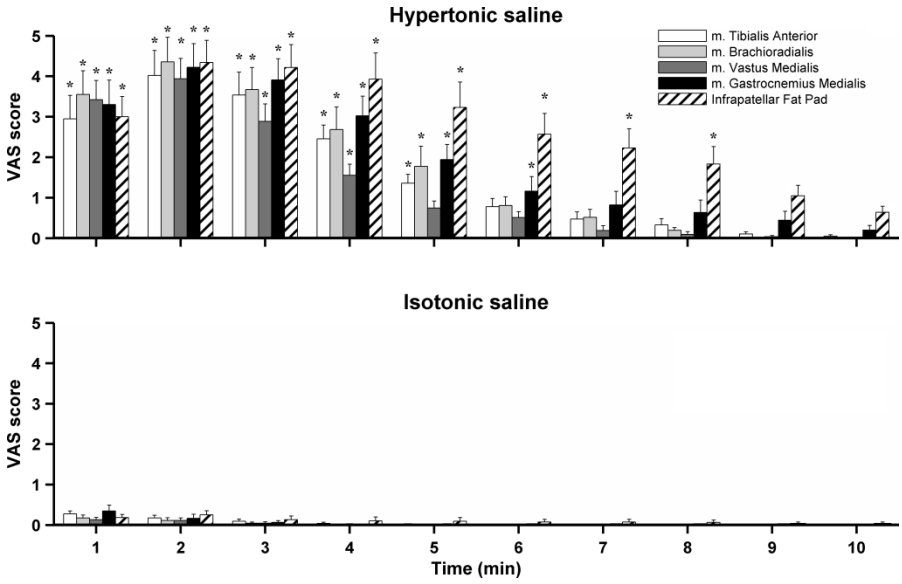

Figure 4.1 Mean (+ standard error of the mean) pain intensity assessed using a Visual Analogue Scale (VAS) after injections of hypertonic and isotonic saline in an agonist muscle of different muscle groups (Study II) and in the infrapatellar fat pad (Study III). * Significantly higher than isotonic saline ($P<0.004$).

It has been previously shown that the MU discharge rates of agonist and synergist muscles are reduced during painful submaximal contractions compared with control conditions (Sohn et al. 2000; Graven-Nielsen et al. 2001; Farina et al. 2004; Hodges et al. 2008), with a correlation between the amount of decrease and pain intensities (Farina et al. 2004). Hence, the increased force variability observed during pain in Studies II and III originates from a compensatory motor strategy adopted in order to sustain the required force output, which is likely to involve

selective recruitment of high-threshold MUs (Hodges et al. 2008), increased MU synchronization (Yao et al. 2000; Dartnall et al. 2008), and volitional increase of central drive (Del Santo et al. 2007). The relative impact of changes in motor unit behaviour is greater in small populations of MUs, which might explain why variability of tangential forces was mostly affected at low force levels in Studies II and III (figure 4.2). Therefore, increased lateral force displacements will have a stronger impact during functional activities with high precision demands, performed at low forces, compared with low-precision activities. Moreover, activation of group III and IV afferents may result in increased variability of the synaptic input to motoneurons (Farina et al. 2011) as well as reduced proprioception through spatial facilitation of reflex pathways from group Ia and Ib afferents (muscle spindles and Golgi tendon organs), further modulating force variability (Schomburg et al. 1999; Yoshitake et al. 2004; Shinohara et al. 2005).

Farina et al. (2005b) have shown that injection of hypertonic saline at the beginning of a sustained contraction decrease the initial discharge rate of active MUs. Interestingly, the discharge rates during both painful and non-painful conditions reached a similar plateau as the contractions progressed and fatigue developed. Although feedback from nociceptive afferents is not the only factor involved in the decrease of discharge rates during fatiguing contractions, this observation indicates that fatigue-induced and pain-induced reduction of central input may share similar underlying mechanisms, corroborating with the consistent increase in force variability across Studies I, II and III (Figure 4.3).

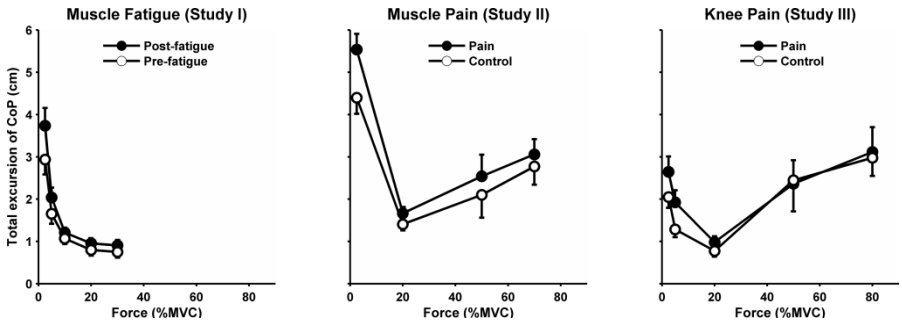

Figure 4.2 Mean (± standard error) total excursion of the center of pressure (CoP) estimated from isometric knee extensions. Larger excursions of the CoP were observed during the effects of muscle fatigue (Study I), experimental muscle pain (Study II) and experimental knee joint pain (Study III) compared with baseline assessments, particularly at low force levels.

Investigations using bi-dimensional grids of surface EMG electrodes have shown distinct patterns of pain adaptations in different areas of the *trapezius* and *masseter* muscles (Madeleine et al. 2006; Castroflorio et al. 2012). Since the precise orientation of forces produced by individual MUs depend on muscle fibre angle and attachments (Herrmann and Flanders 1998), this spatial reorganization of muscle activity contributes to alterations of the direction of the resultant force vector (Tucker and Hodges 2010). The larger ranges of force angle and greater total excursion of the CoP observed during pain compared with baseline in Studies II and III reflect greater changes in force direction, suggesting that the reorganization of muscle activity can occur dynamically during the time course of a sustained contraction. Moreover, the range of force angle increased only during knee extensions (Studies II and III) and plantarflexions (Study II), but not during elbow flexions or dorsiflexions (Study II), supporting the idea that the extent of pain adaptations in the coordination of agonist and synergist muscles vary across muscle groups and tasks, and often between different subjects (Hodges and Tucker 2011). It is likely that the reorganization of muscle activity in larger, stronger muscles, involves a greater number of MUs compared with weaker muscles, leading to greater misalignments of the resultant force vector.

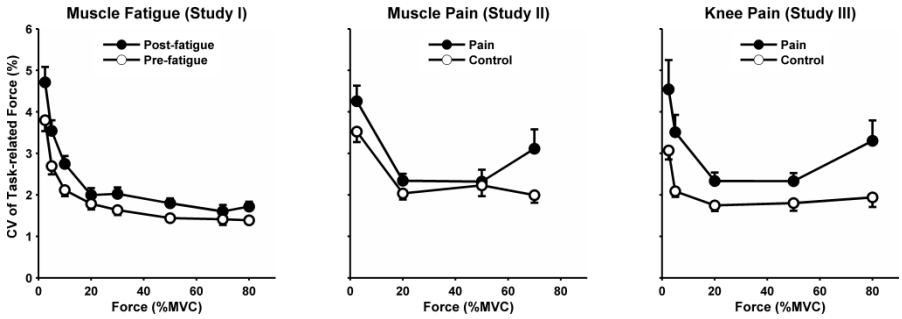

Figure 4.3 *Mean (± standard error) coefficient of variation of the task-related component of knee extension force increased consistently during the effects of muscle fatigue (Study I), experimental muscle pain (Study II) and experimental knee joint pain (Study III) compared with baseline assessments*

Despite pain-induced increase in force fluctuations and larger ranges of force angle in Studies II and III, the mean amplitude of the surface EMG was generally not significantly affected by pain, except during 80% MVC knee extensions in Study III. It has been shown that adaptations of the motoneuron pool associated with pain (e.g. inhibition of MUs, recruitment of additional units, modulation of discharge rates, and increased MU synchronization) may not be detected using bipolar surface EMG (Tucker and Hodges 2009). Therefore, it is likely that multiple mechanisms acted simultaneously and balanced the magnitude of surface EMG

signals in Studies II and III, overcoming potential inhibitory effects associated with pain. This is consistent with the observation that the mean force magnitude and mean force angle were also not significantly affected by pain, indicating that, despite pain, subjects were able to sustain the required force-matching task. However, the increased variability of task-related and tangential force components (figures 4.2 and 4.3) demonstrate that a less efficient (or at least less steady) motor strategy was adopted during pain compared with baseline assessments.

The reduction in m. *vastus medialis* EMG observed in Study III during painful compared with non-painful 80% MVC knee extensions was associated with inability to sustain the required target force. At such high contraction level, all MUs in the motoneuron pool are recruited, even in large muscles (Kukulka and Clamann 1981; De Luca et al. 1982b). Hence the observed decrease in muscle activity most likely reflects a reduction of quadriceps strength, caused by pain-induced central inhibition of reflex pathways (Graven-Nielsen et al. 2002; Henriksen et al. 2011b). Furthermore, during painful contractions, the same target force may impose a more strenuous effort compared with non-painful conditions as a result of inhibitory mechanisms (Sørensen et al. 2012), and the increased activity of m. *vastus medialis* observed post-pain at 80% MVC may originate from the subjects' expectation of a greater effort, resulting in a tendency to overshoot.

In summary, experimental pain in the muscles and in the knee fat pad significantly increases variability of task-related and tangential forces during sustained isometric contractions, particularly at low target forces. The absence of changes in surface EMG activity despite reduced force steadiness at low and moderate target forces suggests heterogeneous pain adaptations in muscle activity as a potential cause. Impairments in the precise control of task-related and tangential force components caused by pain are likely to contribute to the decrease in performance of functional tasks, commonly observed in patients with chronic pain.

4.2 CHRONIC PAIN AND FORCE VARIABILITY

The reorganization of muscle activity and the changes in motor unit behaviour underlying pain adaptations are generally believed to be part of a protective mechanism against further pain or injury (Lund et al. 1991; Hodges and Tucker 2011). While it may provide short-term benefits in the acute stages of pain, if the motor adaptation is excessive or persists after cessation of pain, it can result in overload of different otherwise non-painful structures and thus contribute to recurrence or chronicity of pain (Hides et al. 1996; Sterling et al. 2001; Hodges 2011). In that case, the impairments in the generation and steadiness of force observed during acute pain conditions in healthy individuals (Tucker and Hodges 2010; Farina et al. 2012; Study II; Study III) might be perpetuated in patients with chronic pain.

In fact, increased force variability has been observed in patients with different chronic musculoskeletal pain disorders such as knee osteoarthritis (Hortobágyi et al. 2004), chronic neck/shoulder pain (Schulte et al. 2006; Muceli et al. 2011), and subacromial impingement syndrome (Bandholm et al. 2006) compared with healthy controls. Such impairments in force steadiness, combined with the reduced proprioception that is commonly observed in patients with chronic pain (Bennell et al. 2003; Hortobágyi et al. 2004), affect the ability of these patients to generate and control smooth forces during daily activities. Corroborating, it has been shown that force steadiness of the quadriceps muscle is a good predictor of functional performance in patients with knee or hip osteoarthritis during chair rising and stair climbing (Hortobágyi et al. 2004; Seynnes et al. 2005; Pua et al. 2010). Significant correlations were also found between the CV of isometric plantarflexion force and parameters of postural stability such as variability of the centre of pressure during quite standing (Kouzaki and Shinohara 2010) and sustainable time during single-leg standing (Oshita and Yano 2010). Furthermore, high force variability of the quadriceps muscle is associated with an increased risk of fall in elderly people (Carville et al. 2007).

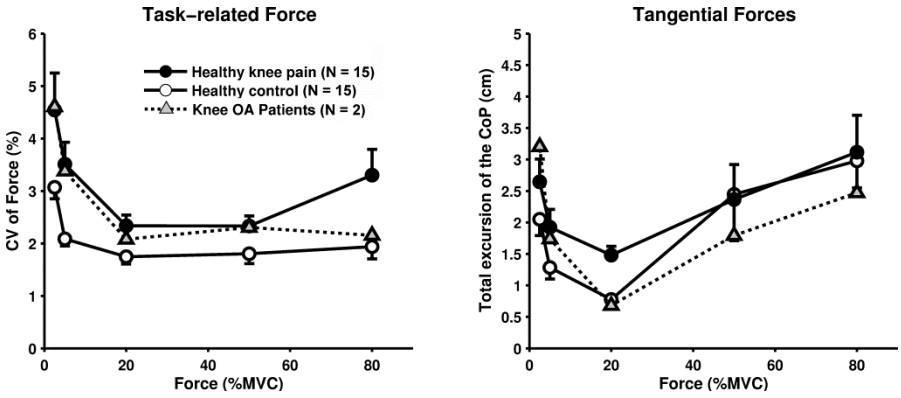

Figure 4.4 *Mean (± standard error) CV of force and total excursion of the CoP, representing variability of task-related and tangential force components. Data from healthy subjects were extracted from Study III, whereas preliminary data from patients with knee osteoarthritis were extracted from an ongoing experiment. From these limited results, it may be speculated that experimental and chronic pain elicit comparable increase in task-related and tangential force variability, at least during contractions at low force levels.*

Although conservative recommendations for the management of osteoarthritis emphasize muscle strengthening (Zhang et al. 2008), knee extensor steadiness

training may act as an important cofactor for the improvement of functional performance, particularly in patients with relatively well preserved muscle strength (Pua et al. 2010). Corroborating, it has been suggested that conscious attention and precision is required during training in order to produce changes in muscle coordination (Tsao and Hodges 2007) and cortical reorganization (Remple et al. 2001). Therefore, force steadiness training with the proper feedback is likely to improve the efficiency of rehabilitation programs for patients with chronic pain disorders.

Preliminary analysis of data from an ongoing investigation assessing multidirectional force variability in patients with knee osteoarthritis suggest that the impairments in force output observed in these patients are comparable with those elicited by experimental knee pain in Study III, at least at low force levels (Figure 4.4). Although these preliminary results refer to a very limited number of patients (N = 2), it is possible to speculate that, if the results remain consistent, increased force variability at low force levels in patients with knee osteoarthritis is mostly caused by pain *per se*, and not by other mechanisms associated with the chronic condition such as structural damage, inflammation and fear-avoidance. In that case, the association of pain relief with steadiness training may be beneficial for the recovery of these patients, although the potential risk of overload needs to be carefully considered in the design of a specific rehabilitation program.

Concluding remarks

The present work showed that the standard deviation of force signals increase monotonically with increasing force levels not only in task-related but also tangential force components. It was also shown that impairments in motor control during fatigue and pain increase variability of the three dimensional components of the force output, particularly at low target forces. The observed changes were dependent on the characteristics of the muscle group performing the task, such as the number of agonist and synergist muscles. Despite increased force variability, the results indicate that the overall performance during steadiness tasks, assessed by the mean magnitude and direction of the resultant force vector, was only marginally affected, suggesting that fatigue and pain have a strong influence during tasks that demand precise control of fine forces, while less accurate tasks might not be significantly affected.

The results reported in the preset work support that increased muscle activity and load sharing between muscles are the main factors responsible for the increase in three-dimensional force variability during fatigue. During pain, the mean muscle activity, assessed using bipolar surface EMG electrodes, was not significantly affected (except during contractions close to maximal voluntary force) despite a consistent increase in three-dimensional force variability. Since the increase in force variability during pain ultimately originates from changes in muscle activity, it is likely that a heterogeneous reorganization of activity within and between muscles compensated for potential inhibitory effects associated with pain and balanced the magnitude of the surface EMG.

Parameters of force variability reflect the dynamic control of forces originated from the collective output of a group of muscles. Since pain causes adaptations in multiple levels of the motor control system, the assessment of impairments in force steadiness provide an important tool to evaluate the motor stability of chronic pain patients. Moreover, interventions based on steadiness training may contribute to improve the ability of an individual to perform activities of daily life such as stair climbing and skilful hand tasks. Thus, the inclusion of this type of training in rehabilitation programs for patients with chronic musculoskeletal pain disorders may increase the efficiency of recovery of functional performance. From a clinical perspective, the assessment of multidirectional forces is relatively simple compared with, for example, multi-electrode EMG systems, constituting an advantage for the evaluation of patients. Association of pain relief treatment with training can be further beneficial for the patients, but the potential risks of overload and structural damage needs to be carefully considered.

Tables

Table 1. Overview on the interaction between muscle fatigue and force variability in humans

Reference	Fatigue task	Force-matching task	Parameters assessed	Main findings
Stiles (1976)	Continuous extension of the hand for 15–45 min	Parameters assessed during fatigue task	- RMS of displacement amplitude - Frequency of force fluctuations	- RMS of displacement increased more than 100 times at the end of fatigue task - Frequency of force fluctuations decreased from 8-9 Hz to 4-6 Hz
Stiles and Rietz (1977)	Continuous elevation of the heel for 10–45 min	Parameters assessed during fatigue task	- RMS of displacement amplitude - Frequency of force fluctuations - RMS of EMG from m. *soleus*	- RMS of displacement increased more than 100 times at the end of fatigue task, and was associated with increased RMS of soleus EMG - Frequency of force fluctuations decreased from 7-8 Hz to 5-6 Hz
Gottlieb and Lippold (1983)	10% MVC isometric middle finger extension until exhaustion	Parameters assessed during fatigue task	- Frequency analysis of force fluctuations	- Increased power of force fluctuations at 8-12 Hz as fatigue developed, as well as the development of another peak in power spectrum at 4-6Hz, superimposed with the existing 8-12 Hz tremor, showing that the two components are independent
Löscher et al. (1994)	30% MVC isometric plantarflexion until	Parameters assessed during fatigue task	- RMS and MNF of force signals - RMS and MNF of EMG from *gastrocnemius* and	- Increased RMS of force and RMS of EMG of both muscles as fatigue developed, with a concomitant decrease in MNF of force and EMG - Correlation between RMS of EMG and RMS of force

Table 1. Overview on the interaction between muscle fatigue and force variability in humans				
Reference	**Fatigue task**	**Force-matching task**	**Parameters assessed**	**Main findings**
	exhaustion		*soleus* muscles	(particularly for soleus) suggest alterations in motor unit firing rate, recruitment and synchronization
Löscher et al. (1996)	30% MVC isometric plantarflexion until exhaustion	Parameters assessed during fatigue task	- RMS of force - RMS of EMG from *gastrocnemius* and *soleus* muscles - Ratio between amplitudes of H and M waves (H/M)	- Increased RMS of force as fatigue developed, with a steeper increase after 60% of endurance time - Increased H/M ratio as fatigue developed for m. *gastrocnemius*, but not m. *soleus*, with steeper increase after 50% endurance time - Increased RMS of EMG as fatigue developed for both muscles, indicating increased excitatory drive to m. *triceps surae*, probably resulting in motor unit recruitment and increased motor unit firing rates
Sparto et al. (1997)	One long isometric trunk extension at variable target torques until exhaustion (55% – 95% MVC)	Parameters assessed during fatigue task	- RMS and SD of torque error - RMS and MDF of EMG from *erector spinae*, *latissimus dorsi*, and *internal oblique* muscles	- Increased RMS of torque error at the end of fatigue task, indicating decreased motor performance, although no changes were observed in SD of torque error - Increased RMS of EMG in m. *internal oblique* (25% larger) and in *m. latissimus dorsi* (70% larger) and decreased MDF of EMG in *erector spinae* at the end of fatigue task, probably due to greater recruitment in secondary trunk extensor muscles to compensate for the decline in force-generating capabilities of primary extensors - Increased lateral shear force at the end of fatigue task, but no changes in antagonist co-contraction
Cresswell and Löscher (2000)	30% MVC isometric plantarflexion	Parameters assessed during fatigue task	- RMS and MNF of torque signal	- Increased RMS at the end of fatigue task for all conditions, with lower RMS at ischemic and vibration conditions compared with baseline, probably due to reduced afferent

Table 1. Overview on the interaction between muscle fatigue and force variability in humans				
Reference	**Fatigue task**	**Force-matching task**	**Parameters assessed**	**Main findings**
	until exhaustion performed at baseline, after vibration of Achilles tendon and under ischemic conditions			input, which balanced the gain in afferent loop - Decreased MNF at the end of fatigue task only at baseline condition
Ebenbichler et al. (2000)	30%, 50%, and 70% MVC isometric knee extension	Parameters assessed during fatigue tasks	- SD of force - Power of force signals at 6-20 Hz	- SD of force increased as fatigue developed at 30% and 50%, but not 70% MVC - Power of force at 6-20 Hz was higher during 70% and 50% compared with 30% at the beginning of the contraction, but a general decrease in force power with fatigue resulted in similar power for all force levels at the end of the fatigue task, possibly due to recruitment of larger motor units, with lower firing rates
Semmler et al. (2000a)	15% MVC isometric elbow flexion until exhaustion, repeated before and after 4-week	Parameters assessed during fatigue task	- MVC force - SD of force	- Reduced MVC force after 4-week immobilization - SD of force increased as fatigue developed only before immobilization, but not after, suggesting that either larger motor units were not recruited or that discharge rates did not decline to minimal values during the fatigue contraction

Table 1. Overview on the interaction between muscle fatigue and force variability in humans				
Reference	**Fatigue task**	**Force-matching task**	**Parameters assessed**	**Main findings**
	immobilization of the arm			
Hunter et al. (2002)	15% MVC isometric elbow flexion until exhaustion during force task (exert upward force against sensor) and position task (support an inertial load with the same force)	Parameters assessed during fatigue task	- CV of force and SD of acceleration (vertical and horizontal) - EMG from elbow flexors and extensors	- Increased CV of force and SD of acceleration at the end of fatigue task, with higher relative increase during position compared with force task (vertical and horizontal) - Increased EMG activity of all elbow flexors at the end of fatigue task - Similar rate of increase of EMG for both tasks, but greater endurance time during force compared with position task, probably due to differences in MU recruitment
Hunter and Enoka (2003)	20% MVC isometric elbow flexion until exhaustion (performed 3 times, 7days interval)	Parameters assessed during fatigue task	- CV of force - EMG of elbow flexors and extensors - Endurance time	- Increased CV of force and EMG activity of all elbow flexors at the end of fatigue task - Slower rate of increase of biceps EMG and greater endurance time at 3rd compared to 1st session
Hunter et al.	20% MVC	Parameters	- SD of vertical and	- Similar EMG, SD of acceleration, and endurance time

Table 1. Overview on the interaction between muscle fatigue and force variability in humans				
Reference	**Fatigue task**	**Force-matching task**	**Parameters assessed**	**Main findings**
(2003)	isometric elbow flexion sustaining an inertial load until exhaustion (performed 3 times, 7days interval)	assessed during fatigue task	horizontal acceleration - EMG of elbow flexors and extensors - Endurance time	across the 3 sessions, indicating similar descending drive - Increased SD of vertical (but not horizontal) acceleration at the end of fatigue task, but no differences across sessions - At the end of fatigue task, EMG was highest for m. *brachialis* and lowest for short head of m. *biceps* compared with other elbow flexors (these changes differed from that during force task (Hunter and Enoka 2003))
Johnson et al. (2004)	Sustained low-force isometric contraction of m. *first dorsal interosseous*, keeping a constant firing rate of 1 MU	Parameters assessed during fatigue task	- SD of force - Surface and intramuscular EMG (amplitude, MDF, MU characteristics)	- Increased SD of force and MU firing rate variability - Although firing rate of the target MU was kept constant, increased amplitude and decreased MDF of EMG were observed, reflecting increased MU population
Kouzaki et al. (2004)	- 2.5% MVC isometric knee extension for 60 minutes - 5, 10, 15, 20, 30% MVC isometric knee extension for	Parameters assessed during fatigue task	- SD and power spectrum of force signals - integrated EMG (iEMG) from quadriceps muscles (RF, VM, VL)	- Increased SD of force at the end of fatigue task - Alternation of activity between *rectus femoris* (RF) and *vasti* (VM-VL), which modulated force fluctuations: - Higher SD of force during high RF compared with VM-VL activity, and increased power spectrum of force at high frequencies (8-12 Hz) - Higher correlation between SD of force and iEMG of RF compared with VM-VL

Table 1. Overview on the interaction between muscle fatigue and force variability in humans				
Reference	**Fatigue task**	**Force-matching task**	**Parameters assessed**	**Main findings**
	40 seconds			
Clark et al. (2005)	25% MVC isometric knee extension until exhaustion during normal and ischemic blood flow conditions	Parameters assessed during fatigue task	- CV of force - RMS of EMG from quadriceps and hamstrings muscles	- Increased force fluctuations at the end of fatigue task during both blood flow conditions - Women showed higher force fluctuations and higher overall (pooled) EMG activity at the end of fatigue task compared with men
Mottram et al. (2005a)	Isometric elbow flexion at 3.5% above recruitment threshold of a specific MU during force task (exert upward force against sensor) and position task (support an inertial load with the same force) for 161 ± 96 seconds	Parameters assessed during fatigue task * MU recruitment threshold assessed before and after both tasks	- MVC force - MU recruitment threshold - CV of force and SD of acceleration (vertical and horizontal) - EMG from *biceps*, *brachialis*, *triceps*, and upper *trapezius*	- Increased CV of force and SD of acceleration at the end of fatigue task, with higher relative increase during position compared with force task (vertical and horizontal) - Similar EMG force levels of all muscles and similar decline in MVC force and MU recruitment threshold after both tasks (force and position) - Higher mean arterial pressure, heart rate, rate of perceived exertion, and greater decline in MU firing rate during position compared with force task

Table 1. Overview on the interaction between muscle fatigue and force variability in humans

Reference	Fatigue task	Force-matching task	Parameters assessed	Main findings
Huang et al. (2006)	Sustained 25 and 75% MVC isometric index finger abduction	Parameters assessed during fatigue task	- RMS of finger force and acceleration - Surface EMG amplitude and MDF	- Increased finger force and acceleration variability during fatigue task, with higher increases for acceleration - Increased EMG amplitude and decreased EMG MDF
Lavender and Nosaka (2006)	6x5 repetitions of concentric or eccentric exercise at 50% of isometric MVC force	30, 50, and 80% MVC isometric elbow flexion	- MVC force - Range of motion (as a separate task) - CV of force * Assessed at before, 1h and 1-5 days after fatigue task	- Decreased MVC force and range of motion after both fatigue tasks; greater decrease after eccentric compared with concentric exercise - Increased CV of force immediately following and 1h after eccentric (but not concentric) exercise for all target forces show that changes in force fluctuations do not follow the time course of indicators of muscle damage
Semmler et al. (2007)	Repeated series of 40% MVC concentric or eccentric elbow flexion until a reduction of 40% in isometric MVC force	- Isometric MVC elbow flexion - 5, 20, 35, 50% MVC isometric elbow flexion * Reference MVC obtained before, after, and 24h after fatigue	- MVC force - CV of force - Average rectified EMG from *biceps*, *brachialis*, *brachioradialis*, and *triceps* - Percentage power spectrum in 0-4, 4-8, 8-12, 12-20 Hz bands	- Decreased MVC force after fatigue, but recovered 24 hours after concentric (but not eccentric) exercise - Increased CV of force and elbow flexors EMG after eccentric (but not concentric) exercise, both recovering 24 hours after; higher increases during low (5, 20%) compared with high (35, 50%) force levels - Force power decreased at 0-4 Hz and increased at 8-12 Hz after eccentric exercise, recovering 24 hours after * Recruitment of larger motor units may cause increased CV of force, and the effects are greater at low forces, i.e. in small MU populations
Dartnall et al. (2008)	Repeated series of 40%	- 2.5, 5, 10, 20, 35, and 50%	- CV of force - EMG amplitude	- Increased CV of force after fatigue task at all force levels, but after 24 hours, increased CV only at low forces

Table 1. Overview on the interaction between muscle fatigue and force variability in humans				
Reference	**Fatigue task**	**Force-matching task**	**Parameters assessed**	**Main findings**
	MVC eccentric elbow flexion until a reduction in 40% in isometric MVC force	MVC isometric elbow flexion (15s; MVC recorded at each session) - Isometric elbow flexion at low level, sustaining at least one active MU	- MU firing rate, firing rate variability, and synchronization index * Assessed at before, 0 and 24h after fatigue task	- Increased m. *biceps* EMG after fatigue at moderate and high forces, but only at 50% MVC after 24 hours - Mean discharge rate and synchronization index increased at 0 and 24h after fatigue task, but MU firing rate variability did *not* change with fatigue * Recovery of EMG and CV of force indicate only minor role of MU synchronization
Dundon et al. (2008)	Repeated series of 40% MVC eccentric or 30% MVC concentric elbow flexion until a reduction of 30% in isometric MVC	- 5, 10, 20, 40, 60% MVC isometric elbow flexion (12s) - Electrical stimulation at 1, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 Hz	- CV of force - EMG amplitude of elbow flexor muscles * Assessed before, 0, 2, and 24h after fatigue task	- Increased CV of force and EMG amplitude of m. *biceps* after eccentric exercise, particularly at low force levels, which lasted more than 24 hours - After concentric exercise, increased force fluctuations at low force levels and increased EMG at moderate force levels, both lasting less than 2 hours - During electrical stimulation, higher decrease of force at low compared with high stimulation frequency, recovering after 2 hours for concentric (but not eccentric) exercise. This low-frequency fatigue resulted in increased force fluctuations during 20Hz stimulation only following eccentric (but not concentric) exercise
Missenard et al. (2008)	Repeated 60% MVC isometric	7, 13, 33, 53% MVC isometric elbow flexion	Regression analysis between mean force and SD of force	- Fatigue did *not* affect the linear scaling of SDN (log-log slopes of regression line between mean and SD of force close to 1), but caused an increase in the linear gain of the SD of

Table 1. Overview on the interaction between muscle fatigue and force variability in humans				
Reference	**Fatigue task**	**Force-matching task**	**Parameters assessed**	**Main findings**
	elbow flexion and extension (20s) until exhaustion	(10s)		force proportional to the target force level
Reeves et al. (2008)	40% MVC isometric trunk extension until exhaustion	- Parameters assessed during fatigue task - Subjects also performed 10, 20, 40, 60, 80% MVC isometric trunk flexion and extension (no fatigue)	- SD of force signal - EMG amplitude and MDF from m. *erector spinae* (RA, EO, IO, TE, LE)	- Increased SD of force and decreased MDF of all muscles at the end of fatigue task - Increased SD of force and with increasing force level - All muscles increased activity with increasing effort of trunk flexion; but only IO and EO increased during trunk extensions; increased antagonist activity is needed to stabilize the agonist moment
Turner et al. (2008)	Repeated series of 50% 1-RM eccentric elbow flexion until a reduction of 40% of isometric MVC force	- Isometric MVC elbow flexion - 1-RM concentric elbow flexion - 10, 20, 40% 1-RM isometric elbow flexion (inertial load) at 60, 90 and 120º elbow flexion	- MVC and 1-RM forces - Averaged rectified EMG from *biceps*, *brachioradialis* and *triceps* muscles - SD of wrist acceleration (normalized by the load lifted [$m/(s^2.kg)$]) * Assessed at before, 0 and 24h after fatigue task	- Increased SD of acceleration and increased EMG of all muscles during fatigue for all tasks, with recovery 24 hours after only during eccentric task - Higher SD of acceleration following fatigue task at: - 10% 1-RM compared with 20 and 40% - 60º compared with 120º - Concentric compared with eccentric and isometric tasks * No load or angle differences before or 24 hours after, suggesting muscle damage as the main cause of motor impairments

Table 1. Overview on the interaction between muscle fatigue and force variability in humans				
Reference	**Fatigue task**	**Force-matching task**	**Parameters assessed**	**Main findings**
		angle - 10, 20, 40% 1-RM concentric and eccentric elbow flexion		
Contessa et al. (2009)	Repeated force profile consisted of 50% MVC (3s) and 20% MVC (50s) isometric knee extension	Parameters assessed during repeated 20% MVC task	- CV of force - Mean and CV of MU firing rate - Cross-correlation of firing rates of MUs with each other, and with force signals - MU synchronization	- Increased force fluctuations and increased common drive input with endurance time, which was *not* associated with increased firing rate variability or MU synchronization - CV of force was significantly correlated with the level of common drive and with the cross-correlation of firing rates - Increased recruitment of MUs * Small population size (4 subjects)
Dartnall et al. (2009)	Repeated series of 75% MVC eccentric elbow flexion until a reduction of 40% in isometric MVC	- Isometric MVC elbow flexion (3s) - 5, 10, 20, 35, 50% MVC isometric elbow flexion (10s) - Recruitment threshold isometric elbow flexion (3s) - Slow force	- CV of force - Surface EMG amplitude from m. *biceps* and m. *triceps* - Intramuscular EMG from m. *biceps* and m. *brachialis*: recruitment threshold, firing rate at recruitment, minimum and CV of firing rate * Assessed at before, 0 and 24h after fatigue task	- Increased force fluctuations at 0 and 24 hours after fatigue - Increased m. *biceps* and m. *triceps* EMG amplitude after fatigue task, with recovery of triceps EMG after 24 hours - Decreased MU recruitment threshold for m. *biceps*; reduced de-recruitment threshold for biceps and m. *brachialis*; increased firing rate at m. *biceps* and m. *brachialis* after fatigue, with no changes in CV of firing rate, suggesting that increased neural drive was necessary to maintain tonic MU discharge rate after eccentric exercise - Increased minimum firing rate for m. *biceps* and m. *brachialis*

Table 1. Overview on the interaction between muscle fatigue and force variability in humans

Reference	Fatigue task	Force-matching task	Parameters assessed	Main findings
		reduction (1% MVC every 10 seconds) after recruitment threshold task		
Holtermann et al. (2009)	25% MVC isometric elbow flexion until exhaustion	Parameters assessed during fatigue task	- CV of force - Motor unit synchronization	- Increased CV of force and increased motor unit synchronization at the end of fatigue task - Moderate correlation between motor unit synchronization and CV of force, but no associations between the "de-trended" values, suggesting a common fatigue modulation rather than a causal relation
Missenard et al. (2009)	1) Repeated 60% MVC isometric elbow flexion and extension (20s) 2) The same as 1) 3) Repeated 60% MVC isometric plantarflexion	1) 7, 13, 33, 53% MVC isometric elbow flexion (10s) 2) EMG-matching at 7, 13, 33, 53% MVC elbow flexion (10s) 3) Electrically sustained 5, 10, 20, 30, 40% MVC plantarflexion	- SD and CV of force - Surface and intramuscular EMG amplitude from elbow flexors	- Increased force fluctuations at all force levels after fatigue in (1). In (2), fluctuations increased only at low force levels - In (3), force fluctuations remained relatively unchanged - SDN (due to increased muscle activation) is the main factor responsible for the increase in force variability at moderate force levels, and peripheral contractile properties are *not* responsible for the increased variability in (1) and (2)

Table 1. Overview on the interaction between muscle fatigue and force variability in humans

Reference	Fatigue task	Force-matching task	Parameters assessed	Main findings
Meszaros et al. (2010)	Repeated series of 75% MVC eccentric or concentric elbow extension until a reduction of 25% in eccentric MVC	- Eccentric, concentric and isometric MVC elbow extension - Double pulse and single pulse electric stimulation - 10% MVC isometric elbow extension (30s)	- CV of isometric force - m. *triceps brachii* surface EMG RMS and MDF - Ratio between torque evoked by double/single stimulation	- Increased EMG amplitude and trend of increased force fluctuations at 10% MVC after eccentric, but not concentric fatigue task - Decreased amplitude and MDF of EMG during MVC tasks after both eccentric and concentric fatigue tasks - Double/single stimulation torque ratio remained unchanged after 3 minutes of fatigue task, but increased after 10 minutes (similar for eccentric and concentric)
Singh et al. (2010)	Series of squat exercises	15 and 20% MVC isometric knee extensions (15s)	- Normalized mean, peak, and standard deviation of the absolute force error - Mean and median frequencies (MNF, MDF)	- Increased magnitude of force fluctuations and shift of force signals towards higher frequencies after fatigue task
Svendsen and Madeleine (2010)	20% MVC isometric elbow flexion until exhaustion	- Parameters assessed during fatigue task - Subjects also performed 10, 20, 30, 40, 50, 60, 70, 80, 90% MVC isometric (5 sec), and a ramp (5-	- SD, CV and sample entropy of three-dimensional (task-related and tangential) force components - Error between target and exerted forces	- Increased SD and CV of force at the end of fatigue task, with no changes in force error or sample entropy - Task-related forces showed higher SD, but lower CV and sample entropy compared with tangential force components, revealing interaction between task-related and tangential force components - SD and error increased with force level - During ramp contraction, force error, SD and entropy increased with force level, but CV decreased

Table 1. Overview on the interaction between muscle fatigue and force variability in humans

Reference	Fatigue task	Force-matching task	Parameters assessed	Main findings
		50% MVC, 2 min) elbow flexion		- Men showed higher force SD and entropy compared with women, but lower CV of force
Keller et al. (2011)	Sustained 20% MVC isometric elbow flexion * Cortical and brachial plexus stimulation at start and end of fatigue task	Parameters assessed during fatigue task	- CV of force - Surface EMG amplitude from elbow flexors and extensors	- Increased force fluctuations and increased EMG of m. *biceps*, m. *brachioradialis* and m. *triceps* at the end of fatigue task - Cortical and brachial plexus stimulation did not influence the increase in fluctuations of the elbow flexor muscles, indicating similar supraspinal fatigue for men and women

Table 2. Overview on the interaction between pain and force variability in humans				
Reference	**Pain condition and study design**	**Tasks performed**	**Parameters assessed**	**Main findings**
Akebi et al. (1998)	- Low back pain: acute (< 1 month), sub-acute (between 1 and 6 months), and chronic (>6 months) - Case-control design	- MVC isokinetic trunk flexion and extension at 60º/sec and 120º/sec	- CV of force	- Patients showed higher CV of force than controls, illustrating that CV of force could be considered an adjunctive index for follow-up of low back pain patients - CV of force was also higher in women compared with men, and higher at 120º/sec compared with 60º/sec, but no effects of age were observed
Descarreaux et al. (2004)	- Low back pain - Case-control design	- MVC "single impulse" trunk flexion and extension - 50 and 75% MVC "single impulse" trunk flexion and extension (10 trials, no feedback)	- VAS pain score - MVC force - Time to peak force, time to peak force variability, and peak force variability * Patients were divided in 2 subgroups: 'short' and 'long' time to peak force	- Higher VAS scores in patients compared with controls, with the highest scores for the 'short' patient subgroup - Similar MVC force and peak force variability for patients and controls - Patients in the 'long' subgroup showed higher time to peak force variability compared to 'short' and controls, reflecting a protective strategy to limit pain
Farina et al. (2004)	- Experimental muscle pain (m. *tibialis*	- isometric MVC dorsiflexion - 10% MVC	- VAS pain score - CV of force - Motor unit firing rate	- Higher VAS scores following injection of hypertonic saline compared with non-painful conditions - No differences across pain conditions in CV of force or

Table 2. Overview on the interaction between pain and force variability in humans				
Reference	**Pain condition and study design**	**Tasks performed**	**Parameters assessed**	**Main findings**
	anterior) using injections of hypertonic saline - Placebo-controlled crossover design (isotonic saline used as placebo)	isometric dorsiflexion (20s)	- Muscle fibre conduction velocity	muscle fibre conduction velocity - Decreased motor unit firing rate, with a negative correlation between firing rate and VAS scores
Hortobágyi et al. (2004)	- Knee osteoarthritis pain - Case-control design	- MVC isometric, concentric, and eccentric knee extension force - Functional tests (gait (18 m), climb up and down 12-step stairs, get-up-and-go test) - Position-matching task at 15, 30, 45, 60, 75º knee angle	- VAS pain score - Knee pain (0-4 scale) - MVC force - Time to perform functional tasks - Position error - SD and mean absolute error of force	- Patients showed higher VAS scores, lower MVC force and longer time to perform functional tasks compared with controls, reflecting patients' impaired proprioception - Patients showed higher SD of force, higher force error and greater position errors during concentric and eccentric (but not isometric) tasks, with greater impairments during eccentric task, possibly due to higher neural inhibition and impaired MU recruitment in patients

Table 2. Overview on the interaction between pain and force variability in humans				
Reference	**Pain condition and study design**	**Tasks performed**	**Parameters assessed**	**Main findings**
		- Isometric, concentric, and eccentric knee extension at 50 N and 100 N		
Descarreaux et al. (2005)	- Experimental low back pain using cutaneous electrical stimulation at L3 - Self-controlled design (no placebo condition)	- MVC "single impulse" trunk flexion and extension - 50 and 75% MVC isometric trunk flexion and extension (10 trials, no feedback)	- MVC force - Time to peak force, time to peak force variability, and peak force variability	- No pain-related changes in time to peak force, suggesting a closed loop control strategy, as opposed to chronic low back pain patients - Pain elicited higher absolute error and higher time to peak force variability - Peak torque variability increased during painful compared with non-painful condition only at 75% MVC
Bandholm et al. (2006)	- Subacromial impingement syndrome (SIS) pain - Case-control design	- Isometric MVC shoulder abduction, adduction, internal and external rotation - MVC handgrip - 20, 27.5, 35%	- VAS pain score - Shoulder and handgrip MVC forces - SD and CV of force - EMG RMS from shoulder muscles	- Patients showed higher SD and CV of force compared with controls only during concentric contractions at 35% MVC, probably because habits of continued activity of the shoulders in patients counterbalanced sensory-motor deficit - Higher VAS scores for patients compared with controls - Similar MVC forces and EMG activity between patients and controls - Both groups showed higher SD of force at higher forces

Table 2. Overview on the interaction between pain and force variability in humans				
Reference	**Pain condition and study design**	**Tasks performed**	**Parameters assessed**	**Main findings**
		MVC isometric, concentric and eccentric shoulder abduction		
Schulte et al. (2006)	- Self-reported work-related musculoskeletal pain in the neck/shoulder region - Case-control design	- MVC isometric shoulder elevation and elbow flexion - 30% MVC isometric shoulder elevation and elbow flexion (6 min)	- Borg scale for rating of perceived exertion - SD and CV of force - EMG - Muscle fibre conduction velocity	- Perceived exertion increased over time, but it was not different between groups - Decreased shoulder elevation force and increased CV of shoulder elevation force in cases compared with controls, maybe due to reduced proprioception - No changes in CV of elbow flexion force and no differences in SD of force between groups - No differences in conduction velocity between groups
Del Santo et al. (2007)	- Experimental muscle pain (m. *abductor digiti minimi*, ADM, and m. *biceps brachii*, BB) using injections of ascorbic acid - Self-	- 30% MVC isometric contraction of ADM and BB - 6 transcranial magnetic stimulations were applied to elicit responses from	- VAS pain score - CV of force - RMS of EMG - Area of motor evoked potential (MEP)	- Higher VAS scores following injection of ascorbic acid compared with pre- and post-injection - Pain elicited higher CV of force and larger MEP area during pain compared with pre- and post-pain (both tasks), suggesting that pain-induced reduction in motor excitability was compensated by increased central drive or increased synchronization of corticospinal input, resulting in increased MU synchronization - Increased RMS of EMG from ADM and BB during

Table 2. Overview on the interaction between pain and force variability in humans

Reference	Pain condition and study design	Tasks performed	Parameters assessed	Main findings
	controlled crossover design (no placebo condition)	contralateral ADM and BB		painful compared with non-painful conditions
Descarreaux et al. (2007a)	- Low back pain - Case-control design	- MVC "single impulse" trunk flexion and extension - 50 and 75% MVC "single impulse" trunk flexion and extension (10 trials, no feedback)	- MVC force - Time to peak force, peak force variability, absolute force error - EMG from *erector spinae* (ES), *multifidus* (MUL), *rectus abdominis* (RA), and *external oblique* (EO) muscles (right side only)	- Similar MVC forces for patients and controls - Patients showed longer time to peak force than controls, but no differences in peak force variability or absolute error - No differences in EMG amplitude were observed, but patients showed longer bursts of activity than controls for all recorded muscles, possibly reflecting a protective mechanism caused by fear avoidance effects, since patients reported just mild pain scores during assessments
Descarreaux et al. (2007b)	- Whiplash pain - Case-control design	- MVC "single impulse" cervical flexion and extension - 50 and 75% MVC "single impulse" cervical flexion and	- Time to peak force, peak force variability, absolute error of peak force - EMG from m. *sternocleidomastoideus* (SCM) and m. *paraspinal*	- Patients showed lower MVC force, longer time to peak force, higher peak force variability, and compared with controls, reflecting the effects of chronic symptoms such as reduced MVC force and altered proprioceptive mechanisms - No differences in absolute error of peak force - Higher EMG of m. SCM in patients compared with controls, but no differences in EMG of m. *paraspinal*

Table 2. Overview on the interaction between pain and force variability in humans				
Reference	**Pain condition and study design**	**Tasks performed**	**Parameters assessed**	**Main findings**
		extension (10 trials, no feedback)		
Bandholm et al. (2008)	- Experimental muscle pain (m. *supraspinatus*) using injections of hypertonic saline - Self-controlled crossover design (no placebo condition)	- Isometric MVC shoulder abduction, adduction, internal and external rotation - 20, 27.5, 35% MVC isometric, concentric and eccentric shoulder abduction	- VAS pain score - SD and CV of force - EMG RMS from shoulder muscles	- Higher VAS scores following injection of hypertonic saline compared with pre- and post-injection - Increased SD (but not CV) of force and increased middle deltoid EMG during painful compared with non-painful isometric tasks, probably due to pain-induced changes in MU control strategy and to inhibition of group Ib afferent - No effects of pain during concentric or eccentric contractions - Differences between experimental and chronic pain may reflect long-term central adaptations in chronic patients
Camargo et al. (2009)	- Subacromial impingement syndrome chronic pain - Case-control design	- MVC isometric shoulder abduction - 35% MVC isometric shoulder abduction	- MVC torque - SD, CV and MDF of torque	- Similar MVC torque, SD, CV and MDF of torque between patients and controls
Henriksen et al. (2011a)	- Experimental Achilles tendon	Full cycles of one-legged	- VAS pain score - Peak joint angle	- Higher VAS scores following injection of hypertonic saline compared with non-painful conditions

Table 2. Overview on the interaction between pain and force variability in humans				
Reference	**Pain condition and study design**	**Tasks performed**	**Parameters assessed**	**Main findings**
	pain using injections of hypertonic saline - Placebo-controlled crossover design (isotonic saline used as placebo)	plantar and dorsal flexions (with extended knee)	- Mean angular movement and velocity - SD of resultant ground reaction force (GRF) vector - MDF and MNF of GRF - EMG from plantar and dorsiflexors	- No changes in SD of force during pain - Changes during painful compared with non-painful tasks: Reduced EMG amplitude for all muscles; during concentric phase, reduced angular velocity and increased power at 9-10 Hz; during eccentric phase, increased MNF of GRF and increased power at 9-11 Hz, suggesting increased MU synchronization, selective inhibition of low-threshold MUs and recruitment of larger MUs
Pua et al. (2010)	- Hip osteoarthritis pain - Patients only (no control)	- Climbing 6-step stairs (preferred and fast speeds) - Normal gait (8 m) - Isometric knee extension MVC force	- Correlation between MVC force or SD of MVC force with: - Time for stair climbing - Habitual gait speed * Separate analysis for high and low knee extensor strength	- Knee extensor steadiness was correlated only with fast speed stair climbing (in particular for patients with high strength) indicating that improvements in force steadiness might benefit performance in tasks involving high motor demands - Knee extensor strength was correlated with stair climbing time at both speeds
Zanca et al. (2010)	- Subacromial impingement syndrome (SIS) pain - Case-control design	- MVC isometric medial and lateral shoulder rotation - 50% MVC isometric medial and lateral	- MVC torque - SD and CV of torque	- Similar MVC torque, SD and CV of torque between patients and controls

Table 2. Overview on the interaction between pain and force variability in humans				
Reference	**Pain condition and study design**	**Tasks performed**	**Parameters assessed**	**Main findings**
		shoulder rotation		
Farina et al. (2011)	- Experimental muscle pain (m. *abductor digiti minimi*, ADM) using injections of hypertonic saline - Placebo-controlled crossover design (isotonic saline used as placebo)	- Ramp ADM abduction (0-10% MVC) - 10% MVC isometric ADM abduction * 5 subjects received injection of hypertonic saline in m. *tibialis anterior* during an additional session	- NRS pain score - CV of force - MU recruitment threshold, discharge rate, synchronization, and CV of inter-spike interval (ISI) - Strength of common drive	- Injection of hypertonic saline resulted in higher VAS scores compared with non-painful conditions - Increased CV of force, decreased MU firing rate during painful compared with non-painful conditions - No changes in MU recruitment threshold, CV of ISI, strength of common drive during pain, indicating unchanged level of synaptic noise - No association between CV of ISI and CV of force - CV of force was correlated with low-frequency components of MU spike trains, suggesting higher variability of synaptic input caused increased CV of force * Pain in m. *tibialis anterior* did not change CV of force in ADM, showing that distraction did not influence the results
Muceli et al. (2011)	- Chronic neck pain - Case-control design	Isometric cervical flexion (10 sec) at: (1) 15 N (2) 25% MVC (before and after vibration)	- Pressure pain threshold (PPT) at C2 - MVC force - CV of force - Power spectrum of force in bands 0-3, 4-6, 8-12 Hz - MU discharge rate and discharge variability (in 1) - ARV from EMG (in 2)	- Patients showed lower PPT, lower MVC force, higher CV of force and higher low-frequency (0-3 Hz) power of force signals compared with controls - No group differences in EMG amplitude, MU firing rate or discharge variability - After vibration, patients (but not controls) showed decreased CV of force and low-frequency power, reaching no difference in power spectrum compared with controls after vibration, which suggests impaired afferent input as possible cause of increased CV of force

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