Chapter 2

Motor consequences of experimentally induced limb pain: A systematic review

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Compelling evidence exists that pain may affect the motor system, but it is unclear if different sources of peripheral limb pain exert selective effects on motor control. This systematic review evaluates the effects of experimental (sub)cutaneous pain, joint pain, muscle pain and tendon pain on the motor system in healthy humans. The results show that pain affects many components of motor processing at various levels of the nervous system, but that the effects of pain are largely irrespective of its source. Pain is associated with inhibition of muscle activity in the (painful) agonist and its non-painful antagonists and synergists, especially at higher intensities of muscle contraction. Despite the influence of pain on muscle activation, only subtle alterations were found in movement kinetics and kinematics. The performance of various motor tasks mostly remained unimpaired, presumably as a result of a redistribution of muscle activity, both within the (painful) agonist and among muscles involved in the task. At the most basic level of motor control, cutaneous pain caused amplification of the nociceptive withdrawal reflex, whereas insufficient evidence was found for systematic modulation of other spinal reflexes. At higher levels of motor control, pain was associated with decreased corticospinal excitability. Collectively, the findings show that short-lasting experimentally induced limb pain may induce immediate changes at all levels of motor control, irrespective of the source of pain. These changes facilitate protective and compensatory motor behavior, and are discussed with regard to pertinent models on the effects of pain on motor control.

Introduction

Pain may have profound effects on motor behavior that are mediated at various levels of the nervous system, ranging from spinal reflex circuits to (pre)motor cortices. The effects of pain thus may become manifest in a variety of motor parameters such as reflex amplitude, muscle activity, force production, kinematics, movement strategy and activation of cortical areas involved in motor control. Empirical studies typically focus on a single or a limited number of parameters, whereas pertinent descriptive models generally comprise only a selection of the complex interactions between pain and the motor system. Consequently, a coherent view on the consequences of pain on motor behavior has been lacking. Only recently, Hodges and Tucker (2011) proposed a new theory on motor adaptation to pain involving changes at multiple levels of the motor system.

Acute intense pain has been thought to elicit motor responses that serve to protect the painful limb from further damage. Although such behavior serves a clear short-term benefit for the injured part, it may have long-term negative consequences if it does not dwindle with healing of the initial injury. The presence of chronic pain may lead to abnormalities in motor control, either as a direct effect of pain or as a consequence of adopting a movement strategy that compensates for such direct effects (Hodges and Tucker, 2011). Conversely, abnormalities in motor control may lead to the development of (chronic) pain, e.g., when tissues are overloaded (Arendt-Nielsen and Graven-Nielsen, 2008; Sterling et al., 2001). In clinical pain conditions, multiple factors may play a role in the effects of pain on motor behavior, rendering it difficult to disentangle the separate effects of nociceptive input on the motor system. Experimental procedures to induce pain in healthy volunteers allow for establishing clear-cut, reproducible cause-and-effect relations and thus provide invaluable means to isolate motor consequences of acute pain.

The various procedures to induce pain in a controlled manner have specific advantages and methodological limitations (Arendt-Nielsen and Graven-Nielsen, 2008; Graven-Nielsen, 2006; Staahl and Drewes, 2004). Ideally, the effects of pain are studied by selective activation of nociceptive afferents without causing structural tissue damage. In reality, however, experimental procedures cannot exclusively target nociceptive afferents

but also activate non-nociceptive afferents (Graven-Nielsen, 2006; Mense, 1993). Appropriate control conditions that take into account stimulation of these non-nociceptive afferents are required to draw inferences on the effects of pain on motor control.

This systematic review evaluates the effects of experimentally induced pain on the motor system in healthy humans in order to obtain more insight into the empirical evidence for interactions between pain and the motor system. The source of pain (i.e., skin, joint, muscle or tendon) is expected to have differential effects on motor control, considering that these tissues have different roles in the motor system and projections of nociceptive afferents may vary among various tissue types (Almeida et al., 2004; Millan, 1999). This review is limited to pain localized in the extremities and focuses on the effects of controlled external stimuli that lead to localized pain without causing structural damage.

Literature Search Methods

A literature search was performed in three electronic databases (Medline, EMBASE and Web of Knowledge) to identify potentially relevant studies. The search strategy was developed in collaboration with a specialist in information retrieval of the Leiden University Medical Center Library and comprised a combination of MeSH terms and free text terms related to motor function (including proprioception) combined with terms related to experimental pain (see Supplement 2.1). The results were limited to articles in English, German and Dutch. The most recent search was performed on March 7th 2011.

The selection process is presented in Figure 2.1. The identified studies were first screened by title and abstract, after which the full text of potentially relevant articles was studied. Papers were included if all of the following four criteria were met: *(1)* effects of experimentally induced pain on one or more of the following parameters were studied: spinal reflexes, muscle activity, movement characteristics, proprioception and activation in motor-related brain areas; *(2)* experimental pain was induced by a controlled stimulus leading to localized pain without causing structural damage (i.e., thermal, mechanical, electrical or chemical stimulation); *(3)* pain was localized in the upper extremity or lower

extremity; and *(4)* data were obtained from healthy human subjects. Note that papers were excluded if pain was induced by ischemia or eccentric exercise, because effects of ischemia are non-specific and eccentric exercise may lead to inflammatory reactions and structural damage to muscle tissue (Friden and Lieber, 1992). In addition, reference lists of all included publications as well as reviews on this topic were tracked following the procedure described above. In case there was any uncertainty about inclusion or exclusion, a second, independent reviewer was consulted. Discrepancies between the reviewers were to be resolved by consensus agreement. However, no such discrepancies arose during the process.

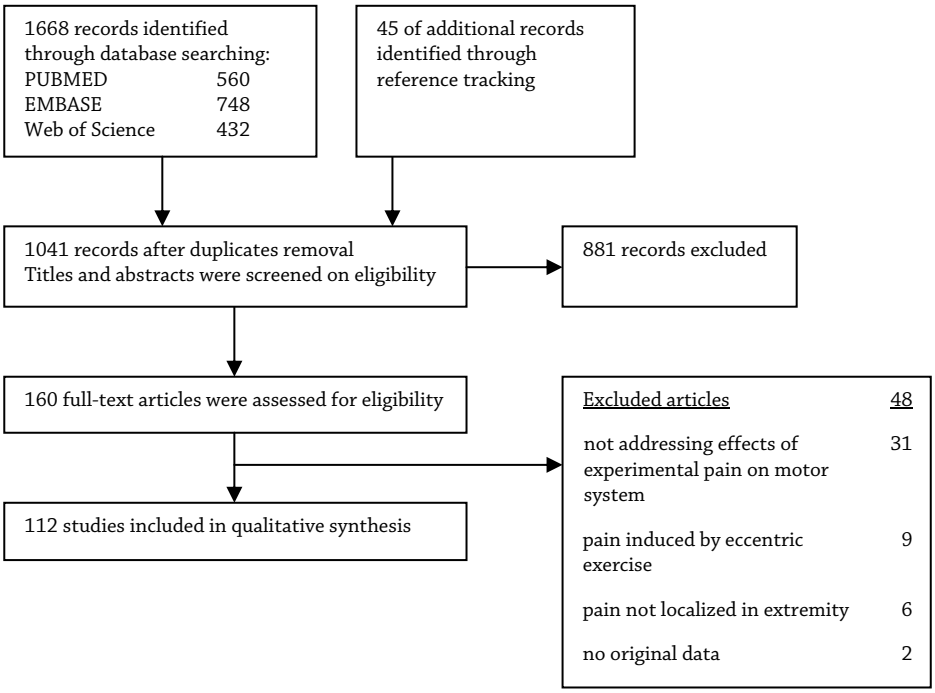

Figure 2.1 Flow chart of study search and selection.

Data regarding the type, intensity and location of pain, the test protocol, outcome parameters and performed motor tasks were extracted using a standard form. Outcome parameters were categorized into one or more of the following aspects of motor function: *(1)* spinal reflexes; *(2)* muscle activity; *(3)* task performance, movement kinetics and kinematics; *(4)* proprioception; and *(5)* brain activation. The systematic review of studies in each category is preceded by a short introduction providing a framework for the topic in question. All studies fulfilling the inclusion criteria are presented in Supplement 2.2 (Tables S2.1-2.8), which summarize the results on the effects of (sub)cutaneous pain, joint pain, muscle pain and tendon pain. If possible, pain intensity is categorized into mild (Visual Analogue Score (VAS) <30mm), moderate (VAS 30-54mm) and severe pain (VAS >54mm) (Collins et al., 1997). Note that some authors did not explicitly report measures of pain intensity, whereas others expressed pain intensity as VAS-peak, VAS-mean or the area under the VAS curve (on the basis of which the average pain level was calculated). Results for each of the aforementioned aspects of motor function are summarized in the text, with *n* indicating the number of studies on which the description of results is based. A more detailed description of the results is provided online (see Supplement 2.3).

Results

The distribution of studies over the various aspects of motor function (Figure 2.2) reveals that research has concentrated on muscle activity and movement characteristics. These aspects of motor function were examined predominantly by means of experimentally induced muscle pain, whereas spinal reflexes and brain activation patterns were mainly examined by means of experimentally induced cutaneous pain. A direct comparison between different pain sources was made in only 9 out of 112 studies. Overall, the effects of (sub)cutaneous pain and muscle pain have received considerable attention, unlike the effects of tendon pain and joint pain.

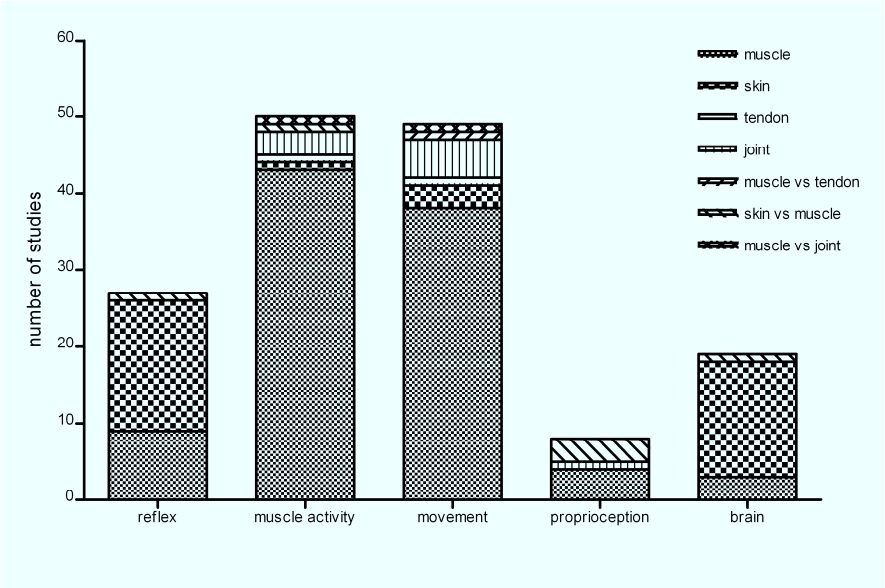

Figure 2.2 Overview of the studies included in this review, grouped by aspects of motor function and sources of pain under study. Several studies addressed more than one aspect of motor function and are thus presented in more than one column. Within a given column, each study can only appear once; the source(s) of pain under study (e.g. 'muscle' or 'muscle vs. skin') are indicated by various patterns.

Spinal reflexes

Spinal reflexes belong to the most basic elements of motor behavior. On this level, the effects of experimentally induced pain have been studied for the nociceptive withdrawal reflex (NWR; *n*=13), the phasic stretch reflex (*n*=2), the H-reflex (*n*=17) and inhibitory spinal circuits (*n*=7; see Table S2.1).

The NWR (for reviews, see Clarke and Harris, 2004; Sandrini et al., 2005) is a spinal reflex elicited by noxious stimulation of cutaneous afferents and has a 'modular organization' in animals (Clarke and Harris, 2004) and humans (Andersen et al., 1999, 2001, 2003; Schmit et al., 2003; Sonnenborg et al., 2001). The evoked motor response represents the most appropriate movement to withdraw the stimulated area from the offending source. Pain stimuli applied to the skin (Andersen et al., 1994; Ellrich and Treede, 1998; Ellrich et al., 2000; Grönroos and Pertovaara, 1993) or muscle (Andersen et al., 2000) consistently caused a modulation of the NWR, which probably served to protect the painful tissue, a finding in line with those obtained from animal research (Clarke and

Harris, 2004). However, effects of phasic muscle pain may depend on the exact timing of the painful intramuscular electrical stimulation (Andersen et al., 2006; Ge et al., 2007). Suppression of the NWR was observed during painful heterotopic stimulation, which was attributed to a 'diffuse noxious inhibitory control' mechanism (Roby-Brami et al., 1987; Serrao et al., 2004; Terkelsen et al., 2001; Willer et al., 1984, 1989).

At the spinal level, motor output is modulated by various excitatory and inhibitory circuits (Pierrot-Deseilligny and Burke, 2005). The most well-known excitatory spinal circuit consists of Ia afferents originating from muscle spindles and projecting to α-motoneurons of the homonymous muscle and synergists, which leads to a reflex contraction of a previously stretched muscle (i.e., the phasic stretch reflex). The H-reflex is evoked by direct stimulation of Ia afferents, thereby bypassing the muscle spindles and fusimotor activity that are involved in the stretch reflex, and is generally assumed to reflect excitability of the motor neuron pool (Knikou, 2008). Inhibitory spinal circuits mediated by Ib interneurons play a role in coordinating the activity of muscles operating at several joints (Jankowska, 1992; Rossi and Decchi, 1997) and protective negative feedback circuits mediated by Renshaw cells inhibit contracting muscles (recurrent inhibition; for a review, see Katz and Pierrot-Deseilligny, 1999). We found insufficient evidence for systematic modulation of the phasic stretch reflex, the H-reflex, or inhibitory circuits by pain stimuli applied to the skin or muscle. The failure to detect systematic modulation of those reflexes does not necessarily imply that pain has no influence on the associated spinal circuits. Findings regarding these spinal reflexes – which are typically prone to methodological issues – were often highly variable and obtained from small samples. Nevertheless, there were some indications that the effects of pain may to some extent be mediated by inhibitory spinal circuits, e.g., through reinforcement of recurrent inhibition during contraction of a painful muscle (Rossi et al., 2003a) or through modulation of the Ib inhibitory pathway (Rossi et al., 1999a, 1999b; Rossi and Decchi, 1995, 1997). As it stands, it is not clear if this modulation depends on the origin of pain.

Muscle activity

The effects of experimentally induced pain on muscle activity have been examined at rest (Table S2.2: n=10), during isometric and dynamic contractions (Tables S2.3: n=23 and

Table S2.4: *n*=14) and during low-load repetitive work (Table S2.5: *n*=5). For isometric and dynamic contractions, the effects of pain on the activity of the (painful) agonist muscle, the non-painful synergists and the non-painful antagonists are presented in separate columns.

Experimentally induced pain generally did not affect resting muscle activity (Birznieks et al., 2008; Cobb et al., 1975; Fernández-Carnero et al., 2010; Ge et al., 2008; Graven-Nielsen et al., 1997a, 1997b; Madeleine and Arendt-Nielsen, 2005; Serrao et al., 2007; Svensson et al., 1998; Xu et al., 2010), but facilitated muscle cramps when latent myofascial trigger points were stimulated (Ge et al., 2008; Serrao et al., 2007; Xu et al., 2010). During both isometric and dynamic contractions, activity of the (painful) agonist (Birch et al., 2000b; Ciubotariu et al., 2004, 2007; del Santo et al., 2007; Ervilha et al., 2004a, 2004b, 2005; Falla et al., 2007, 2008, 2009, 2010; Farina et al., 2005a; Ge et al., 2005; Graven-Nielsen et al., 1997a; Henriksen et al., 2007, 2009a, 200b, 2011; Madeleine et al., 1999a, 1999b, 2006; Martin et al., 2008; Qerama et al., 2005) and its non-painful antagonist (Ervilha et al., 2004a, 2004b; Henriksen et al., 2009b; Madeleine et al., 1999b) generally was reduced by pain arising from the skin, joint, muscle, or tendon. However, parameters derived from the surface electromyography (sEMG) signal of these muscles (i.e., amplitude and median power frequency) often remained unaffected during contractions at a relatively low intensity, i.e., <25% of the maximum voluntary contraction (MVC) for muscles located in the upper or lower limb (Birch et al., 2000a; Farina et al., 2004a, 2005b, 2008; Hirata et al., 2010; Hodges et al., 2008; Madeleine and Arendt-Nielsen, 2005; Tucker and Hodges, 2009) and <15% MVC for muscles located in the shoulder-neck region (Diederichsen et al., 2009; Samani et al., 2010). During dynamic tasks, several findings indicated that inhibition of a muscle was most pronounced when activity was highest (Ervilha et al., 2004a, 2004b; Graven-Nielsen et al., 1997a; Henriksen et al., 2007, 2009a; Hodges et al., 2009). These findings suggest that the likelihood of a muscle being inhibited by pain may depend on its activation level: the stronger the activity, the more likely that its activity will be reduced. However, activity of the painful muscle remained unaffected despite a relatively high intensity of isometric contraction in four out of eight studies (Bandholm et al., 2008; Graven-Nielsen et al., 1997a; Madeleine and Arendt-Nielsen, 2005; Schulte et al., 2004).

Notably, findings at low intensity muscle contractions may depend on the applied EMG technique, since sEMG recordings failed to detect any pain-induced alterations (Birch et al., 2000a; Farina et al., 2004a, 2005b; Hodges et al., 2008; Schulte et al., 2004; Tucker et al., 2009), whereas imEMG recordings showed adaptations in motor unit firing and recruitment (Birch et al., 2000a; Farina et al., 2004a, 2005b, 2008; Hodges et al., 2008; Tucker et al., 2009; Tucker and Hodges, 2009, 2010). Several findings, including unaltered sEMG parameters following electrical stimulation of motor axons (Farina et al., 2005a; Qerama et al., 2005) and unaffected muscle fiber conduction velocity in four out of five studies (Farina et al., 2004a, 2005a, 2005b, 2008; vs. Schulte et al., 2004), indicated that alterations in muscle activation were due to central rather than peripheral effects of pain. Furthermore, several studies revealed signs of redistribution of activity, both within the (painful) agonist (Falla et al., 2008, 2009, 2010; Tucker et al., 2009; Tucker and Hodges, 2009, 2010) and among muscles involved in the task (Bandholm et al., 2008; Ciubotariu et al., 2004; Diederichsen et al., 2009; Ervilha et al., 2004b, 2005; Falla et al., 2007; Graven-Nielsen et al., 1997a; Hodges et al., 2009; Madeleine et al., 1999a, 1999b, 2008; Samani et al., 2009, 2010; Schulte et al., 2004). Reduced activation of painful muscles in some cases was compensated by activation of non-painful synergists (Bandholm et al., 2008; Ciubotariu et al., 2004; Diederichsen et al., 2009; Ervilha et al., 2004b, 2005; Madeleine et al., 1999b; Schulte et al., 2004). However, non-painful synergists often remained unaffected (Birch et al., 2000b; Henriksen et al., 2009a; Hodges et al., 2008; Schulte et al., 2004) or were inhibited just like the (painful) agonist (Ciubotariu et al., 2004, 2007; Ervilha et al., 2004a, 2004b, 2005; Henriksen et al., 2007, 2009b, 2011).

Task performance, movement kinetics and kinematics

The effects of experimentally induced pain on characteristics of motor control have been examined in terms of kinetics, kinematics and other indices of task performance during isometric contractions (Table S2.3: n=22), dynamic contractions (Table S2.6: n=23) and low-load repetitive work (Table S2.5: n=7).

The performance of various motor tasks mostly remained unimpaired by pain arising from skin, joint, muscle, or tendon. Subjects were able to produce a given submaximal

force level (Bandholm et al., 2008; del Santo et al., 2007; Farina et al., 2004a, 2005a, 2005b, 2008; Hodges et al., 2008; Madeleine and Arendt-Nielsen, 2005; Martin et al., 2008; Schulte et al., 2004; Tucker et al., 2009; Tucker and Hodges, 2009, 2010), which was often associated with reduced sEMG activity level of the (painful) agonist muscle (see *Muscle activity*). Maximum voluntary force production was reduced in four out of five studies (Graven-Nielsen et al., 1997a, 2002; Henriksen et al., 2010b; Slater et al., 2003; vs. Slater et al., 2005). In dynamic motor tasks, effects of pain were mostly reflected in the movement kinetics, e.g., in a reduction of peak moments around the joint upon which a painful muscle acted (Bonifazi et al., 2004; Henriksen et al., 2007, 2009a, 2009b, 2010a, 2010b), although impact force just after heel strike was unaffected by pain in a knee extensor muscle (Henriksen et al., 2008). Despite observed alterations in kinetics, changes in movement kinematics were absent (Diederichsen et al., 2009; Henriksen et al., 2007, 2008, 2009b; Maihöfner et al., 2007) or rather subtle (Bonifazi et al., 2004; Ervilha et al., 2004a, 2004b, 2005; Henriksen et al., 2009a, 2011; Jaberzadeh et al., 2003; Madeleine et al., 1998, 1999a, 1999b, 2008). The performance of computer work (Birch et al., 2000b, 2001; Samani et al., 2009, 2010) or manual dexterity tasks (Smith et al., 2006) was not deteriorated by experimentally induced muscle pain. During quiet standing, pain applied to the lower leg muscles led to weight shifting to the non-painful leg (Hirata et al., 2010). Postural stability was slightly reduced by severe pain induced in the bilateral upper trapezius muscles (Vuillerme and Pinsault, 2009) and by pain applied to cutaneous or muscular tissue of the lower leg (Blouin et al., 2003; Corbeil et al., 2004; Hirata et al., 2010; Madeleine et al., 1998, 1999b), but it remained unaffected by pain arising from other sources (Bennell and Hinman, 2005; Corbeil et al., 2004; Madeleine et al., 1999a, 2004).

Proprioception

The sense of positions and movements of one's body parts, as well as the perception of forces produced by muscles, are basic requirements for adequate motor control. Proprioception not only provides information about the internal state of a limb to facilitate movement planning, it also allows for more flexible movement control (Gentilucci et al., 1994; Park et al., 1999) and assists the voluntary control of goal-

directed movements, e.g., by triggering muscle activation sequences (Park et al., 1999) or by timing and coordinating movement sequences (Cordo et al., 1994).

Indications were found of a slight deterioration of proprioception (Table S2.7: *n*=8). Pain stimuli applied to skin or muscle caused a deterioration of movement sense – albeit not in all conditions (Matre et al., 2002; Weerakkody et al., 2008) – and the perception of produced force (Weerakkody et al., 2003). Although it has been reported that pain caused a distortion or loss of position sense (Rossi et al., 1998, 2003b), no quantitative evidence has been presented for impaired joint position sense (Bennell et al., 2005; Matre et al., 2002) or alterations in firing of muscle spindle afferents (Birznieks et al., 2008). Indications were found that muscle pain interfered with processing of other afferent signals from the muscle (Niddam and Hsieh, 2008; Rossi et al., 1998, 2003b). Although most studies did not include a direct comparison between the effects of cutaneous pain, joint pain and muscle pain, it appears that pain arising from muscle tissue may have more pronounced effects on proprioception than pain arising from (sub)cutaneous tissue (Weerakkody et al., 2003).

Brain activation

Since the emergence of functional brain imaging techniques, considerable efforts have been made to identify the cortical and subcortical structures that are activated by pain. Research has concentrated on examining brain activation in response to acute painful stimulation in healthy subjects lying quietly in a scanner. It is well known that pain activates cortical areas involved with perception of intensity and location of the painful stimulus, the regulation of emotional responses accompanying pain, and the distribution of attention (for a review, see Peyron et al., 2000). Although activation of motor-related areas (i.e., primary motor cortex, supplementary motor area, premotor area, cerebellum and/or basal ganglia) has occasionally been reported, this topic has mainly been regarded a side issue. Unfortunately, research has not yet focused on the effects of pain on brain activation patterns during movement planning or execution.

Several studies have addressed the interference between pain and cortical correlates of motor function by examining motor evoked potentials (MEPs) evoked by transcranial magnetic stimulation (TMS) or transcranial electric current stimulation (TECS) over the

primary motor cortex (Table 2.8: *n*=18). In general, MEP amplitude was reduced as a consequence of pain signals originating from skin (Farina et al., 2001; Fierro et al., 2010; Kaneko et al., 1998; Kofler et al., 1998, 2001; Tamburin et al., 2001; Uncini et al., 1991; Urban et al., 2004; Valeriani et al., 1999) or muscle (le Pera et al., 2001; Martin et al., 2008; Svensson et al., 2003), but in some studies it was found to be unaffected (Cheong et al., 2003; Fadiga et al., 2004; le Pera et al., 2001; Martin et al., 2008) or even elevated (Cheong et al., 2003; del Santo et al., 2007; Fadiga et al., 2004). In the case of distally localized pain, inhibition of MEPs evoked in the biceps brachii may be followed by excitation, probably reflecting preparations for hand withdrawal (Kofler et al., 1998, 2001; Urban et al., 2004). Painful stimulation at the hand sometimes caused modulation of corticospinal excitability of a muscle in the contralateral hand (Kofler et al., 2001; Valeriani et al., 1999) or arm (Hoeger Bement et al., 2009).

MEPs provide a measure of corticospinal excitability, which encompasses both cortical and spinal processes. In order to disentangle the effects of pain on cortical processes, assessment of MEPs should therefore be complemented by assessment of cervicomedullary motor evoked potentials (CMEP) or H-reflexes. Unfortunately, such measurements were present in only 5 out of 18 studies, and the results were inconclusive. The reduction of MEP amplitude induced by pain applied at the skin appears not attributable to decreased excitability of spinal motor neurons (Farina et al., 2001; Urban et al., 2004), whereas the reduction of MEP amplitude as a consequence of muscle pain may (partly) reflect decreased excitability of spinal rather than cortical motor neurons (le Pera et al., 2001; Svensson et al., 2003). In contrast, the findings of Martin et al. (2008) suggest that muscle pain may lead to decreased cortical excitability accompanied by opposing alterations at the spinal level.

Furthermore, studies analyzing electroencephalography (EEG) signals in terms of oscillation frequencies (Babiloni et al., 2008) or the exact timing of evoked potentials (Tarkka et al., 1992) provided indications of interference between pain and sensory-motor processes related to the planning and execution of movement (Table S2.8: *n*=2).

Discussion

This systematic review was conducted to obtain a better understanding of how pain affects motor behavior. Since it is unclear if pain from different tissues differentially affects the motor system, we evaluated the various sources of pain separately.

Notably, some motor components (spinal reflexes) were mainly examined by means of experimentally induced cutaneous pain, while others (muscle activity and movement characteristics) were predominantly examined by means of experimentally induced muscle pain (Figure 2.2). Although these differences hamper comparisons across studies, the observed effects on various components of the motor system were largely similar irrespective of the source of pain. Studies on spinal reflexes indicated differential influences of cutaneous pain and muscle pain, but due to the limited amount of available data and the heterogeneity of results it is not possible to draw firm conclusions in this regard.

Although some findings of this systematic review are congruent with existing models, others are not. In line with earlier reports (Arendt-Nielsen and Graven-Nielsen, 2008; Hodges and Tucker, 2011; Knutson, 2000), regardless of the pain source, we found no evidence of muscle hyperactivity as predicted by the 'vicious cycle model' (Johansson and Sojka, 1991; Travell et al., 1942). This model is based on the assumption that pain leads to muscle spasms, whereas evidence pointed at inhibition of painful muscles. The observed inhibition of the (painful) agonist muscle is consistent with the 'pain-adaptation model' (Lund et al., 1991). However, this model predicts excitation of antagonist muscles, for which no evidence was found in this review. On the contrary, a muscle's susceptibility to inhibition by pain seemed to depend on its activity state, rather than its function within a particular movement. Also the 'neuromuscular adaptation model', which predicts alterations in synergies, does not provide a conclusive explanation for the interaction between pain and motor control (Sterling et al., 2001). In particular, this model cannot account for the finding that the synergist's behavior often paralleled that of the (painful) agonist muscle. However, the theory on motor adaptation to pain recently proposed by Hodges and Tucker (2011) was largely in accord with our findings showing that pain affected many components of motor behavior mediated at multiple levels of the motor

system. Under circumstances of acute pain, the observed redistribution of activity within and among muscles as well as the (subtle) changes in mechanical behavior indeed seem to reflect adaptations leading to protection from further pain or injury. Hodges and Tucker (2011) intended to offer an explanation for the substantial variance observed between individuals and tasks, which resulted in a widely applicable theory. Given the relatively homogenous picture that emerges from the present review, it might be suggested that effects of short-lasting, experimentally induced limb pain can be described with higher specificity (Figure 2.3).

The majority of studies focused on the influence of pain on muscle activation during various types of contraction. Pain generally caused a reduction of activity of the (painful) agonist as well as non-painful synergists and antagonists, especially at higher intensity of contraction. Despite the influence of pain on muscle activation, the performance of various motor tasks mostly remained unimpaired, presumably as a result of redistribution of activity, both within the (painful) agonist and among muscles involved in the task. The finding that a given force level was associated with less sEMG activity in the painful muscle also pointed at compensation by other (not recorded) motor units or muscles. Effects of pain were mainly reflected in movement kinetics as a reduction of maximum force or peak moment, resulting in subtle alterations in movement kinematics. Although there were indications of a slight deterioration of proprioception, no evidence was found of detrimental effects on motor control. Given the observed activation-dependent inhibition of muscle activity, this sensory impairment is unlikely to play a major role in mediating the effects of pain on motor control because, if so, more complex alterations in timing and coordination of movement sequences would have been expected (Cordo et al., 1994).

Because muscle activation and movement characteristics are the result of many processes mediated at various levels of the motor system, their responses to pain do not allow identification of the exact mechanisms that underpin the interaction between pain and the motor system. Given that small diameter afferents have projections both at the spinal and the supraspinal level (Almeida et al., 2004; Millan, 1999), it is not surprising that motor control was found to be affected by pain at its most basic level, i.e., spinal reflexes, as well as its highest level, i.e., cortical processes related to movement planning

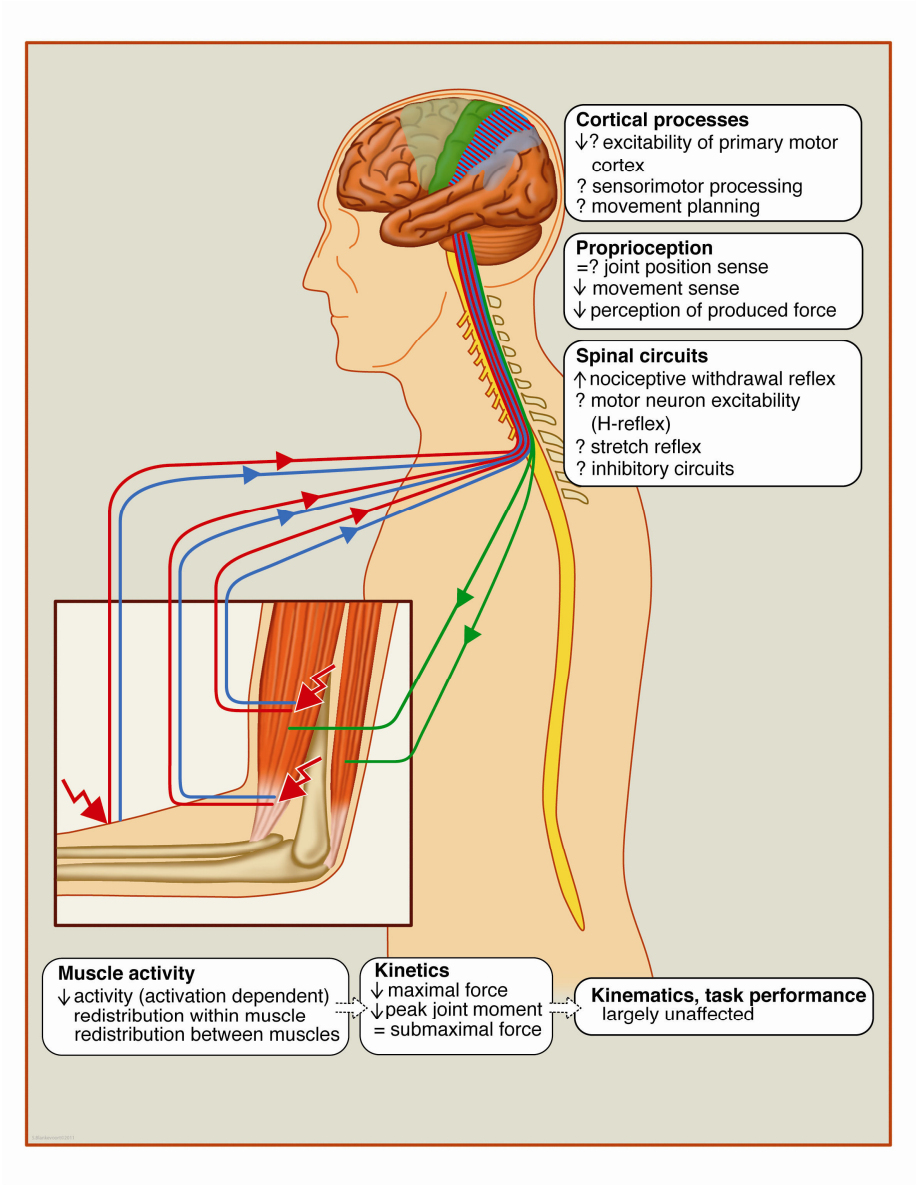

Figure 2.3 Motor consequences of experimental limb pain induced in skin, muscle or tendon. The main findings regarding the effects of nociceptive afferent signals (red) on motor control, which involves interaction between non-nociceptive afferent signals (blue) and motor efferent signals (green), are presented in text boxes. Dotted arrows between the lower three text boxes suggest a causal relationship between the effects of pain on muscle activity, kinetics and kinematics, but the relation between these parameters has not been directly addressed as such.

and execution. Findings regarding spinal reflexes were often highly variable and obtained from small samples. This may partly explain why we found limited evidence for systematic modulation of the H-reflex, the stretch reflex or inhibitory circuits. In contrast, pain caused a consistent modulation of the NWR, as has also been observed in animal research (Clarke and Harris, 2004).

At the highest level of motor control, EEG studies provided indications of pain interfering with cortical sensory-motor processes related to movement planning and execution. Studies using TMS or TECS over the primary motor cortex showed that pain arising from skin or muscle leads to reduced excitability of the corticospinal motor pathway. The question remains, however, if and to what extent these changes are attributable to altered spinal excitability. Attempts to disentangle the cortical and spinal contributions to alterations in corticospinal excitability have been made in a limited number of studies, which provided inconclusive results. Unfortunately, studies using functional brain imaging techniques have focused on brain activation at rest (Peyron et al., 2000), leaving the issue of how pain affects brain activation during movement planning or execution unaddressed.

The research on experimentally induced pain covered in this review delineates the effects of acute and transient pain stimuli on motor control and allowed to disentangle the intricate cause-and-effect relation between pain and movement. However, the findings cannot be translated to clinical pain conditions (Edens and Gil, 1995) which likely are associated with long-term adaptations to pain, a key aspect of the theory proposed by Hodges and Tucker (2011). Additionally, clinical pain conditions are commonly associated with structural damage that may induce additional effects on movement. Moreover, emotional and cognitive responses to (chronic) pain may greatly affect motor control, e.g., movement strategies may be altered by fear of pain (Vlaeyen and Linton, 2000). Such responses, if present, are probably different in experimental conditions as participants are aware that the pain will quickly resolve. Also, in some studies, participants were made familiar with the nociceptive stimulus prior to the experimental session in order to minimize a potential emotional component of the pain.

Many other factors affect the impact of pain on motor function as well, e.g., the severity, duration and location of pain, additional activation of non-nociceptive afferents,

and the state of the motor system (i.e., at rest or during planning or execution of movement). Unraveling the impact of pain on motor function thus requires diligent experimental control of many factors, which represents a major methodological challenge. Moreover, similar to gender differences in perception and tolerance of pain (Fillingim et al., 2009; Racine et al., 2012), the results of several studies suggest that gender-specific factors may influence the motor responses to pain (Falla et al., 2008, 2010; Ge et al., 2005; Madeleine et al., 2006). However, only two studies explicitly assessed potential gender-specific differences in motor consequences of pain. Surprisingly, the potential influence of this factor on the results was not addressed in the majority of studies (e.g., gender distribution was not reported in 23% of studies).

As regards the overall picture emerging from the studies included in this review, several limitations have to be acknowledged. Firstly, sample size was typically small (ranging from 1 to 36 subjects, with only 48% of the studies including more than 10 subjects). Secondly, 63% of the studies lacked an appropriate condition to control for possible non-nociceptive effects of pain stimuli. Thirdly, research has concentrated on relatively easily accessible aspects of motor function (i.e., muscle activity and movement characteristics; Figure 2.1), culminating in a limited number of coherent parameters. Several findings indicated that the observed changes result from central rather than peripheral effects of pain. Due to methodological issues and heterogeneity regarding outcome parameters, however, findings remained largely inconclusive for parameters that may provide insight into processes mediating the effects of pain at different levels of the central nervous system (i.e., spinal reflexes and cortical correlates of motor function). This motivates future examination of the impact of pain on spinal reflexes and cortical correlates of motor function, taking special care of methodological considerations. In this context, it should be noted that research on the effects of pain on spinal reflexes and brain activation has mainly focused on the motor system at rest. For a full appreciation of the interaction between pain and motor control, it is essential to examine the effects of pain on spinal reflexes and brain activation not only at rest, but also during movement planning and execution.

Acknowledgment

The authors thank Jan Schoones of the Walaeus Library for his help with the literature search.

Supplement 2.1: Search strategy

The search strategy was optimized for each of the consulted databases, taking into account the database-specific technical variations. The search terms used for Pubmed are presented below. The search terms used for the other databases are published online at http://onlinelibrary.wiley.com/doi/10.1002/j.1532-2149.2012.00186.x/suppinfo

Pubmed search terms

("motor system"[tw] OR "motor neurons"[mesh] OR "motor neuron"[tw] OR "motor neurons"[tw] OR "motoneuron"[tw] OR "motoneurons"[tw] OR "Motor Cortex"[mesh] OR "Motor Cortex"[tw] OR "Motor area" [tw] OR "premotor cortex"[tw]OR "premotor area"[tw] OR "cerebellum"[mesh] OR "cerebellum"[tw] OR "supplementary motor area"[tw] OR "basal ganglia"[mesh] OR "basal ganglia"[tw] OR "Evoked Potentials, Motor"[mesh] OR "motor evoked potentials"[tw] OR "motor evoked potential"[tw] OR "muscle tonus"[mesh] OR "muscle tone"[tw] OR "muscle activity"[tw] OR "muscle activation"[tw] OR "muscular activity"[tw] OR "muscular activation"[tw] OR "motor unit"[tw] OR "motor units"[tw] OR "muscle contraction"[tw] OR "muscle contractions"[tw] OR "Muscle Contraction"[mesh:noexp] OR "Excitation Contraction Coupling"[mesh] OR "Isometric Contraction"[mesh] OR "Isotonic Contraction"[mesh] OR "Muscular Contractions"[tw] OR "Muscular Contraction"[tw] OR "Muscle Strength"[mesh] OR "Muscle Strength"[tw] OR "maximal voluntary contraction"[tw] OR "maximal voluntary contractions"[tw] OR (("motor function"[tw] OR "motor task"[tw] OR "motor tasks"[tw] OR "movement"[tw] OR gait[tw])

AND ("kinetics"[tw] OR "kinetic analysis"[tw] OR "kinetic parameters"[tw] OR "kinematics"[tw] OR "kinematic analysis"[tw] OR "kinematic parameters"[tw] OR "EMG"[tw] OR "electromyography"[tw])) OR (excitability[tw] AND motor[tw]) OR "EMG-activity"[tw] OR "motor control"[tw] OR "neuromuscular control"[tw] OR "activation pattern"[tw] OR "activation patterns"[tw] OR "motor pattern"[tw] OR "motor

patterns"[tw] OR ((coordination[tw] OR "co-ordination"[tw] OR timing[tw] OR strategy[tw]) AND (muscle[tw] OR movement[tw] OR motor[tw])) OR "Neuromuscular adaptation"[tw] OR "proprioceptive sense"[tw] OR "proprioceptive senses"[tw] OR propriocepsis[tw] OR "proprioception"[mesh] OR proprioception OR kinesthesia[tw] OR kinaesthesia[tw] OR proprioreceptor[tw] OR proprioreceptors[tw] OR "muscle spindle"[tw] OR "muscle spindles"[tw] OR "stretch reflex"[tw] OR "stretch reflexes"[tw] OR "golgi tendon organ"[tw] OR "golgi tendon organs"[tw] OR "movement sense"[tw] OR "position sense"[tw])

AND ("induced pain"[tw] OR "experimental muscle pain"[tw] OR "experimental pain"[tw] OR (("pain induced" OR "induced pain") AND (experimentally OR "chemical"[tw] OR "chemically"[tw] OR "mechanical"[tw] OR "mechanically"[tw] OR "pinprick"[tw] OR "pressure"[tw] OR "thermal"[tw] OR "thermally" OR "electrical"[tw] OR "electrically"[tw])) OR ((nociceptive[tw] OR noxious[tw]) AND ("cutaneous stimulus"[tw] OR "cutaneous stimuli"[tw] OR "cutaneous stimulation"[tw])) OR ((capsaicin[tw] OR "capsaicin"[mesh] OR "hypertonic saline"[tw] OR "Saline Solution, Hypertonic"[mesh] OR "laser evoked potential"[tw] OR "laser evoked potentials"[tw] OR "intramuscular glutamate"[tw]) AND pain) OR "painful stimuli"[tw] OR "painful stimuli"[tw] OR "chemical pain" OR "mechanical pain" OR "electrical pain" OR "thermal pain" OR "pressure pain"[tw] OR "heat pain"[tw])

NOT (animal NOT human) AND (English[lang] OR French[lang] OR German[lang] OR Dutch[lang])

Supplement 2.2: Overview of included studies

All studies fulfilling the inclusion criteria are presented in Tables S2.1-2.8 on p. 37-60, which summarize the results on the effects of (sub)cutaneous pain, joint pain, muscle pain and tendon pain.

Supplement 2.3: Results

A detailed description of the results can be found online.
(http://onlinelibrary.wiley.com/doi/10.1002/j.1532-2149.2012.00186.x/suppinfo)

Table S2.1 Effects of experimentally induced pain on spinal reflexes

Reference [a]	*N*	(♂/♀)	Pain Method [b]	Intensity [c]	Location [d]	Reflex Location [e]	Results
Nociceptive withdrawal reflex							
(Sub)cutaneous pain							
Andersen et al., 1994	12	(12/0)	TH	● – ●●● [NR]	Foot sole [4]	TA	↑
Andersen et al., 1995	8	(?)	CH+MC/TH	●● [NR]	Foot dorsum [4]	BF/RF	↑
Ellrich and Treede, 1998	11	(6/5)	TH	NR	Foot sole [4]	TA	↑
Ellrich et al., 2000	2	(?)	TH	NR	Foot sole [4] (distal/middle/proximal)	TA	↑ / ↑ / ↑
					Foot sole [4] (distal/middle/proximal)	BF	↑ / ↑ / ↑
	1	(?)	TH	NR	Foot dorsum [4] (standing)	TA / BF	↑ / ↑
Grönroos and Pertovaara, 1993	5	(?)	CH⁺	● [NR]	Foot dorsum [5]	BF	↑ *
			CH	● [NR]	Above medial malleolus [5]	BF	↑ *
	1	(?)	CH	● [NR]	Foot dorsum [C, 5]	BF	↑ *
					Hand dorsum [C, 5]	BF	=
Roby-Brami et al., 1987	5	(4/1)	EL	●●● [NR]	Finger IV+V [C, 4]	BF	↓
Serrao et al., 2004	36	(16/20)	TH	●●● [NR]	Hand [C, 5]	BF	↓
Terkelsen et al., 2001	12	(12/0)	TH	NR	Foot [C, 5]	BF	↓
					Hand [C, 5]	BF	↓
Willer et al., 1984	10	(8/2)	TH	● – ●●● [NR]	Hand [C, 5]	BF	↓ *
Willer et al., 1989	11	(3/8)	TH	● – ●●● [NR]	Hand [C, 5]	BF	↓ *
Muscle pain							
Andersen et al., 2000	12	(12/0)	CH	●● [P]	TA [5]	ST	↑
					SOL [5]	ST	↓
Andersen et al., 2006	18	(?)	EL	● [M]	TA [5]	ST	↑
Ge et al., 2007	12	(10/2)	EL	●●● [M]	TA [5]	ST	↓
	10	(8/2)			TA [C,5]	ST	↓
	10	(8/2)			TZ [5]	ST	↓

Table S2.1 Effects of experimentally induced pain on spinal reflexes *(continued)*

Reference [a]	*N*	(♂/♀)	Pain Method [b]	Intensity [c]	Location [d]	Reflex Location [e]	Results
Phasic stretch reflex							
Muscle pain							
Matre et al., 1998	14	(14/0)	CH [+]	●● [M]	SOL	SOL / active SOL	↑ / ↑
	9	(9/0)	CH [+]	●● [M]	TA	SOL / active SOL	↑ / ↑
Matre et al., 1999	10	(10/0)	CH [+]	●●● [M]	SOL	SOL / active SOL	↑ / =
H-reflex							
(Sub)cutaneous pain							
Andersen et al., 1994 [1]	3	(3/0)	TH	● – ●● [NR]	Foot sole	SOL	=
Andersen et al.,1995 [1,2]	8	(?)	CH	NR	Foot dorsum	SOL	=
Ellrich and Treede, 1998 [2]	1	(?)	TH	NR	Foot sole	TA / SOL	↓ / =
Ellrich et al., 2000 [2]	2	(?)	TH	●●● [NR]	Foot sole (distal/middle/proximal)	SOL	↑ / = / ↓
					Foot sole (distal/middle/proximal)	PM	↑ / = or ↓ / = or ↓
Farina et al., 2001 [1]	6	(4/2)	CH	● [P]	FCR	FCR	=
Grönroos and Pertovaara, 1993 [1,2]	4	(?)	CH	● [M]	Lower leg, posterior-distal	SOL	=
Rossi and Decchi, 1995 [1]	4	(?)	CH	●●● [P]	Foot dorsum	SOL / Q	↑= / ↑=
Rossi et al., 1996 [1]	1	(?)	EL	● [NR]	Foot sole	TA	↑
Rossi and Decchi, 1997 [1]	5	(?)	CH	●●● [P]	Above EDB	SOL	↑
					Above TA	SOL	↑
Urban et al., 2004 [1,3]	10	(5/5)	EL	NR	Finger II	APB / BB	↑ / ↑
Willer et al., 1989 [1,2]	11	(3/8)	TH	● – ●●● [NR]	Hand [C]	SOL	=
Muscle pain							
Ge et al., 2007 [1]	11	(?)	EL	●●● [M]	TA	SOL	=
Le Pera et al., 2001 [1,2]	11	(8/3)	CH [+]	●● [P]	FCR	FCR	↓
Matre et al., 1998 [1,2,3]	7	(7/0)	CH [+]	●● [M]	SOL	SOL / active SOL	= / =
				●● [M]	TA	SOL / active SOL	= / =

H-reflex *(continued)*							
Muscle pain (continued)							
Rossi and Decchi, 1997 [1]	5	(?)	CH	●●● [P]	EDB	SOL	↓
					TA	SOL	↓
Rossi et al., 1999a [1]	3	(?)	CH	●●● [P]	EDB	SOL / Q	↓ / ↑=
Rossi et al., 1999b [1]	5	(3/2)	CH	●●● [P]	EDB	SOL	↓
Rossi et al., 2003a [3]	7	(?)	CH	●●● [P]	SOL	SOL / active SOL	↑ * / ↑ *
Ib inhibitory pathway							
(Sub)cutaneous pain							
Rossi and Decchi, 1995	4	(?)	CH	●●● [P]	Foot dorsum	SOL / Q	↑ * / ↑ *
Rossi and Decchi, 1997	5	(?)	CH	●●● [P]	Foot dorsum (above EDB)	SOL	↑ *
					Above TA	SOL	=
Muscle pain							
Rossi and Decchi, 1997	5	(?)	CH	●●● [P]	EDB	SOL	↓ *
					TA	SOL	↑↓
Rossi et al., 1999a	3	(?)	CH	●●● [P]	EDB	SOL / Q	↓ * / ↓ *
Rossi et al., 1999b	5	(?)	CH	●●● [P]	EDB	SOL	↓ *
Recurrent inhibition							
Muscle pain							
Rossi et al., 2003a	7	(?)	CH	●●● [P]	SOL	SOL / active SOL	↑ * / =
Cutaneous silent period							
(Sub)cutaneous pain							
Inghilleri et al., 1997	6	(?)	EL	NR	Finger IV+V	FDI	=
Uncini et al., 1991	8	(5/3)	EL	NR	Finger II	OP	=
Vibration-induced flexion reflex							
(Sub)cutaneous pain							
Takakura et al., 2004	12	(9/3)	EL	●●● [NR]	Hand dorsum	Finger II	↓

[a] Methodological aspects of studies on the H-reflex are indicated by [1] appropriate stimulus intensity; [2] constant size of the M-wave; [3] low level voluntary muscle activation; [b] Pain was induced chemically (CH), electrically (EL), mechanically (MC) or thermally (TH), with [+] indicating the presence of a non-nociceptive control condition; [c] Reported intensity of pain is categorized into mild ●, moderate ●● and severe ●●● pain; [M] = mean pain; [P] = peak pain; NR = not reported; [d] The nociceptive withdrawal reflex was elicited by painful stimulation of the foot sole or sural nerve ([4]) or by painful stimulation of the foot dorsum or tibial nerve ([5]); [e] Reflexes were studied in passive muscles, unless indicated otherwise.

APB, abductor pollicis brevis; BB, biceps brachii; BF, biceps femoris; ECR, extensor carpi radialis; EDB, extensor digitorum brevis; FCR, flexor carpi radialis; FDI, first dorsal interosseous; OP, opponens pollicis; PM, foot plantar muscles; Q, quadriceps; RF, rectus femoris; SOL, soleus; ST, semitendinosis; TA, tibialis anterior; TZ, trapezius; [C] contralateral; ↑ and ↓ indicate significant ($p<0.05$) facilitation and inhibition of reflexes, '↑=' indicates a transient facilitation, '=' indicates the absence of significant effects, and * indicates that findings correlate with subjective pain sensation.

Table S2.2 Effects of experimentally induced pain on muscle activity at rest

Reference	*N*	(♂/♀)	Pain Method [a]	Intensity [b]	Location	Results Muscle activity	Cramp provocation
(Sub)cutaneous pain							
Birznieks et al., 2008	15	(11/4)	CH	●● ^{P}	Above TA	= ^{S}	No
Muscle pain							
Birzinieks et al., 2008	15	(11/4)	CH	●● ^{P}	TA	= ^{S}	No
Cobb et al., 1975	6	(?)	CH	●● – ●●● ^{P}	ECR	↑ ^{S} *	No
	1	(?)	CH	●● – ●●● ^{P}	ECR	↑ ^{S} *, = ^{IM}	No
Fernández-Carnero et al., 2010	12	(10/2)	CH $^{+}$	●● ^{P}	IS – MTrP	= ^{S,IM}	No
Ge et al., 2008	14	(10/4)	CH $^{+}$	●●● ^{P}	GM – MTrP	↑ ^{S,IM}	Yes
				●● ^{P}	GM – non-MTrP	= ^{S,IM}	No
Graven-Nielsen et al., 1997a	9	(9/0)	CH $^{+}$	●● ^{P}	TA	= ^{S}	No
Graven-Nielsen et al., 1997b	6	(?)	CH $^{+}$	●● ^{P}	TA	= ^{IM}	No
Madeleine and Arendt-Nielsen, 2005	12	(12/0)	CH $^{+}$	●● ^{M,P}	BB	= ^{S}	No
Serrao et al., 2007	13	(6/7)	CH $^{+}$	●● ^{P}	FHB	= $^{S, M}$	Yes
Svensson et al., 1998	10	(10/0)	CH $^{+}$	●● ^{P}	TA	↑= ^{S,IM}	No
Xu et al., 2010	12	(8/4)	MC	●●● ^{P}	EDC – MTrP	↑ ^{S,IM} *	Yes
				●● ^{P}	EDC – non-MTrP	= ^{S,IM}	No

[a] Pain was induced chemically (CH) or by mechanical stimulation (MC), with $^{+}$ indicating the presence of a non-nociceptive control condition; [b] Reported intensity of pain is categorized into mild ●, moderate ●● and severe ●●● pain; ^{M} = mean pain; ^{P} = peak pain;

BB, biceps brachii; ECR, extensor carpi radialis; EDC, extensor digitorum communis; FHB, flexor hallucis brevis; GM, gastrocnemius; IS, infrasupinatus; TA, tibialis anterior; MTrP, (latent) myofascial trigger point; ^{IM} intramuscular EMG recordings; ^{S} surface EMG recordings; ↑ and ↓ indicate significant (p<0.05) increase and decrease, '↑=' indicates a transient increase, '=' indicates the absence of significant effects, and * indicates that findings correlate with subjective pain sensation.

Table S2.3 Effects of experimentally induced pain on muscle activity and performance during isometric contractions

Reference	*N*	(♂/♀)	Pain			Task [c]			Results			
			Method [a]	Intensity [b]	Location	Contraction	Intensity (% MVC)	Duration (s)	Agonist Amplitude / Frequency	Synergist Amplitude	Antagonist Amplitude	Performance [d]
Joint pain												
Henriksen et al., 2010b	17	(9/8)	CH [+]	●● [M]	IFP	FL knee	100	NR				↓[*] torque
						EX knee	100	NR				↓[*] torque
Tucker and Hodges, 2009	8	(4/4)	CH	●●● [M]	IFP	EX knee	"low"	10-20		↓[IM]		= force [#]
Tucker et al., 2009	7	(?)	CH	●●● [M]	IFP	EX knee	≈ 7	30	=[S]	↓[IM]		= force, SD
Tucker and Hodges, 2010	9	(?)	CH	●● [M]	IFP	EX knee	"low"	10		↓[IM]		= force [#]
	6	(?)	CH	●● [M]	IFP	EX knee	"low"	10		↓[IM]		= force [#]
Muscle pain												
Bandholm et al., 2008	9	(?)	CH	●● [M]	SU	AB arm (90°)	20, 27.5, 35	10	=[S]	↑[S] DLa, =[S] IS, =[S] TZl, TZu, =[S] DLm	=[S] LD, SA	↑ SD = CV
Birch et al., 2000a	9	(0/9)	CH	●● [P]	ECU	EX wrist	0→10	10	=[IM]	=[IM]		= force [#]
							10	60	=[IM]	=[IM]	=[S] ECR, =[S] FCR	= force [#]
Ciubotariu et al., 2004	10	(6/4)	CH	●●● [P]	TA	DFL ankle	50, 80	max (≈133, 51)	↓[S]	↓[S]	↓[S] EHL, =[S] GM, GL, =[S] SOL	↓ torque ↓ T_{end}
				●●● [P]	GL	PFL ankle	50, 80	max (≈301, 85)	↓[S]	↓[S]	↓[S] GM, ↑[S] SOL, =[S] TA, EHL	↓ torque ↓ T_{end}
Ciubotariu et al., 2007	10	(6/4)	CH	●–●● [M,P]	TA	DFL ankle	0→80	3	↓[S]		↓[S] EHL	= torque [#]
							100	3	↓[S]		↓[S] EHL	= torque
	10	(6/4)	CH	●–●● [M,P]	GL	PFL ankle	0→80	3	↓[S]		↓[S] GM, =[S] SOL	= torque [#]
							100	3	↓[S]		↓[S] GM	= torque
del Santo et al., 2007	8	(5/3)	CH	●●● [P]	ADM	AB finger V	30	5	↑[S] *			= force ↑CV
				●●● [P]	BB	FL elbow	30	5	↓[S] *			= force ↑CV

Muscle pain (continued)											
Falla et al., 2008	9	(9/0)	CH $^{+}$	●● ^{P}	TZu	AB arm (90°)	≈ 15-20	60	↓^{S}	↓^{S}	
	9	(0/9)	CH $^{+}$	●●● ^{P}	TZu	AB arm (90°)	≈ 15-20	60	↓^{S}	↓^{S}	
Falla et al., 2009	9	(9/0)	CH $^{+}$	●● ^{P}	TZu	AB arm (90°)	≈ 15-20	60	↓^{S}		
Falla et al., 2010	10	(0/10)	CH $^{+}$	●●● ^{P}	TZu	AB arm (90°)	≈ 15-20	60	↓^{S}	=^{S}	
Farina et al., 2004a	12	(5/7)	CH $^{+}$	●–	TA	DFL ankle	10	20	=^{S}	=^{S}	= torque$^{\#}$
				●●● ^{M,P}						↓^{IM} *	= SD
Farina et al., 2005a	12	(6/6)	CH $^{+}$	●–●● ^{M,P}	TA	DFL ankle	30	10	↓^{S} *	=^{S}	= torque$^{\#}$
Farina et al., 2005b	11	(7/4)	CH $^{+}$	●● ^{M,P}	TA	DFL ankle	25	240	=^{S}	=^{S}	= torque$^{\#}$
										↓^{IM}	
Farina et al., 2008	16	(11/5)	CH $^{+}$	●● ^{M,P}	TA	DFL ankle	10	15		↓^{IM} *	= torque$^{\#}$
							≈ 4.4	180	=^{S}	=^{IM} $^{\#}$	= torque
Ge et al., 2005	10	(10/0)	CH $^{+}$	●●● ^{P}	TZu^{B}	AB arm (90°)	≈ 15-20	5	↓^{S}	↓^{S}	
								180	↑^{S}	↑^{S}	
	9	(0/9)	CH $^{+}$	●●● ^{P}	TZu^{B}	AB arm (90°)	≈ 15-20	5	↓^{S}	=^{S}	
								180	=^{S}	=^{S}	
Graven-Nielsen et al., 1997a	19	(19/0)	CH $^{+}$	●● ^{P}	TA	DFL ankle	80	max (≈31)	=^{S}	=^{S}	= torque$^{\#}$
											↓T_{end}
	9	(9/0)	CH $^{+}$	●● ^{P}	TA	DFL ankle	100	4	↓^{S} *	=^{S}	↓* torque$^{\#}$
Graven-Nielsen et al., 2002	8	(5/3)	CH $^{+}$	● ^{A}	RF	EX knee	100	4			↓ torque$^{\#}$
Hodges et al., 2008	10	(10/0)	CH	●● ^{P}	GL	PFL ankle	“low”	20	=^{S}	↓^{IM} (N=1)	=^{S} GM, SOL ↓^{IM} GM, SOL	= force$^{\#}$
Jaberzadeh et al., 2003	12	(7/5)	CH	●● ^{M}	EDC	EX finger III	“low”	120				= tremor
Madeleine and ‘rendt-Nielsen, 2005	12	(12/0)	CH $^{+}$	●● ^{M,P}	BB	FL elbow	10, 30, 50, 70	5	=^{S}	=^{S}		= force$^{\#}$ = SD
							0→50	25	=^{S}	=^{S}		= force$^{\#}$

Table S2.3 Effects of experimentally induced pain on muscle activity and performance during isometric contractions *(continued)*

Reference	*N*	(♂/♀)	Pain			Task			Results			
			Method [a]	Intensity [b]	Location	Contraction [c]	Intensity (% MVC)	Duration (s)	Agonist Amplitude / Frequency	Synergist Amplitude	Antagonist Amplitude	Performance [d]
Muscle pain (continued)												
Madeleine et al., 2006	10	(10/0)	CH +	●● M	TZu	AB arm (90°)	≈ 15-20	90	↓ S	= S		
Martin et al., 2008	7	(?)	CH	●● P	BB	FL elbow	20	20	↓ S			= torque
Qerama et al., 2005	18	(?)	CH	●● P	BB	FL elbow	100	3	↓ IM	↓ IM		
	14	(?)	CH	●● P	BB	FL elbow	100	3	↓ IM	↓ IM		
Schulte et al., 2004	15	(13/2)	CH +	●● P	BB	FL elbow	40	max (≈89)	= S	= S	= S BR, DL, ↑ S TZu	= force # = CV, T_{end}
							40	10	= S	= S	= S BR, DL, ↑ S TZu	= force #
							100	3	= S	= S	= S BR, DL, ↑ S TZu	= force = CV
Slater et al., 2003	12	(6/6)	CH +	●● P	ECR	EX wrist	100	NR				↓ * force
				●●● P	SUP	EX wrist	100	NR				↓ force
	12	(5/7)	CH	●●● P	ECR	EX wrist	100	NR				↓ force
Slater et al., 2005	20	(10/10)	CH	●●● P	ECR	EX wrist	100	NR				= force
						Hand grip	100	NR				= force
Tucker et al., 2009a	7	(6/1)	CH	●● M	FPL	FL thumb	≈ 1.5	10-20		↓ IM	= IM EPL	= torque #
Tendon pain												
Slater et al., 2003	12	(6/6)	CH	●●● P	CEO	EX wrist	100	NR				↓ force

[a] Pain was induced chemically (CH), with [+] indicating the presence of a non-nociceptive control condition; [b] Reported intensity of pain is categorized into mild ●, moderate ●● and severe ●●● pain; [M] = mean pain; [P] = peak pain; [A] = mean pain as calculated from area under the VAS curve; [c] AB, abduction; DFL, dorsal flexion; EX, extension; FL, flexion; MVC, maximum voluntary contraction; PFL, foot plantar flexion; [d] Effects on task performance are described by $T_{end,}$ endurance time; SD, standard deviation; CV, coefficient of variance; [#] used as target value.

ADM, abductor digiti minimi; BB, biceps brachii; BR, brachioradialis; CEO, common extensor origin; DL, deltoideus; DLa, anterior deltoideus; DLm, middle deltoideus; ECR, extensor carpi radialis; ECU, extensor carpi ulnaris; EDC, extensor digitorum communis; EHL, extensor hallucis longus; EPL, m extensor pollicis longis; FCR, flexor carpi radialis; FPL, flexor pollicis longis; GL, lateral gastrocnemius; GM, (medial) gastrocnemius; IS, infraspinatus; IFP, infrapatellar fat pad; LD, latissimus dorsi; RF, rectus femoris; SA, serratus anterior; SOL, soleus; SU, supraspinatus; SUP, supinator; TA, tibialis anterior; TZl, lower trapezius; TZu, upper trapezius; [B] bilateral; [IM] intramuscular EMG recordings; [S] surface EMG recordings; ↑ and ↓ indicate significant ($p<0.05$) increase and decrease, '=' indicates the absence of significant effects, 'NR' denotes 'not reported' and * indicates that findings correlate to subjective pain sensation.

Table S2.4 Effects of experimentally induced pain on muscle activity during dynamic contractions

Reference	*N*	(♂/♀)	Pain Method [a]	Intensity [b]	Location	Task description [c]	Results [d, e] Agonist	Synergist	Antagonist
Joint pain									
Hodges et al., 2009	10	(3/7)	CH	●● – ●●● [P]	IFP	EX knee (stair up)	↓[S] VL, =[S] VM (delayed *)		
						EX knee (stair down), eccentric	=[S] VL , VM		
Muscle pain									
Bandholm et al., 2008	9	(?)	CH	●● [M]	SU	AB arm, 20-35% MVC	=[S] ***SU***	↑[S] IS, TZl ** =[S] DL, TZu	=[S] LD, SA
						AB arm, 20-35% MVC, eccentric	=[S] ***SU***	=[S] IS, TZl, =[S] DL, TZu	=[S] LD, SA
Diederichsen et al., 2009	11	(11/0)	CH	●● [P]	SU	AB arm, 10% MVC	=[IM] ***SU***	↓[S] IS, Dla, Tzu, ↑[S] TZl, =[S] DLm	↑[S] LD, =[S] SA
Ervilha et al., 2004a	15	(11/4)	CH	● [M]	BB	FL elbow	↓[S] ***BB*** **	↓[S] BR, =[S] TZ	↓[S] TB
Ervilha et al., 2004b	10	(7/3)	CH	●● [M]	BB	FL elbow	↓[S] ***BB*** **	↓[S] BR, ↑[S] TZ (before start)	↓[S] TB
					TB		↓[S] ***BB*** **	↓[S] BR, ↑[S] TZ (before start)	↓[S] ***TB***
				● [M]	BB	FL elbow	=[S] ***BB*** **	=[S] BR	=[S] TB
					TB		=[S] BB	=[S] BR	=[S] ***TB***
	15	(13/2)	CH	● [M]	BB	FL elbow	=[S] ***BB*** (low accuracy ↓**)	=[S] BR	=[S] TB
					TB		=[S] BB (low accuracy ↓**)	=[S] BR	=[S] ***TB***
Ervilha et al., 2005	10	(6/4)	CH [+]	●● [M]	BB	FL elbow, repeated (120s)	↓[S] ***BB***	↓[S] BR ** ↑[S] TZu	=[S] TB
				●●● [M]	BB + TB		↓[S] ***BB***	↓[S] BR ** ↑[S] TZu	=[S] ***TB***

Muscle pain (continued)								
Ervilha et al., 2005, *continued*	10	(6/4)	CH $^{+}$	●● ^{M}	BB	EX elbow, repeated (120s)	= ^{S} TB	↑^{S} TZu	↓^{S} BR ** = ^{S} ***BB***
				●●● ^{M}	BB + TB		= ^{S} ***TB***	↑^{S} TZu	= ^{S} BR, ***BB***
Falla et al., 2007	9	(5/4)	CH $^{+}$	●●● ^{P}	TZu	FL shoulder, rhythmic (150s)	↓^{S} ***TZu***	↑^{S} TZl, TZu ^{C} = ^{S} TZm ^{B}, TZl ^{C}	
Graven-Nielsen et al., 1997a	10	(10/0)	CH $^{+}$	●● ^{P}	TA	Walking	= ^{S} ***TA***		↑^{S} GM (stance)
					GM		↑^{S} ***GM*** (after toe-off)		↓^{S} TA (stance)
Henriksen et al., 2009a	15	(9/6)	CH $^{+}$	●●^{M}	GLUTmd	Walking	↓^{S} ***GLUTmd*** **	= ^{S} VM, VL, ST = ^{S} BF, GLUTmx	
Henriksen et al., 2007	20	(10/10)	CH $^{+}$	●● ^{M}	VM	Walking	↓^{S} ***VM*** (before heel strike) ↓^{S} ***VM*** (stance eccentric) = ^{S} ***VM*** (stance concentric)	↓^{S} VL (before heel strike) = ^{S} VL (stance)	= ^{S} BF, ST
Henriksen et al., 2009b	20	(10/9)	CH $^{+}$	● ^{M}	VM	Forward lunge, contact phase	↓^{S} ***VM***	↓^{S} VL	↓^{S} BF, ST
Hirata et al., 2010	9	(5/4)	CH $^{+}$	●● ^{P}	TA	Standing, static or with perturbations	= ^{S} ***TA*** ^{B}		= ^{S} GM ^{B}
				●●● ^{P}	GM		= ^{S} ***GM*** ^{B}		= ^{S} TA ^{B}
				●●● ^{P}	GM + TA		= ^{S} ***GM*** ^{B}***, TA*** ^{B}		
Madeleine et al., 1999b	6	(6/0)	CH	●● ^{P}	TA	Forward stepping (leading leg)	↓^{S} ***TA*** **	↑^{S} TA ^{C} (before start) = ^{S} GM ^{C}, SOL ^{B} = ^{S} VL ^{B}, BF ^{B}	↓^{S} GM **
Tendon pain									
Henriksen et al., 2011	16	(8/8)	CH $^{+}$	● ^{M}	AT	PLF ankle, standing rhythmic	↓^{S} SOL	↓^{S} GL, GM, ↓^{S} PL, PB	↓^{S} TA

Footnote on p. 48

[a] Pain was induced chemically (CH), with [+] indicating the presence of a non-nociceptive control condition; [b] Reported intensity of pain is categorized into mild ●, moderate ●● and severe ●●● pain; [M] = mean pain; [P] = peak pain; [c] AB, abduction; EX, extension; FL, flexion; MVC, maximum voluntary contraction; PLF, foot plantar flexion; [d] Painful muscles are printed in ***bold italics***; [e] Results pertain to muscles ipsilateral to the side of pain, unless indicated otherwise.

AT, Achilles tendon; BB, biceps brachii; BF, biceps femoris; BR, brachioradialis; DL, deltoideus; DLa, anterior deltoideus; DLm, middle deltoideus;GL, lateral gastrocnemius; GLUTmd, gluteus medius; GLUTmx, gluteus maximus; GM, (medial) gastrocnemius; IFP, infrapatellar fat pad; IS, infraspinatus; LD, latissimus dorsi; PB, peroneus brevis; PL, peroneus longus; SA, serratus anterior; SOL, soleus; ST, semitendinosis; SU, supraspinatus; TA, tibialis anterior; TB, triceps brachii; TZl, lower trapezius; TZm, middle trapezius; TZu, upper trapezius; VL, vastus lateralis; VM, vastus medialis; [B] bilateral; [C] contralateral; [S] surface EMG recordings; [IM] intramuscular EMG recordings; ↑ and ↓ indicate significant ($p<0.05$) increases or decreases, '=' indicates the absence of significant effects, * indicates that findings correlate to subjective pain sensation, and ** indicates that findings were more evident during periods of highest activation.

Table S2.5 Effects of experimentally induced pain on muscle activity and movement characteristics during computer work and other types of low load repetitive work

Reference	*N*	(♂/♀)	Pain Method [a]	Intensity [b]	Location	Task description	Results [c] Activity of painful muscle	Activity of other muscles	Kinetics	Kinematics
Muscle pain										
Birch et al., 2000b	13	(13/0)	CH [+]	● [M,P]	ECU	CW - low precision	↓[S] ECU **	= [S] FCR, TZ		= T_{cycle}, performance
						CW - high precision	= [S] ECU	= [S] FCR, TZ		= T_{cycle}, performance
Birch et al., 2001	12	(12/0)	CH	●● [M,P]	TZu	CW - high precision				= T_{cycle}, performance
				● [M,P]	ECU	CW - high precision				↓ T_{cycle}, = performance
Madeleine et al., 1998	13	(13/0)	CH	●●● [P]	SOL	LLRW - standing			↑ ΔCOP_{ML}	= ankle movement
Madeleine et al., 1999a	10	(10/0)	CH	●●● [P]	TZu	LLRW	↓[S] TZu (↑[S] MPF)**	↓[S] DLa (=[S] MPF) =[S] DLm (↑[S] MPF) =[S] IS (↑[S] MPF; altered pattern)	= ΔCOP	↑ T_{cycle} ↑ rotation arm ↑ FL trunk
Madeleine et al., 2008	20	(?)	CH	●● [P]	TZu, IS	LLRW	Cycle-to-cycle variability: =[S] TZu, IS	=[S] DLm, ↓[S] DLa (non-active period)		↑ SD T_{event} ↑ SD arm movements ↑ SD arm start position ↑ SD FL-EX trunk = SD trunk start position
Samani et al., 2009	12	(12/0)	CH	●● [M]	TZu	CW - passive pause	↑[S] TZu	↑[S] TZm, =[S] TZl (↓ RRT)		= performance
						CW - active pause	↑[S] TZu ↓[S] TZm variability	↑[S] TZm, =[S] TZl (↓ RRT)		= performance
Samani et al., 2010	12	(12/0)	CH	●● [M]	TZu	CW	=[S] TZu (= RRT)	↓[S] ECR, =[S] FCU (↓ RRT)		= performance

Footnote on p. 50

[a] Pain was induced chemically (CH), with [+] indicating the presence of a non-nociceptive control condition; [b] Reported intensity of pain is categorized into mild ●, moderate ●● and severe ●●● pain; [M] = mean pain; [P] = peak pain; [c] Results refer to EMG amplitude, unless indicated otherwise; MPF, median power frequency; RRT, relative resting time; Effects on movement kinetics are described by ΔCOP, displacement of center of pressure, with $_{ML}$ medial-lateral. Effects on movement kinematics are described by EX, extension; FL, flexion; SD, standard deviation; T_{cycle}, cycle duration; T_{event}, event duration.

CW, computer work; DLa, anterior deltoideus; DLm, middle deltoideus; ECR, extensor carpi radialis; ECU, extensor carpi ulnaris; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; IS, infraspinatus; LLRW, low-load repetitive work; SOL, soleus; TZl, lower trapezius; TZm, middle trapezius; TZu, upper trapezius; [S] surface EMG recordings. ↑ and ↓ indicate significant (p<0.05) increases and decreases, '=' indicates the absence of significant effects, * indicates that findings correlate to subjective pain sensation, and ** indicates that findings were more evident during periods of highest activation.

Table S2.6. Effects of experimentally induced pain on movement characteristics during dynamic contractions

Reference	*N*	(♂/♀)	Pain			Task description	Results	
			Method [a]	Intensity [b]	Location		Kinetics [c]	Kinematics [d]
(Sub)cutaneous pain								
Blouin et al., 2003	10	(10/0)	TH [+]	●● [M]	Above GM [B]	Standing (static)	↑ $\Delta COP_{AP, ML}$ ↑ $\nu COP_{AP, ML}$ ↑ COP variability	
Corbeil et al., 2004	10	(10/0)	EL	●● [M]	Hand dorsum	Standing (static)	= $\Delta COP_{AP, ML}$ = $\nu COP_{AP, ML}$	
				● –	Foot dorsum	Standing (static)	↑* $\Delta COP_{AP, ML}$	
				●●● [M]			= $\nu COP_{AP, ML}$	
Maihöfner et al., 2007	12	(2/10)	CH	●● [M]	Forearm (dorsal)	Reach-and-grasp		= T_{mov}, path curvature
Joint pain								
Bennel and Hinman, 2005	12	(6/6)	CH	●●● [M]	IFP	Standing (static, stepping, or perturbations)	= $\Delta COP_{AP, ML}$	
Henriksen et al., 2010a	34	(16/18)	CH [+]	● [M]	IFP	Walking	↓M_{peak} AD knee ↓M_{peak} FL-EX knee	= φ FL knee (heelstrike) ↓ φ_{peak} FL knee (early stance) ↓ φ_{peak} EX knee (late stance)
Henriksen et al., 2010b	18	(9/9)	CH [+]	●● [M]	IFP	FL knee (isokinetic, max) EX knee (isokinetic, max)	↓* torque ↓* torque	
Muscle pain								
Bandholm et al., 2008	9	(9/0)	CH	●● [M]	SU	AB arm (20-27.5-35% MVC, concentric) AB arm (20-27.5-35% MVC, eccentric)	= force variability = force variability	

Table S2.6. Effects of experimentally induced pain on movement characteristics during dynamic contractions *(continued)*

Reference	*N*	(♂/♀)	Pain			Task description	Results	
			Method [a]	Intensity [b]	Location		Kinetics [c]	Kinematics [d]
Muscle pain (continued)								
Bonifazi et al., 2004	8	(8/0)	CH	●● [P]	PEM	One-arm bench press (10 kg, 25-40% MVC)	↓[B] force, power	↓* v [B] ↑ $T_{power,peak}$
					TB	One-arm bench press (10 kg, 25-40% MVC)	↓[B] force, = power	= v = $T_{power,peak}$
Diederichsen et al., 2009	11	(11/0)	CH	●● [P]	SU	AB arm (10% MVC)		= v [#]
Ervilha et al., 2004a	15	(11/4)	CH	● [M]	BB	FL elbow (70° amplitude, low accuracy)		↑ $T_{reaction}$, T_{mov} ↓ A, a, v_{peak}
Ervilha et al., 2004b	10	(7/3)	CH	●● [M]	BB or TB	FL elbow (30°amplitude, low accuracy)		↑ $T_{reaction}$, $T_{mov,}$, $T_{v,peak,}$ = A, a
				● [M]	BB or TB	FL elbow (90°amplitude, low accuracy)		↑ $T_{v,peak}$, = $T_{reaction}$, T_{mov} = A, a
	15	(13/2)	CH	● [M]	BB or TB	FL elbow (70°amplitude, low/high accuracy)		↑ $T_{reaction}$, $T_{v,peak,}$ = T_{mov}, = A, a
Ervilha et al., 2005	10	(6/4)	CH [+]	●● [M]	BB, or BB + TB	FL-EX elbow (repeated, 120s)		= T_{mov} = A, a
Henriksen et al., 2007	20	(10/10)	CH [+]	●● [M]	VM	Walking	↓ M EX knee = M AD knee = F_{comp} knee	= φ_{peak} FL knee
Henriksen et al., 2008	20	(10/10)	CH [+]	● [NR]	VM	Walking	= F_{impact} (heelstrike)	= α_{peak} FL knee = φ FL knee (heelstrike)

Muscle pain (continued)								
Henriksen et al., 2009a	15	(6/9)	CH^{+}	●● ^{M}	GLUTmd	Walking	↓ M_{peak} AB hip ↓ M_{peak} AD knee = M_{peak} INV ankle	↓ φ AD hip (midstance) ↓ φ EX hip (end stance) ↓ φ EX knee (midstance) = φ ankle, step length ↑ φ trunk (to side of pain)
Henriksen et al., 2009b	20	(10/9)	CH^{+}	● ^{M}	VM	Forward lunge (contact phase)	↓ M EX knee = M AD knee = M hip, ankle	= φ_{peak} FL knee, hip = φ_{peak} DFL ankle = T_{mov}
Hirata et al., 2010	9	(4/5)	CH^{+}	●● ^{P} ●●● ^{P} ●●● ^{P}	TA GM GM + TA	Standing (static or perturbations)	↑ ΔCOP to foot ^{C} ↑ νCOP_{ML} ↑ ΔCOP_{AP}, νCOP_{ML}, ↑ ΔCOP to foot ^{C}	
Jaberzadeh et al., 2003	12	(7/5)	CH	●● ^{M}	EDL	FL-EX digit III		↑ tremor amplitude = tremor frequency
Madeleine et al., 1999b	6	(6/0)	CH	●● ^{P}	TA (stepping leg)	Forward stepping	↓ M_{peak} knee, ankle = $\Delta COP_{AP, ML}$ ↑ COP area ^{C}	↓ ω knee, = φ ankle, knee ↓ ν step, ↑ $T_{reaction}$ = T_{mov}, step length
Madeleine et al., 2004	11	(4/7)	CH	●● ^{M,P}	TZu	Standing (static)	= $\Delta COP_{AP, ML}$	
Smith et al., 2006	19	(7/12)	CH	●● ^{M} ● ^{M}	FDI	Modified pegboard task Grip-and-lift task		= ^{B} number of sticks = ^{B} grip-lift delay
Vuillerme and Pinsault, 2009	16	(16/0)	EL	●●● ^{M}	TZu^{B}	Standing (static)	↑ $\Delta COP_{AP, ML}$, $\nu COP_{AP, ML}$	
Tendon pain								
Henriksen et al., 2011	16	(8/8)	CH^{+}	● ^{M}	AT	PFL ankle (standing, rhythmic)	= force variability ↑ 10Hz component of force	↓ φ_{peak} DFL ankle = φ_{peak} PFL ankle ↓ ν concentric, = ν eccentric

[a] Pain was induced chemically (CH), thermally (TH) or electrically (EL), with [+] indicating the presence of a non-nociceptive control condition; [b] Reported intensity of pain is categorized into mild ●, moderate ●● and severe ●●● pain; [M] = mean pain; [P] = peak pain; [NR] = 'not reported'; [c] Effects on movement kinetics are described by ΔCOP and vCOP, displacement and velocity of the center of pressure, with [AP] anterior-posterior and [ML] medial-lateral; $M_{(peak),}$ (peak) joint moment calculated from force platform recordings; F_{comp}, compression force; F_{impact}, impact force; [d] Effects on movement kinematics are described by A amplitude, v velocity, and a acceleration of movement; $\varphi_{(peak)}$ (peak) angle, ω angular velocity, and α angular acceleration of a given joint; T_{mov}, movement time; $T_{power,peak}$, time to peak power; $T_{reaction}$, reaction time; $T_{v,peak}$, time to peak velocity; [#] used as target value.

AB, abduction; AD, adduction; AT, Achilles tendon; BB, biceps brachii; DFL, foot dorsal flexion; EDL, extensor digitorum longus; EX, extension; FDI, first dorsal interossei; FL, flexion; GLUTmd, gluteus medius; GM, (medial) gastrocnemius; IFP, infrapatellar fat pad; INV, inversion; MVC, maximum voluntary contraction; PEM, pectoralis major; PFL, foot plantar flexion; SU, supraspinatus; TA, tibialis anterior; TB, triceps brachii; TZu, upper trapezius; VM, vastus medialis; [B] bilateral; [C] contralateral; ↑ and ↓ indicate significant (p<0.05) increases and decreases, '=' indicates the absence of significant effects, and * indicates that findings correlate to subjective pain sensation.

Table S2.7 Effects of experimentally induced pain on measures of proprioception

Reference	*N*	(♂/♀)	Pain			Aspect of proprioception	Location	Results [c]
			Method [a]	Intensity [b]	Location			
(Sub)cutaneous pain								
Birznieks et al., 2008	15	(11/4)	CH	●● [P]	Above TA	Muscle spindle activity	TA (relaxed)	=
Weerakkody et al., 2003	8	(?)	TH	●● [P]	Above BB - indicator	Force matching	Elbow	↓* force indicator
					Above BB - reference	(match force produced		↑* force indicator
					Forearm (medial) - indicator	by reference arm)		=
					Forearm (medial) - reference			=
	3	(?)	TH	●● [P]	Above SOL	Force matching	Elbow	=
Weerakkody et al., 2008	12	(?)	CH	●● [P]	Above FPL	Movement sense (passive)	Finger I	=
	10	(?)	CH	●●● [P]	Finger I	Movement sense (passive)	Finger I	↓
Joint pain								
Bennel et al., 2005	16	(5/11)	CH	●●● [M]	IFP	Joint position sense (active)	Knee	= accuracy
								= precision
Muscle pain								
Birznieks et al., 2008	15	(11/4)	CH	●● [P]	TA	Muscle spindle activity	TA (relaxed)	=
Matre et al., 2002	11	(0/11)	CH [+]	●● [M]	TA + SOL	Joint position sense (passive)	Ankle	= accuracy
						Movement sense (passive)		↓
	12	(0/12)	CH [+]	● [M]	TA	Joint position sense (passive)	Ankle	= accuracy
						Movement sense (passive)		=
	10	(0/10)	CH	●● [M]	TA	Joint position sense (passive)	Ankle	= accuracy
						Movement sense (passive)		=
Niddam and Hsieh, 2008	8	(8/0)	CH	●●● [P]	APB	Perception of APB stimulation	n.a.	↓

Table S2.7 Effects of experimentally induced pain on measures of proprioception *(continued)*

Reference	*N*	(♂/♀)	Pain			Aspect of proprioception	Location	Results [c]
			Method [a]	Intensity [b]	Location			
Muscle pain								
Rossi et al., 1998	7	(5/2)	CH	●●● [P]	EDB	Joint position sense	Ankle	"↓ * "
						Perception of EDB nerve stimulation	n.a.	↓ *
Rossi et al., 2003b	6	(?)	CH	●●● [P]	FDI	Joint position sense	Fingers	"↓ * "
						Perception of FDI stimulation	n.a.	"↓ * "
Weerakkody et al., 2003	5	(?)	CH [+]	●● [P]	BB - indicator	Force matching	Elbow	↓* force indicator
					BB - reference			↑* force indicator
Weerakkody et al., 2008	11	(?)	CH	●● [P]	FPL	Movement sense (passive)	Finger I	↓
	10	(?)	CH	●●● [P]	FCR	Movement sense (passive)	Finger I	=

[a] Pain was induced chemically (CH) or thermally (TH), with [+] indicating the presence of a non-nociceptive control condition; [b] Reported intensity of pain is categorized into mild ●, moderate ●● and severe ●●● pain; [M] = mean pain; [P] = peak pain; [c] Results between " " were not quantified.

APB, abductor pollicis brevis; BB, biceps brachii; EDB, extensor digitorum brevis; FCR, flexor carpi radialis; FDI, first dorsal interossei; FPL, flexor pollicis longus; IFP, infrapatellar fat pad; SOL, soleus; TA, tibialis anterior; ↑ and ↓ indicate significant (p<0.05) increases and decreases, '=' indicates the absence of significant effects, 'n.a.' denotes 'not applicable', and * indicates that findings correlate to subjective pain sensation.

Table S2.8 Effects of experimentally induced pain on cortical correlates of motor function

Reference	*N*	(♂/♀)	Pain			Task description		Results		
			Method [a]	Intensity	Location	Method [c]		MEP amplitude [d]		CMEP/H-reflex amplitude
Transcranial stimulation studies										
(Sub)cutaneous pain										
Cheong et al., 2003	30	(12/18)	CH	●–●● [M]	Over FCR	TMS	Active (10, 30% MVC)	↑* FCR, = ECR, OP		
Fadiga et al., 2004	12	(6/6)	MC	●● [M]	Finger I	TMS	Active (% MVC NR)	↑ OP		
				●●● [M]			Relaxed	= OP		
Farina et al., 2001	11	(6/5)	CH	● [P]	Over FDI	TMS	Relaxed	↓ FDI, = APB, ADM		= FDI [F]
	6	(4/2)	CH	● [P]	Over FCR		Relaxed	↓ FCR, = ECR		= FCR [H]
Fierro et al., 2010	7	(4/3)	CH	●–●● [M,P]	Hand dorsum	TMS	Relaxed	↓ APB		
Hoegher Bement et al., 2009	25	(?)	MC	●–●●● [M,P]	Finger II	TMS	Relaxed	↑* BR[C]		
Kaneko et al., 1998	6	(6/0)	EL	NR	Finger II	TMS	Active (30% MVC)	[SL] = APB	[LL]↓ APB	
Kofler et al., 1998	5	(3/2)	EL	●●● [NR]	Finger II	TMS	Relaxed	[SL] = TE, BB	[LL]↓ TE, ↑ BB	
Kofler et al., 2001	6	(?)	EL	●●● [P]	Finger II	TMS	Relaxed	[SL]↓ TE, TB	[LL]↓ TE	
								[SL] = BB	[LL]↑ TB, BB	
								[SL]↑↓ ADM	[LL]↑↓ ADM	
	7	(?)	EL	●●● [P]	Finger II	TECS	Relaxed		[LL]↓ TE	
	7–11	(?)	EL [+]	●–●●● [P]	Finger II	TMS	Relaxed		[LL]↓ * TE	
									[LL] ↑ TB, BB, ADM	
	6	(?)	EL [+]	●–●● [P]	Finger V	TMS	Relaxed	[SL]↓ TE, TB	[LL]↓ TE, TB	
								[SL]↑ BB, = ADM	[LL]↓ ADM, ↑ BB	

Table S2.8 Effects of experimentally induced pain on cortical correlates of motor function *(continued)*

Reference	*N*	(♂/♀)	Pain Method [a]	Intensity [b]	Location	Task description Method [c]		Results MEP amplitude [d]		CMEP/H-reflex amplitude
Transcranial stimulation studies *(continued)*										
(Sub)cutaneous pain (continued)										
Kofler et al., 2001 *continued*	6	(?)	EL [+]	●–●● [P]	Finger II [C]	TMS	Relaxed	[SL] = TE, TB [SL] = BB, ADM	[LL]↓ TE, = TB [LL]= BB, ADM	
le Pera et al., 2001	12	(10/2)	CH [+]	●● [P]	Over ADM	TMS	Relaxed	[SL] = ADM		
Tamburin et al., 2001	6	(2/4)	EL [+]	NR	Finger II	TMS	Relaxed	[SL]↓ ADM	[LL]↓ ADM	
					Finger V		Relaxed	[SL]↓ ADM	[LL]↓ ADM	
					Finger II+V		Relaxed	[SL]↓ ADM	[LL]↓ ADM	
Uncini et al., 1991	8	(5/3)	EL	NR	Finger II	TECS	Active (50% MVC)	[SL]↓ OP	[LL]↓ OP	
Urban et al., 2004	10	(5/5)	EL	NR	Finger V	TMS	Relaxed	[SL]↓ APB, ADM [SL]↓ BB, DL = ADM [C]	[LL]↓ APB, ADM [LL]↑ BB, DL [LL] = ADM [C]	↑ APB, BB [H]
Valeriani et al., 1999	5	(3/2)	TH [+]	● [NR]	Hand dorsum	TMS	Relaxed	[SL]↓ FDI [B]	[LL]↓ FDI [LL] = FDI [C]	
	4	(?)	TH	● [NR]	Hand dorsum	TECS	Relaxed	[SL]= FDI	[LL] = FDI	
Valeriani et al., 2001	5	(1/4)	TH	● [NR]	Hand dorsum	TMS	Relaxed		[LL]↓ BB	
					Upper arm (lateral)		Relaxed		[LL] ↓ BB [N=3] [LL] = BB [N=2]	
	3	(?)	TH	● [NR]	Hand dorsum	TMS	Active		[LL] = BB	
						TECS	(%MVC NR)		[LL] = BB	

Muscle pain									
del Santo et al., 2007	8	(5/3)	CH	●●● [P]	ADM	TMS	Active	↑ * ADM	
					BB		(30% MVC)	↑ * BB	
le Pera et al., 2001	10	(7/3)	CH [+]	●●● [P]	ADM	TMS	Relaxed	↓ ADM, = ADM [C]	
	10	(7/3)	CH [+]	●● [P]	FDI		Relaxed	↓ FDI	
	11	(8/3)	CH [+]	●● [P]	FCR		Relaxed	↓ FCR	↓ FCR [H]
Martin et al., 2008	6	(?)	CH [+]	●● [P]	BB	TMS	Relaxed	= BB, TB	↑ BB, TB [CMEP]
							Active FL (20% MVC-force)	↓ BB, TB	= BB, TB [CMEP]
	6	(?)	CH [+]	●● [P]	BB		Active FL (20% MVC-EMG)	= BB, TB	↑ BB, TB [CMEP]
							Active EX (20% MVC-EMG)	= BB, ↓ TB	= BB, ↑TB [CMEP]
Svensson et al., 2003	10	(8/2)	CH	●● [M]	FDI	TMS	Relaxed	↓ FDI, = FCU	↓ FDI [CMEP N=2]
EEG studies									
(Sub)cutaneous pain									
Babiloni et al., 2008	18	(?)	EL	●● [NR]	Finger II	EEG	Move finger II [C]	alpha ERD (anticipation to integration of painful and motor information)	
							Move finger II	↓ alpha ERD (interference with sensory-motor processing)	
Tarkka et al., 1992	7	(7/0)	TH	NR	Hand (lateral)	EEG	Reaction time	↑ reaction time, ↑ latency between N2 EEG-potential and EMG activity in FDI (efferent component of central processing time)	

Footnote on p. 60

[a] Pain was induced chemically (CH), electrically (EL), thermally (TH), or mechanically (MC), with [+] indicating the presence of a non-nociceptive control condition;

[b] Reported intensity of pain is categorized into mild ●, moderate ●● and severe ●●● pain; [M] = mean pain; [P] = peak pain; NR = not reported; [c] Motor evoked potentials (MEPs) were elicited by Transcranial Magnetic Stimulation (TMS) or Transcranial Electric Current Stimulation (TECS) over the primary motor cortex; EX, extension; FL, flexion; MVC, maximum voluntary contraction. [d] Results pertain to muscles ipsilateral to the side of pain, unless indicated otherwise; [B] bilateral; [C] contralateral; Findings for acute painful stimulation are presented separately for intervals between painful stimulus and MEP eliciting stimulus ≤50ms (short-latency; [SL]) and >50ms (longer-latency; [LL]). Alpha ERD denotes the event-related desynchronization in alpha band (8-12 Hz) of the EEG signal.

ADM, abductor digiti minimi; APB, abductor pollicis brevis; BB, biceps brachii; BR, rachioradialis; DL, deltoideus; ECR, extensor carpi radialis; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; FDI, first dorsal interossei; OP, opponens pollicis; TB, triceps brachii; TE, thenar eminence; [F] F-wave;

[H] H-reflex; [CMEP] cervicomedullary motor evoked potential; ↑ and ↓ indicate significant ($p<0.05$) increases or decreases, '=' indicates the absence of significant effects, and * indicates that findings correlate to subjective pain sensation.