Anticipatory postural adjustments during a reaction time task and their reorganization due to knee pain

PhD Thesis

by

Shiozawa, Shinichiro

2023

Abbreviations used in the thesis

AP	: anterior-posterior
APAs	: anticipatory postural adjustments
BF	: biceps femoris
CNS	: central nervous system
CoM	: centre of mass
CoP	: centre of pressure
EMG	: electromyography
ERE	: erector spinae muscles
GAS	: gastrocnemius
LBP	: low back pain
ML	: medial-lateral
OA	: osteoarthritis
RMS	: root mean square
RT	: reaction time
SOL	: soleus
TA	: tibialis anterior
VL	: vastus lateralis
VM	: vastus medialis

Table of contents

Preface

This PhD thesis is based on the three below mentioned research papers that reported studies performed at the Center for Sensory-Motor Interaction (SMI), Aalborg University, Denmark from 2009 to 2016:

Paper 1: Shinichiro Shiozawa, Rogerio Pessoto Hirata, Thomas Graven-Nielsen: Reorganised anticipatory postural adjustments due to experimental lower extremity muscle pain. Human Movement Science 2013 32(6):1239-1252

Paper 2: Shinichiro Shiozawa, Rogerio Pessoto Hirata, Johanne Bruun Jeppesen, Thomas Graven-Nielsen: Impaired anticipatory postural adjustments due to experimental infrapatellar fat pad pain. European Journal of Pain 2014 19(9):1362-1371

Paper 3: Shinichiro Shiozawa, Rogerio Pessoto Hirata, Thomas Graven-Nielsen: Center of pressure displacement of standing posture during reaction time tasks is reorganised due to experimental lower extremity muscle pain. PLoS One 2015 10(12):e0144933.

Acknowledgements

I would like to thank all the participants of the experiments in this project for their cooperation; they performed various motor tasks despite the experimental knee pain. I thank Prof. Makoto Tominaga for supporting the thesis finalization. In addition, I thank Prof. Thomas Graven-Nielsen and Dr. Rogerio Pessoto Hirata, who continuously supported this project, provided scientific comments, and led key discussions. I could not have asked for more tolerant and eager supervisors for my PhD study.

I would like to thank the staff members of the SMI in Aalborg University for their invaluable assistance to my project. They always helped me to solve problems regarding my experiments and data analysis. In particular, I thank Hongling Nie and Johanne Bruun Jeppesen; this PhD project could not have been accomplished without their devoted work and support.

I would like to thank all the PhD scholars on the doctoral course of the Department of Health Science and Technology. I spent much time studying with them and all our discussions were invaluable. This has been a precious experience

Last but not the least, I would like to thank my lovely wife, Etsuko, and our three lovely children, Hirofumi, Keisuke, and Mikinobu, for their continuous support.

The present project has been supported by a collaborative grant between the Danish Agency for Science, Technology, and Innovation and the Japanese Science and Technology Agency and a grant from the Japanese Society for the Promotion of Rehabilitation.

Shinichiro Shiozawa

2023

1 Introduction

Knee joint pain is a common clinical issue. Knee osteoarthritis (OA) has a high prevalence (5.6–46.0% in older adult males, 10.3–61.0% in older adult females, and 18.4–46.2% in both sexes) in Europe, Asia, and North and South America (Guccione et al., 1993; Tennant et al., 1995; Zhang et al., 2001; Senna et al., 2004; Muirden, 2005; Sharma et al., 2006; Cecchi et al., 2008; Lawrence et al., 2008; Yoshimura et al., 2009; Jørgensen et al., 2011; Kim et al., 2011; Tang et al., 2016). Musculoskeletal disorders and pain associated with knee OA, are being increasingly reported as the proportion of older adults continues to rise globally. Advances in medical practice have prolonged longevity. Hence, pain due to musculoskeletal disorders, including knee joint pain, may become an issue in future; thus, it is a crucial topic in pain research. Several researchers described a conceptual model in which biological damage induces symptoms and functional changes and suppresses health-related self-consciousness (Wilson and Cleary, 1995; Ferrans et al., 2005). Hence, biological damage-induced knee pain may affect the association between certain parameters of physical factors and health-related self-consciousness.

The relationship between knee pain and postural control is another important issue in pain research because knee joint pain increases older adults' risk of falls during daily living activities (Foley et al., 2006). Musculoskeletal disorders, including those causing knee pain, are a key issue in the public health systems of several countries; currently, in Japan, older adults require continuous nursing care owing to regular falls and musculoskeletal disorders (Nakamura, 2008). Hence, the present study on knee pain-related postural control sought to clarify changes in the neuromuscular mechanism of postural control and potentially contribute knowledge to the public health system. Older adults with knee pain experience postural control difficulties. Patients with knee OA have more body sway than healthy older adults (Wegener et al., 1997; Hassan et al., 2001; Hatfield et al., 2016). Knee joint degeneration reportedly increased both the area and the length of postural sway while standing under both eyes-open and eyes-closed conditions in older adult females, although no effects were observed in older adult males under the eyes-open condition (Masui et al., 2006). In static standing under the eyes-open condition, patients with

knee OA had higher muscle activity of the vastus medialis (VM) than healthy older adults (Lyytinen et al., 2010). Additionally, in comparison with older adults without pain, patients with knee OA demonstrated decreasing vastus lateralis (VL) and biceps femoris (BF) activity during a reaching task (Venema and Karst, 2012). However, the relationship between knee pain and postural control remains partly understood because knee OA in older adults includes other pathological factors, such as joint degeneration (Kellgren and Lawrence, 1957; Koshino and Machida, 1993), morphological degenerative changes in muscles (Fink et al., 2007), impaired physical conditions (Guccione et al., 1993; Slemenda et al., 1998; Watanabe et al., 2010), decreased spinal cord reflex thresholds (Courtney et al., 2009), and sensitisation (Arendt-Nielsen et al., 2010; Arendt-Nielsen et al., 2015). Hence, a practical method that distinguishes knee pain from other pathological factors aids in the investigation of the effects of knee pain on postural control.

Assessing the effects of knee pain during anticipatory postural adjustment (APA) is an effective approach to determine the impact of knee pain on automatic motor control and predictive mechanism of postural control. Typically, APAs or feedforward postural control is generated by the central nervous system (CNS) to maintain equilibrium while standing. Lee et al. have explained APAs as follows: 'Consider what happens when one leg is actively lifted sideways while subjects maintain balance on the other. Since the centre of gravity's force vector is initially projected midway between the two feet, the body would fall to the side of the lifted leg if no anticipatory action were taken. To maintain balance, the voluntary movement must be preceded by a counterbalancing movement that shifts the centre of gravity over the leg on which the person intends to remain standing' (Lee et al., 1995). The counterbalancing effect in the predictive phase is feedforward postural control. Rapid shoulder flexion movement in a standing position induces activation of the bilateral BF as a typical APA, wherein the activation onset of ipsilateral BF occurs earlier than the activation onset of target movement muscle (the deltoid); this is another example of more detailed neuromuscular function (Belen'kii et al., 1967; Girolami et al., 2010). Rising onto toes quickly during quiet standing requires rapid movement of the ankle joints. However, the bilateral VM and VL are activated before ankle movement (Cowan et al., 2001). Anticipatory postural

adjustment induced by several reaction time (RT) tasks is an essential motor control pattern and forms an important mechanism for postural control, which prepares a stable posture for the forthcoming body perturbation. For example, a standing posture will be unstable in the anterior direction during rapid forward elevation of the arm in the absence of APAs. Both RT and self-paced tasks during standing are able to induce APAs (De Wolf et al., 1998). Reaction time tasks use random timed sound cues or light cues to initiate target movement and indicate more time delay of automatic postural muscle activity compared with self-paced tasks (De Wolf et al., 1998). Reaction time tasks may better clarify some changes of muscle activity on automatic postural control because the postural muscle activity during RT tasks is identified separately and not in conjunction with the target movement (Taylor, 2005). Therefore, the RT task is a reasonable method to investigate the effect of knee-related pain on automatic posture control. However, the reorganization of APA mechanisms due to knee-related pain remains partly understood, despite clinical studies reporting that musculoskeletal pain affects APAs (Cowan et al., 2002; Mouchnino et al., 2005; Venema and Karst, 2012). Moreover, knee-related pain may affect the APA mechanisms for each RT task.

Three investigative approaches were used in this project. First, a neuromuscular function approach was used to investigate the effects of knee-related muscle pain on APAs. An experimental pain model was used for the VM and tibialis anterior (TA), in the absence of other pathological factors. Knee-related pain was found to have induced early activation onset and reduced muscle activity of the postural muscles during APAs. Early activation onset of postural muscles occurred in the muscles on the contralateral side of the painful muscle, whereas reduced muscle activity of the postural muscles occurred in the painful muscles and in the ipsilateral thigh muscles.

Second, several biomechanical parameters were used investigate the effects of knee-related muscle pain on APAs. The experimental pain model used the aforementioned muscles. The displacement of the centre of pressure (CoP) during APAs on the painful and non-painful sides and the net CoP was calculated by using two force plates. Displacement of the CoP and net CoP were reduced on the painful side.

Third, a neuromuscular function approach was used to investigate the effect of infrapatellar fat pad pain on APAs. The infrapatellar fat pad pain model was used. A delayed muscle activation onset in the postural muscles on the painful side during APAs was induced by pain, whereas early onset of postural muscle activation was demonstrated on the non-painful side during APAs. Furthermore, pain reduced the amount of postural muscle activity on the painful side during APAs.

2 Pain and Motor Control

2.1 Pain mechanism

Pain perception involves transmission of information related to tissue damage along afferent inputs to the brain via the respective nociceptors, peripheral nerves (thin myelinated (Group III or Aδ) and unmyelinated (Group IV or C) fibres), spinal cord pathways, and thalamus (Willis, 1995). The sensory nerves of muscles and deep tissues have sense organs (Stacey, 1969). All joint structures, except joint cartilage, are innervated by free nerve endings (Reinert, 1998). Furthermore, the tissues, vascular walls, fascia, and aponeurosis of the tendons have several free nerve endings (Stacey, 1969; Mense and Stahnke, 1983). Pain is generated by biochemical changes and mechanical, chemical, and thermal stimuli. Chemical stimuli such as acid or capsaicin induces C-fibre nociceptor activation. Mechanical stimuli activate nociceptors as well. Thermal stimuli induce the activation of Aδ and C-fibre nociceptors. The primary afferent nociceptor is activated by inflammatory mediators at the site of tissue injury. This acidic 'inflammatory soup' includes peptides (bradykinin), lipids (prostaglandins), neurotransmitters (serotonin and ATP) and nerve growth factor (NGF). These factors sensitize (reduce the threshold) or excite nociceptor terminals (Julius and Basbaum, 2001).

2.2 Motor control and knee pain

Previous studies have demonstrated the effect of knee pain on motor control. Knee pain without joint degeneration alters the firing rates of motor units during knee extension tasks (Tucker and Hodges, 2009). The activation onset of the VM in the patellar tendon reflex in knee extensor dysfunction was delayed compared with the activation onset of the VL, although the activation onset of the VM was earlier than the activation onset of the VL in healthy participants (Voight and Wieder, 1991). Moreover, experimental knee pain inhibits muscle strength and activity in maximum isometric and isokinetic contractions during knee extensions via CNS modulation (Graven-Nielsen et al., 2002; Henriksen et al., 2011). Experimental infrapatellar fat pad pain alters knee extension performance and direction and hampers the stability of the

force exerted during isometric knee extension (Tucker and Hodges, 2010; Salomoni and Graven-Nielsen, 2012). Experimental knee pain increases the velocity of postural sway in the anterior-posterior (AP) and medial-lateral (ML) directions when standing on a movable platform (Hirata et al., 2012). Moreover, it induces a decrease in muscle activity in painful and co-activated muscles during walking (Henriksen et al., 2007), ascending or descending a staircase (Hodges et al., 2009), and forward lunging (Henriksen et al., 2009). Experimental knee pain decreases the peak angle of the knee joint during walking and forward lunging (Henriksen et al., 2007; Henriksen et al., 2009).

Experimental pain models in humans clarify the mechanisms of deep tissue pain, including the knee joint (Bank et al., 2013). In the present study series, hypertonic saline was injected into the quadriceps femoris muscle, TA, and infrapatellar fat pad in each motor task and the evoked experimental pain was located around the knee joint. Hence, these experimental pain models help investigate the relationship between knee-related pain and motor control, which have already been summarised in previous studies (Knutson, 2000; Arendt-Nielsen and Graven-Nielsen, 2008; Hodges and Tucker, 2011; Bank et al., 2013).

2.3 Postural control and pain

Musculoskeletal pain affects postural control during static standing. Hirata et al. demonstrated that hypertonic saline injection-induced calf muscle pain produced a more rapid CoP trajectory than that in the non-pain condition (Hirata et al., 2010). During quiet standing, single muscle (gastrocnemius (GAS)) and double (TA and GAS) muscle pain conditions induced a high-speed ML CoP trajectory compared with a non-pain condition. Unilateral double muscle (TA and GAS) leg pain produced a more rapid CoP trajectory than single muscle pain (Hirata et al., 2010). Furthermore, double muscle pain indicated a shift in body weight from the painful limb to the non-painful limb (Hirata et al., 2010).

Hypertonic saline injection-induced VM and VL pain condition demonstrated greater body sway displacement (AP direction) than in the non-pain condition. Hypertonic saline injection-induced thigh muscle pain produced higher body sway speed (ML direction) and greater body sway area during quiet

standing than those observed in the non-pain condition (Hirata et al., 2011). Hip pain due to experimentally induced pain in the gluteus medius had a limited effect on balance, although it impaired standing balance in a single-leg squat task (Hatton et al., 2015). This effect of musculoskeletal pain on postural control may be pain location-specific and motor task-dependent, if the pain is in the lower extremity and in the absence of other pathological factors.

Experimentally induced infrapatellar fat pad pain produced greater AP postural sway than the non-pain condition (Hirata et al., 2012). Bilateral infrapatellar fat pad pain produced greater ML postural sway than that in the non-pain condition during standing (Hirata et al., 2012). Moreover, hypertonic saline injection-induced infrapatellar fat pad pain altered the angle of the lower extremity joints during quiet standing (Hirata et al., 2012). Leg muscles and knee-related pain during quiet standing affected CoP parameters and joint angles, and the pain may have induced postural instability. Experimentally induced infrapatellar fat pad pain altered the interference between the brain and muscle activities during motor tasks (Poortvliet et al., 2019).

Experimental plantar pain resulted in a greater CoP area, higher body sway velocity, and more CoP instability (ML and AP) than that in the non-pain condition and in case of palmar pain (Pradels et al, 2011). Knee-related pain and plantar pain during static standing produced pain location-dependence in postural adjustment. Furthermore, treatment of pain in the lower extremity could potentially recover postural control. As mentioned, previous studies have been conducted on postural control and lower extremity pain; however, only a few have addressed the relationship between knee-related pain and APAs. The next chapter presents the three studies that investigated the effects of experimental knee-related pain, induced by hypertonic saline injection, during APAs.

Previous studies have demonstrated that unstable postural control in older adults with knee OA is a matter of concern. For example, in patients with severe knee OA, postural sway while standing depends on the surface characteristics (Hirata et al., 2013) and has direction specificity (Hirata et al., 2013). A study on knee pain, muscle weakness, and stiffness in older adults reported the CoP data for patients with mild knee OA in a squat position (Petrella et al., 2017). Moreover, this study indicated that CoP

amplitude and velocity in older adults during squatting were related to physical function and stiffness. The plasticity of the neural mechanism underlying motor control has been demonstrated by biomechanical orthoses (Moyne-Bressand et al., 2017). However, clarifying postural stability in patients with knee OA is challenging because postural sway in patients with chronic pain is influenced by certain pathological factors. Therefore, studies on experimental knee pain can be used to clarify postural stability related to chronic knee pain.

3 Postural Control and Anticipatory Postural Adjustments

Postural control is the stabilisation of the centre of mass (CoM) in space for balance and orientation. It involves stabilising the CoP of each posture in a base-of-support via the CNS (Horak and Nashner, 1989; Horak, 2006). Each postural adjustment is a result of sensory input-motor control interactions. Postural control strategies are associated with CNS-mediated predictions of the body position over time (feedforward strategy) or post-perception control (feedback strategy). The following three major sensory systems are required for the accurate recognition of the body's spatial position: 1) somatosensory, 2) vestibular, and 3) visual (Winter, 1995; Mergner and Rosemeier, 1998).

Anticipatory postural adjustments are automatic predictive mechanisms that stabilise the body's CoM within the base-of-support before voluntary perturbation. In particular, several postural muscle activities are generated before a voluntary movement onset that could cause a postural perturbation (Belen'kii et al., 1967; Bouisset & Zattara, 1981; Bouisset and Zattara, 1987). Several target movements or motor tasks have been used to induce APA-related postural muscle activity, including shoulder flexion, stepping, and ankle movements in RT tasks or self-pace triggers (Belen'kii et al., 1967; Cowan et al., 2001; De Wolf et al., 1998). Posterior postural muscles, such as the BF, are activated if a perturbing force is generated anteriorly (Belen'kii et al., 1967). Moreover, knee extensors, such as the VM and VL, are activated if a perturbing force is generated by lower extremity movements (Cowan et al., 2002). Major parameters for evaluating postural muscle activation are the onset of activation and level of activity of postural muscles, measured via electromyography (EMG). Anticipatory postural adjustment is a robust feedforward mechanism, even under abnormal sensory conditions, such as those present in chronic pain patients (Leinonen et al., 2001). Furthermore, patients with a lack of sensation in their extremities exhibited APAs during a load-release task of the elbow joint (Forget and Lamarre, 1990).

Muscle responses of APAs are task-dependent and task-specific (Aruin and Shiratori 2004; Aruin, 2006). The neural networks for APAs and target movement may be independent pathways, although APAs are directed by target movement (Viallet et al., 1992; Massion et al., 1999; Taylor, 2005). Hence, the neural network for APAs is believed to be isolated from the corticospinal pathway of voluntary

movement (Viallet et al., 1992; Massion et al., 1999; Taylor, 2005). For example, APA muscle activation in an upper limb voluntary movement task was maintained even when the related muscle activation was paused via transcranial magnetic stimulation (Taylor, 2005). A previous study reported that corticospinal excitability during an APA with dynamic shoulder movement appeared to be greater than that during static tasks (Chiou et al., 2016). This study posited motor cortex excitability as an essential aspect of APA mechanisms involving the postural muscles, although APA-related muscle activity is not under voluntary motor control. Moreover, inhibition and activation of the brain for control of trunk muscles were clarified when voluntary shoulder movement was performed under sound cues (Massé-Alarie et al., 2018). In a one-leg-raise task, the interaction between the α motor neurons of the soleus (SOL) and TA during APAs was investigated using an H-reflex. This results demonstrated that the agonist–antagonist interaction in the supporting leg during the APAs was modulated by the supra-spinal neural pathway because the Ia inhibition of the SOL was faster than the facilitation of the TA (Komiyama and Kasai, 1997). Thus, the motor cortex and the corticospinal, supra-spinal, and spinal pathways contribute to the APA mechanism.

Characteristics of APAs are as follows: 1) these are generated in a feedforward manner by the CNS, 2) these are reorganized by the starting position and sensory inputs, 3) these are dependent on each target movement, 4) these involve neural pathways independent from the corticospinal pathway, and 5) these are modulated by higher brain functions, rather than the spinal cord.

4 Anticipatory Postural Adjustments and Pain

4.1 Aim of the PhD project

This project aimed to examine the influence of experimental knee-related pain on APAs related to RT tasks in healthy adults without pathological factors (Figure 1). Intra-muscular (Studies 1 and 2) or infrapatellar fat pad (Study 3) hypertonic saline injection-induced knee pain models was used. Knee pain effects on APAs were detected by assessing the neuromuscular function (Studies 1 and 3) and biomechanical measurements (Study 2).

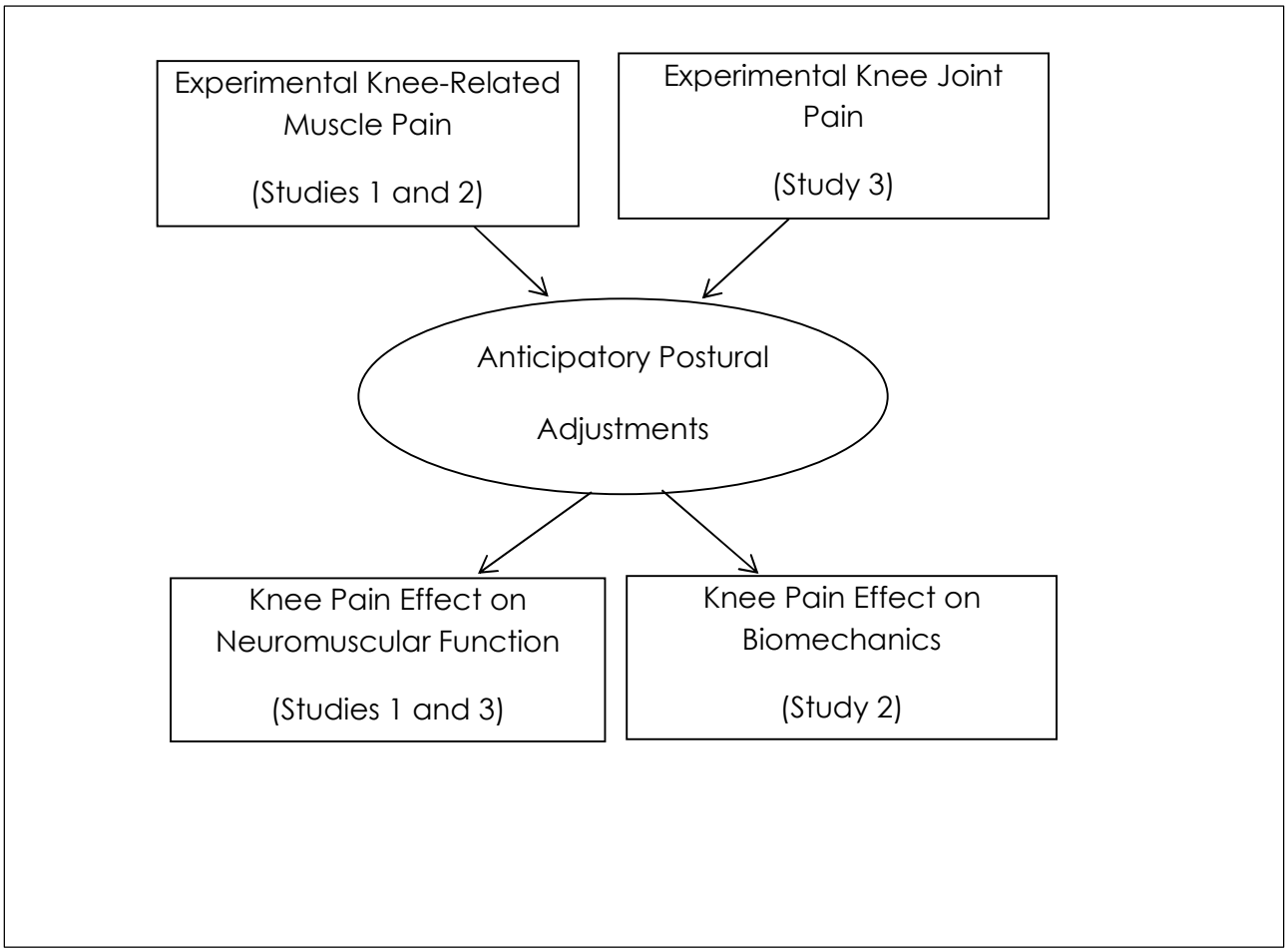

Figure 1: Model of the interaction between knee-related pain and APAs investigated in this thesis

4.2 Hypothesis and goals

It was hypothesised that knee-related pain decreases the peak and amount of postural muscle activity in the painful side during APA. This may have been an adaptation strategy to protect the tissue in the painful area. Knee-related pain induced early activation onset of postural muscles in the non-painful side during APA; it was a compensatory function to maintain standing posture. Studies 1 and 3 may possibly clarify the reorganization of postural muscle activity during APA. These studies investigated both adaptation strategy and compensatory function on automatic postural control. Moreover, Study 2 hypothesised that knee-related pain decreased postural sway during APA, which may have induced postural unbalance under knee-related pain condition.

The goal of all three studies was to focus on both adaptation strategy and compensatory function to clarify the effect of knee-related pain for the reorganization of APA. Furthermore, these study results may contribute to a better of understanding human posture control mechanisms, which may be used to solve knee-related pain issues in older adults in the future.

4.3 Previous studies on musculoskeletal pain and postural muscle activity during APAs

Musculoskeletal pain during APAs has been investigated (Table 1). Specifically, the effects of neck, low back (LBP), hip, and knee pain on APAs have been demonstrated in clinical and experimental pain studies (Table 1). The activation onset of postural muscles before a target movement was a typical variable investigated during APAs (Belen'kii, 1967). Accordingly, both surface and intramuscular EMG measurements were used. In particular, evaluation of the deep muscles of the neck and low back requires an intramuscular EMG method to detect the onset of postural muscle activation. Alternatively, ultrasound measurement may be used in the future to detect the onset of activation of some postural muscles during APAs (Vasseljen et al., 2006; Vasseljen et al., 2009).

The activation onset of the postural muscles during APAs during a shoulder flexion task was delayed in patients with neck pain and LBP compared with that in healthy adults (Hodges and Richardson, 1996;

Hodges and Richardson, 1998; Hodges, 2001; Falla et al., 2004; Moseley et al., 2004; Moseley et al., 2004; Moseley and Hodges, 2005; Tsao et al., 2008).Patients with LBP had reduced trunk muscle activity levels during APAs in a standing shoulder flexion task (Hodges, 2001). Furthermore, chronic LBP hindered the adjustability of trunk muscle activity during APAs compared with that in healthy participants (Jacobs et al., 2009). Moreover, 4-week trunk muscle training improved the delayed activation onset of the deep trunk muscles during a shoulder flexion task (Tsao and Hodges, 2008). Patients with patellofemoral pain syndrome have alteration of the synchronised onset of both the VM and VL during bilateral heel and toe lifts while standing compared with healthy control participants (Cowan et al., 2002). Knee pain altered the onset timing between the VM and VL during standing ankle movement tasks (Cowan et al., 2001). Nevertheless, patients with patellofemoral pain syndrome did not exhibit delayed activation onset of the postural muscles during APAs compared with control participants (Cowan et al., 2001). Moreover, these patients demonstrated inhibited peak muscle activity in the postural muscles during APAs. However, patients with LBP demonstrated delayed activation onset of the postural muscles during APAs (Hodges and Richardson, 1996, 1998). Compared with healthy participants, patients with knee OA demonstrated reduced muscle activity levels in the VL and BF during a reaching task (Mouchnino et al., 2005; Venema and Karst, 2012). Moreover, these patients demonstrated an earlier activation onset of the GAS than control participants during the same task. Patients with knee OA demonstrated an earlier activation onset of the VL when stepping down on the painful side than healthy participants (Mouchnino et al., 2005). This finding was notable because clinical and experimental studies have mainly reported a delayed activation onset of the postural muscles during APAs in individuals with painful conditions (Hodges and Richardson, 1996; Hodges and Richardson, 1998; Hodges, 2001; Hodges et al., 2003; Falla et al., 2004; Moseley et al., 2004; Moseley et al., 2004; Moseley and Hodges, 2005; Tsao et al 2008; Tsao and Hodges, 2008; Massé-Alarie et al., 2012). The effect of knee pain on postural muscles during APAs enabled several reorganizations of APA mechanisms different from those used in the context of neck pain and LBP. Thus, knee pain might contribute to postural control of bilateral limbs since both can be controlled separately by the CNS, while the neck-trunk structure is difficult to control

separately. However, the specific nature of the relationship between knee pain and APAs remains unclear because the results of the aforementioned studies included pain and other pathological factors. In addition, these studies did not focus on the effects of pain on patients' painful and non-painful sides. A previous study used the hypertonic saline injection-induced infrapatellar fat pad pain model to investigate pain effects when ascending and descending a staircase (Hodges et al., 2009). The activation onset and activity level of the quadriceps femoris muscle were measured. Furthermore, onset of muscle activation was indicated as the time relative to foot contact. Infrapatellar fat pad pain altered the relative onset of activation between the VM and VL when ascending the stairs. Therefore, the effect of infrapatellar fat pad pain during standing was task-dependent and muscle-specific. Furthermore, pain inhibited activation of the VL in a feedforward manner. The inhibition of thigh muscle activities during APAs under pain conditions might be a selective effect on lower extremity muscles. However, the contribution of infrapatellar fat pad pain to each limb during static standing remains unknown. A previous study demonstrated changes in thigh muscle activity during walking as a dynamic movement condition in the presence of infrapatellar fat pad pain (Henriksen et al., 2010). The studies in this PhD project used experimental knee-related muscle pain and infrapatellar fat pad pain to investigate the effect of knee-related pain during APAs.

4.4 Participants of this PhD project

The study design was randomized and blinded. All three studies were performed in accordance with the tenets of the Declaration of Helsinki and were approved by the local ethical committee (Ethics Committee of the North Denmark Region: N-20080022). The number of participants, all healthy males, in Studies 1, 2, and 3 were as follows: nine (mean age, 29 years; range: 21–38); nine (mean age, 29 years; range: 23–38), and twelve (mean age, 30 years; range: 21– 39), respectively. The number of participants to be enrolled was selected to provide a power of 0.84 to detect a difference of 20% between the baseline and pain sessions in the amount of alteration during pain session; it was based on an estimated standard deviation of 15% in

change normalized EMG, with a type I error rate of 0.05 and two-tailed, if nine participants remained in three studies.

4.5 Protocol of data acquisition and data analysis for experimental pain

An experimental protocol of six sessions was used in all three studies (Figure 2). Two baseline sessions were scheduled as the first and fourth sessions, two injection sessions were the second and fifth sessions, and the two remaining sessions were post-injection sessions. Each session included 20 trials for 2 RT tasks, which were alternated; odd and even numbers in each session were a unilateral shoulder flexion task and a bilateral heel lift, respectively.

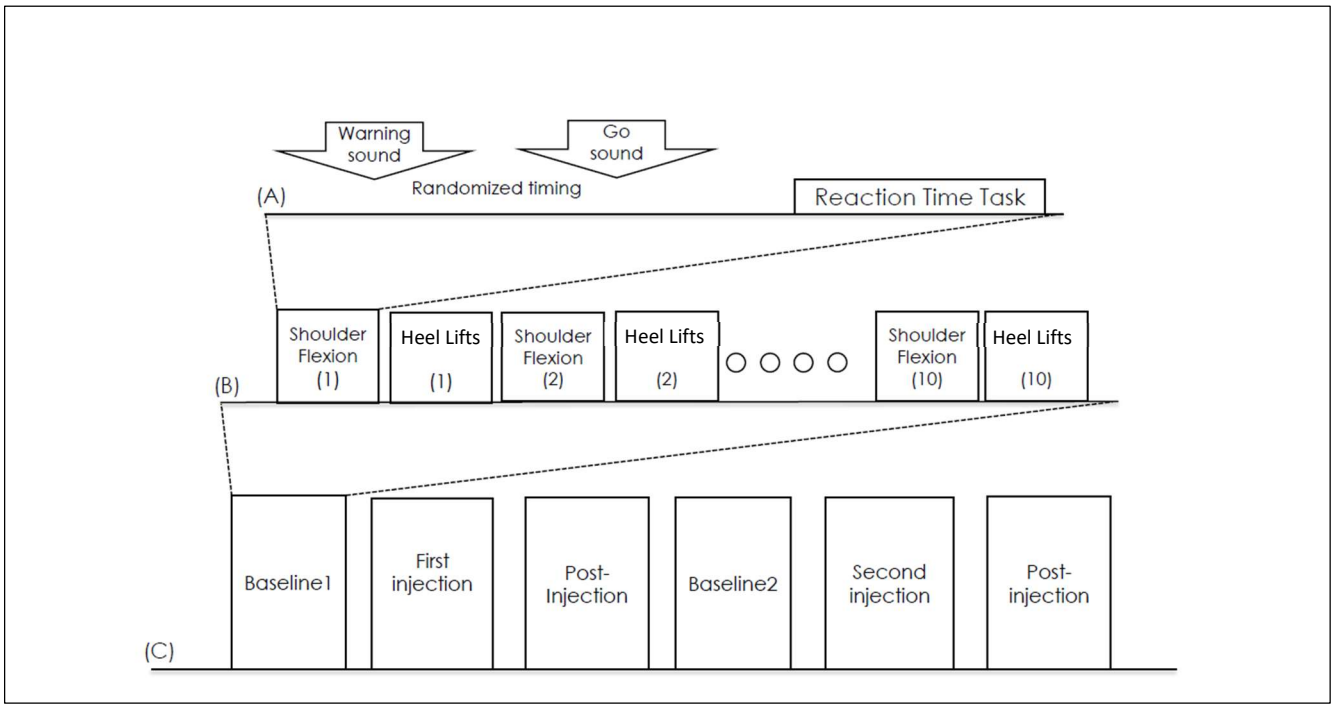

***Figure 2*:** Experimental protocol of the studies

A, B, and C are a trial, single session, and sequence of sessions, respectively. The second cue of two signals during a trial was the start signal (A). Shoulder flexion and bilateral heel lifts were alternated as reaction-time tasks (B). Six sessions for each pain condition (VM or TA or infrapatellar fat pad pain) were designed (C).

For EMG studies, bipolar Ag-AgCl surface electrodes (Ambu, Neuroline 720, Copenhagen, Denmark) were used to record EMG on the anterior part of deltoid muscle (AD) on the dominant side and bilateral

erector spinae muscles (ERE, L1 level), VM, VL, BF, TA, or SOL. The studies followed the SENIAM recommendations for skin preparation and electrode placement (Hermens et al., 2000). The ground electrode was placed over the C7 spinous process. The EMG signals were amplified (×2000) by a multichannel EMG amplifier (EMG-USB, LISiN-OT Bioelectronica, Torino, Italy), band-pass filtered (bandwidth 50–750 Hz), and sampled at 2048 Hz. The digitised EMG signals were band-pass filtered (4^{th} order, zero-phase-lag Butterworth filter, 20– 400 Hz) and full-wave rectified. The onset of activation of all muscles after the 'go' signal was automatically identified as the time point where the muscle activity increased by two standard deviations from the background value (calculated in a 50 ms time window immediately after the 'go' signal). The onset of muscle activation was calculated relative to the 'go' signal and was defined as 'EMG reaction time'. Furthermore, the onset of the respective prime movers was subtracted from the activation onset of the postural muscles, and this was defined as 'EMG relative onset' for the postural muscles. A negative EMG relative onset from before activation onset to 100 ms after the activation onset of the respective prime movers (positive relative onset) was categorised as APA. Representative data for APA measurements during RT tasks (e.g., shoulder flexion on the right side) on joint movement and EMG are presented in Figure 3. During shoulder flexion, activation of the AD (target movement muscle) and ipsilateral BF (postural control) represented voluntary shoulder movement and RT-related postural control, respectively. Postural control muscles demonstrated onset of activation before that of the target movement muscle. The red dots in Figure 3 illustrate the detection of muscle activity onset. In Studies 1 and 3, the time window between the 'go' signal and the onset of target movement muscle activation was used to investigate the effect of pain. The short period of time after onset of target movement muscle activation was categorised as the duration during which APAs occurred. This was defined as a feedforward mechanism because the amount of time after the onset of target movement muscle activation was extremely insufficient to receive sensory inputs from several target movements (Belen'kii et al., 1967; Benvenuti et al., 1997; Chabran et al ., 1999; Mezaour et al., 2010; Vedula et al., 2010). In this study, APA was defined as follows: 1) the time before the onset of target

movement muscle activation, 2) the time before the initiation of the target movement, and 3) a short time (approximately 100 ms) after the initiation of the target movement.

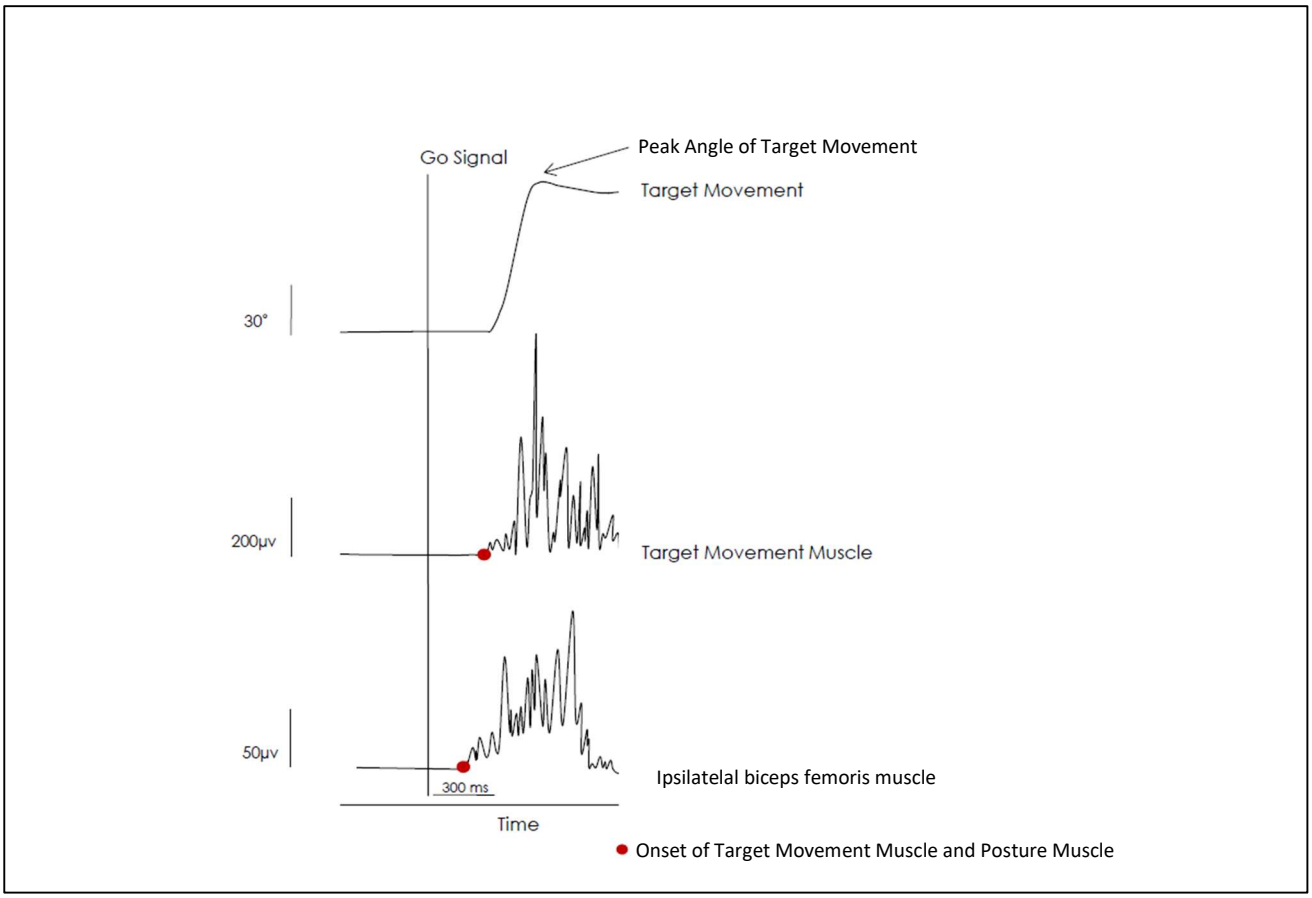

***Figure 3*:** Illustrative target movement trajectory and rectified EMG (target movement and postural muscle) for one typical dataset (single trial). The red dots indicate the onset of target movement muscle activation and postural muscle activation. The arrow indicates the peak angle.

In the CoP assessment, the ground reaction forces and torques from both force plates were amplified, low-pass filtered (10 Hz), and sampled at 2 kHz. The CoP under the ipsilateral and contralateral foot and the net CoP were calculated (Winter, 1995) after recording the ground reaction forces and torques from both force plates (AMTI, USA). The CoP displacement was split into the AP and ML directions, which allowed better characterisation of the ankle and hip strategy during postural control (Winter, 1995, Winter et al., 1996, Winter et al., 2003). The time points for the negative and positive peaks in the AP CoP

displacement were automatically estimated and used as a time window for extracting the other CoP parameters. The first negative and positive peaks of the CoP displacement after the 'go' signal were detected. The first negative peak was interpreted as postural adjustments before movement onset which usually occurred between -50 and 150 ms from movement onset (APA window). The first positive peak was related to movement termination (Figure 4) and usually occurred after the APA window. Knowledge of the relationship between both the anticipatory and focal movement components of postural adjustments help better quantify the possible alterations in pain-related postural control. Thus, the time window between the two peaks was used for the CoP analysis. Furthermore, time points for the negative and positive peaks of CoP displacement were calculated relative to target movement onset and were defined as relative time-to-peak for ipsilateral, contralateral, and net CoP. In the bilateral heel lift task, the relative time-to-peak of the net CoP was estimated by the mean onset value from both calcaneal markers. CoP displacement between the first negative and positive peaks in the AP and ML directions was calculated and defined as peak-to-peak displacement for ipsilateral, contralateral, and net CoP (Figure 4). Additionally, the peak-to-peak CoP velocity (average) in both directions for ipsilateral, contralateral, and net CoP was calculated by dividing peak-to-peak displacement by its respective time interval. Representative data for APA measurements during an RT task (e.g., shoulder flexion on the right side) involving joint movement and CoP displacement is presented in Figure 4. In shoulder flexion, the AP and ML net CoPs represent voluntary shoulder movement and RT task-related postural control. The blue dot in Figure 4 illustrates the detection of activation onset for target movement. The first peak of the AP CoP was indicated before the onset of activation of target muscle movement. The net CoP calculation from the two force plates indicated the AP negative and positive peaks.

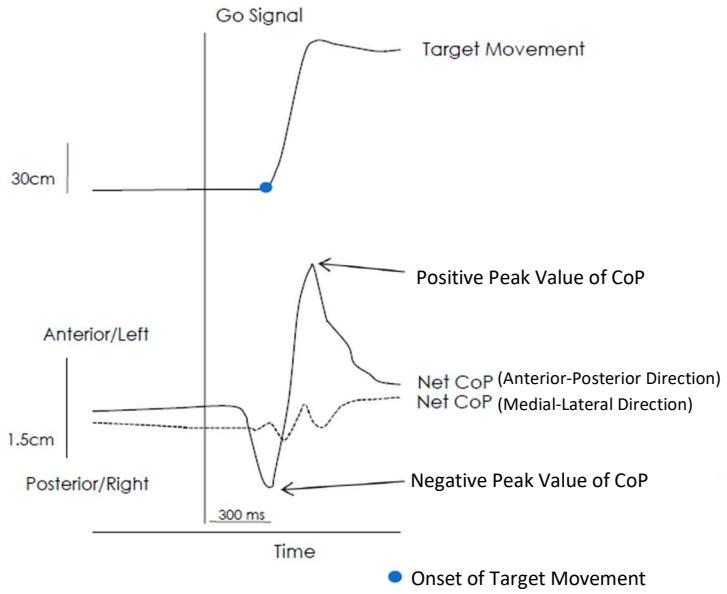

Figure 4: Illustrative target movement trajectory and net CoP displacement in both directions during shoulder flexion for one typical dataset (single trial). The blue dot indicates the onset of activation of target movement. The arrows indicate the peak value of AP CoP displacement.

The kinematic analyses were performed by eight infrared cameras recording at 500 Hz (Qualysis Medical AB, Gothenburg, Sweden). Eleven reflective markers (2 cm diameter) were attached on palpable anatomical landmarks. The orientation of six segments (dominant brachium, trunk line, bilateral legs, and bilateral feet) was tracked and defined by markers placed on dominant side's lateral supracondylar ridge of the elbow, acromion, and iliac crest and bilateral medial femoral condyles, bilateral medial malleoli, bilateral heels, and bilateral first metatarsal head. The shoulder joint angle was defined by two segments: the dominant brachial (a line joining the lateral supracondylar ridge of the dominant elbow and acromion markers) and trunk (a line joining the dominant acromion and iliac crest markers) lines. The ankle joint angle was defined by two segments: the leg (a line joining the femoral medial condyle and medial malleoli markers) and foot (a line joining the heel and first metatarsal head markers) lines. The peak joint angle of shoulder flexion and bilateral heel lift tasks was computed to assess the performance in each

trial. Furthermore, the peak angular velocity of the shoulder and ankle joints in each task was calculated via these defined segments.

All EMG and biomechanics parameters were analysed separately for each RT task. In Study 1, a one-way repeated measures analysis of variance (RM-ANOVA) was used to analyse the baseline maximum RMS EMG amplitude (average across all baseline measures and not normalised) with the postural muscles (bilateral ERE, VM, VL, BF, TA, and SOL for shoulder flexion and bilateral ERE, VM, VL, BF, and TA for bilateral heel lift) as the factor. The baseline time profiles for EMG amplitudes of postural muscles were analysed with a two-way RM-ANOVA with factors of epoch (1–7 or 10) and side (ipsilateral or contralateral). All EMG (EMG onset and RMS EMG peak) and kinematic parameters were further analysed separately for each saline type (isotonic or hypertonic), reaction task (shoulder or heels), and individual muscle. A two-way RM-ANOVA was used to analyse EMG onset and RMS EMG peak amplitude with the pain condition (baseline, injection, and post-injection) as the first factor and side (ipsilateral and contralateral) as the second factor. In Study 2, a three-way RM-ANOVA with side (ipsilateral or contralateral), painful muscle (VM and TA), and saline type (isotonic or hypertonic) was applied in the baseline session data to evaluate the CoP asymmetry between feet, time (baseline, injection, and post-injection), and painful muscle on the following parameters: movement reaction time (unilateral shoulder flexion and bilateral heel lift tasks), relative CoP negative and positive time-to-peak, AP and ML CoP displacement, and the velocity. The CoP parameters for ipsilateral and contralateral sides and net CoP were normalised (%) by baseline values before analysis. In Study 3, a two-way RM-ANOVA (side (ipsilateral and contralateral) and epochs (7 and 10 epochs for shoulder flexion and bilateral heel lift tasks, respectively)) was applied to characterize the asymmetry of postural muscle activity profile using the average values between both baseline conditions. A three-way RM-ANOVA was used to analyse the muscle activity onset with saline, time (baseline, injection, and post-injection), and side as the factors. A three-way RM-ANOVA was used to analyse the EMG amplitude with saline type, time, and epoch as the factors for each side. Newman–Keuls (NK) post hoc test, corrected for multiple comparisons, was applied in case of significant factors or interactions. Statistical significance was set at $p < 0.05$.

4.6 Effect of knee-related muscle pain during APAs based on EMG data

In the shoulder flexion task with VM pain, the EMG relative onset of ipsilateral BF exhibited a significantly earlier onset than at the baseline and post-injection sessions (Figure 5A; RM-ANOVA: $F(2, 16) = 3.79$; $p < 0.05$; NK: $p < 0.01$). The EMG relative onset of the contralateral TA during the bilateral heel lift task exhibited a significantly earlier onset than during the other sessions in both pain conditions (Figure 5B, C; RM-ANOVA: $F(2, 16) = 12.06$; $p < 0.01$; NK: $p < 0.01$). In the bilateral heel lift task of the VM pain condition, the bilateral VM activity (peak RMS EMG) was significantly reduced compared with baseline levels (Figure 6A; RM-ANOVA: $F(2, 16) = 5.0$, $p < 0.05$; NK: $p < 0.05$). A significant reduction of the ipsilateral VL activity was observed immediately after the hypertonic saline injection compared with contralateral VL activity (Figure 6B; RM-ANOVA: $F(2, 16) = 3.66$, $p < .05$; NK: $p < 0.05$). A significant reduction of the ipsilateral VM and TA activities was observed immediately after the hypertonic saline injection into the TA compared with baseline (Figure 6C, D; RM-ANOVA: $F(2, 16) = 3.69$, $p < .05$; NK: $p < 0.05$); this reduction was observed at the post-injection sessions as well for the ipsilateral TA activity (NK: $p < 0.05$). No differences were observed for the shoulder flexion task.

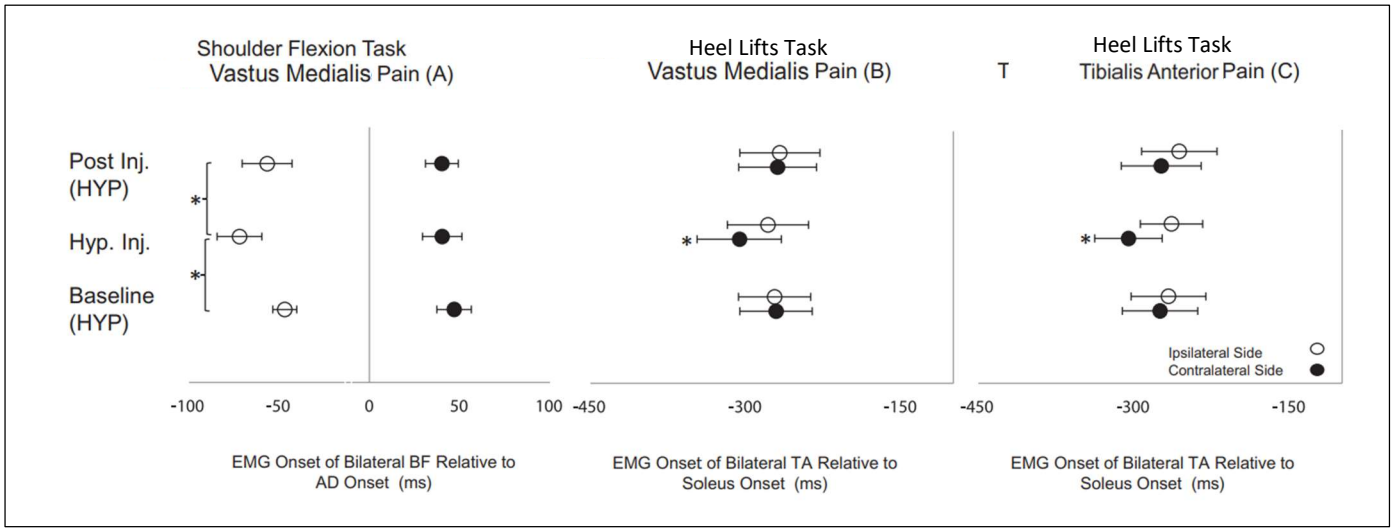

Figure 5: Mean and standard error of EMG onset of bilateral BF (shoulder flexion task, A) and bilateral TA (heels lift task, B and C) illustrated at baseline, injection, and after hypertonic saline injection. Significantly earlier onset than the other sessions is observed (NK: $p < 0.01$). Ipsilateral side (open symbols) is defined as the side exposed to experimental pain. Contralateral side (solid symbols) is the opposite of experimental pain.

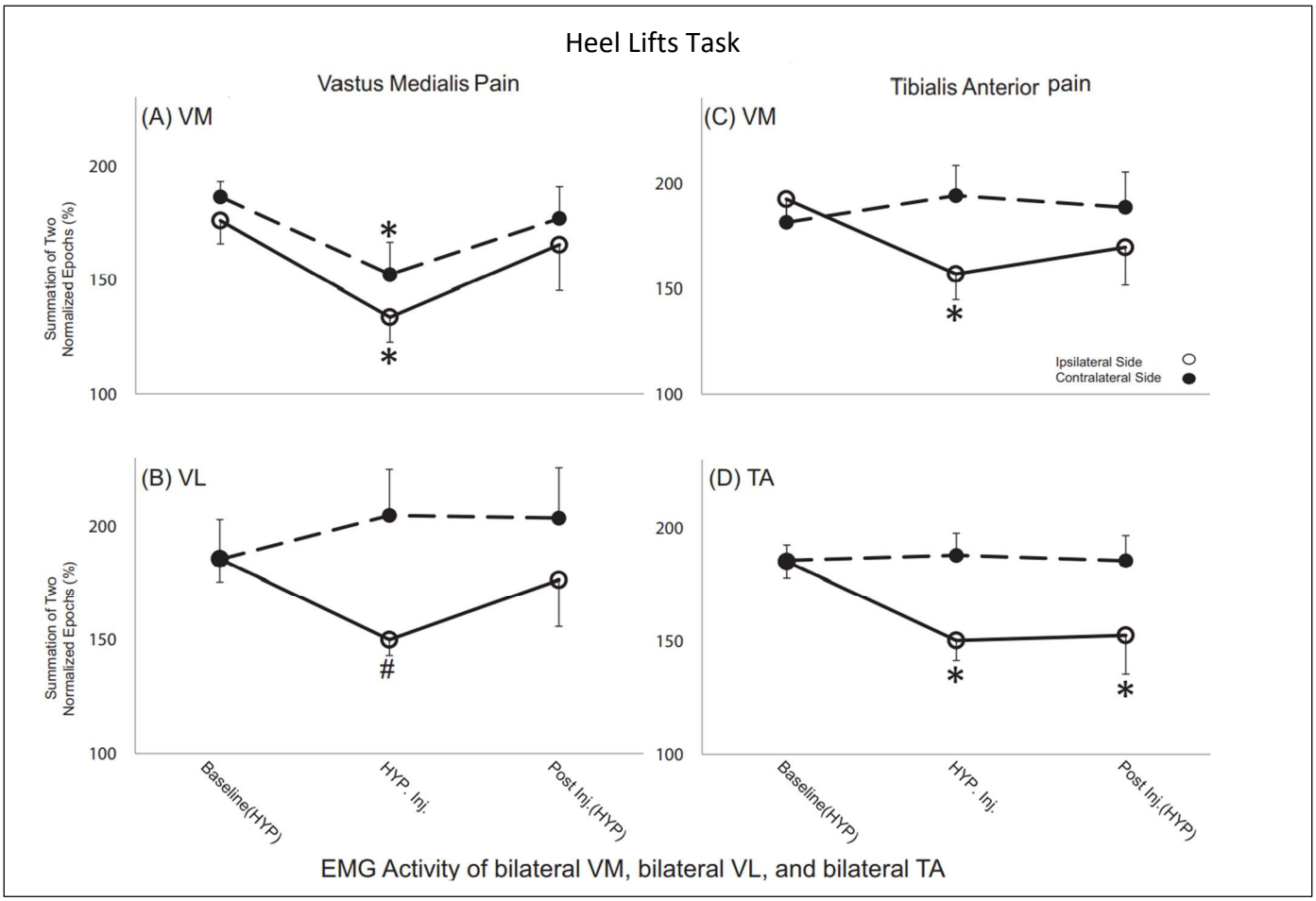

Figure 6: Mean and standard error of normalised peak muscle activity (RMS EMG) of the bilateral VM, VL, and TA during bilateral heel lift task at baseline, injection, and after hypertonic saline injection into the VM (A, B) and TA (C, D) muscles. Significantly reduced maximum activity compared with baseline (/NK: $p < 0.05$) or contralateral side (#NK: $p < 0.05$) is observed. Ipsilateral side (open symbols) is defined as the side exposed to experimental pain. Contralateral side (solid symbols) is the opposite of experimental pain.

In Study 1, a neuromuscular approach was used to assess whether knee-related muscle pain affected APAs on the painful and non-painful sides to protect painful muscles and maintain posture in healthy participants. Hypertonic saline injection-induced VM pain produced an earlier activation onset (relative time from the onset of target muscle movement) of the ipsilateral BF during shoulder flexion than in the no-pain condition. Early activation onset during APAs was observed in the non-painful postural muscles, although the painful limb was on the ipsilateral side. The onset of the target muscle movement in the shoulder flexion task and peak angle and peak angular velocity of the shoulder joints remained unchanged under the pain condition. Hypertonic saline injection-induced pain in the VM and TA caused earlier activation onset of contralateral TA during bilateral heel raises than those observed under the no-pain condition (Study 1). Moreover, consecutive 100-ms time-windows were used to evaluate the effect of pain on peak postural muscle activity during APAs. In the bilateral heel lift task, VM pain reduced the peak muscle activity of the bilateral VM and ipsilateral VL compared with the no-pain conditions, whereas TA pain resulted in a greater reduction in the peak muscle activity of the ipsilateral VM and TA than in the no-pain conditions (Study 1). Early activation onset was observed on the non-painful side and reduced postural muscle activity occurred in the painful and synergistic muscles during APAs. The activation onset of the bilateral SOL during the bilateral heel lift task under the pain condition was delayed compared with the no-pain condition, although the peak angle and peak angular velocity of bilateral ankle joints in the pain condition remained unchanged. Reorganized APAs due to the knee-related muscle pain indicated that early activation onset of postural muscles occurred in the non-painful muscles and on the non-painful side (Study 1). These results indicate a possible compensatory mechanism for postural maintenance during pain. Reorganized APAs due to knee-related muscle pain indicated that reduced peak muscle activity was present in painful and synergistic muscles, which indicated a possible adaptive strategy for protecting painful muscles and limbs. Furthermore, the effect of VM and TA pain produced a bilateral delayed activation onset in the target movement muscles, although the pain was unilaterally located. Therefore, the muscle activity of bilateral voluntary movement was affected by knee-related muscle pain during an RT task. This pain can alter motor control via the higher CNS because

bilateral changes in motor control may be difficult to achieve via a spinal reflex (Schmidt and Thews, 1989). Notably, the effect of reorganized APAs due to knee-related muscle pain was task-dependent (early onset of non-painful muscle activation in the shoulder flexion task; early activation onset on the non-painful side in the bilateral heel lift task; and reduced activity level in the bilateral heel lift task) and it had a different spreading effect (early activation onset in the BF and TA and reduced peak activity levels in the four following muscles: the ipsilateral VM, VL, and TA and contralateral VM) in both the painful and non-painful limbs. Thus, the spread of changes in postural muscle activation may modulate both inhibition and facilitation. Furthermore, such modulations might have both protective and compensatory functions under pain conditions (Hodges & Tucker, 2011). A neuromuscular investigative approach is important to gain an understanding of the effect of knee-related muscle pain during APAs in the CNS. Study 1 demonstrated that knee-related muscle pain during APAs contributed to modulation of neuromuscular activity. Pain may alter the excitability of the corticospinal pathway and other parts of the CNS, as indicated by the earlier pain-related interference in the brain (Poortvliet et al., 2019).

The neuromuscular approach for investigating the effect of knee-related pain during APAs was helpful to understand modulation of leg muscles. The modulation of leg muscles during postural control is well known (Woollacott et al., 1984). The modulation with muscle tendon reflex of leg muscles depended on the direction of tasks (e.g., arm pull or push). Moreover, this reflex indicated that the mechanism of this modulation originated from the supraspinal processes. Furthermore, the excitability of the motor neuron pool was modulated before the lower extremity task (fast stepping) (Komiyama and Kasai, 1997). Flexible control by the CNS is needed to maintain a standing posture during APAs. However, the effect of knee-related pain on the muscle activity modulation of the ankle joint and leg remained partly understood. In the non-pain condition, SOL muscle activity decreased before the onset of target movement (Study 1). A decrease of SOL activity during APA was believed to modulate the flexibility of ankle joint movement in the ipsilateral side. These ipsilateral side movements were important counter movements of the target movement. Rapid arm movement will lead to a collapsed standing posture, if the counter movement does not occur. Pain in the TA indicated that ipsilateral SOL and TA modulation

during unilateral shoulder movement was affected. The decrease of SOL activity (SOL activity ratio (standardized SOL activity/standardized TA activity in each epoch)) was not evoked during the APA (Figure 7). Results of the TA pain study demonstrated that this pain could possibly inhibit the counter movement of the ipsilateral leg.

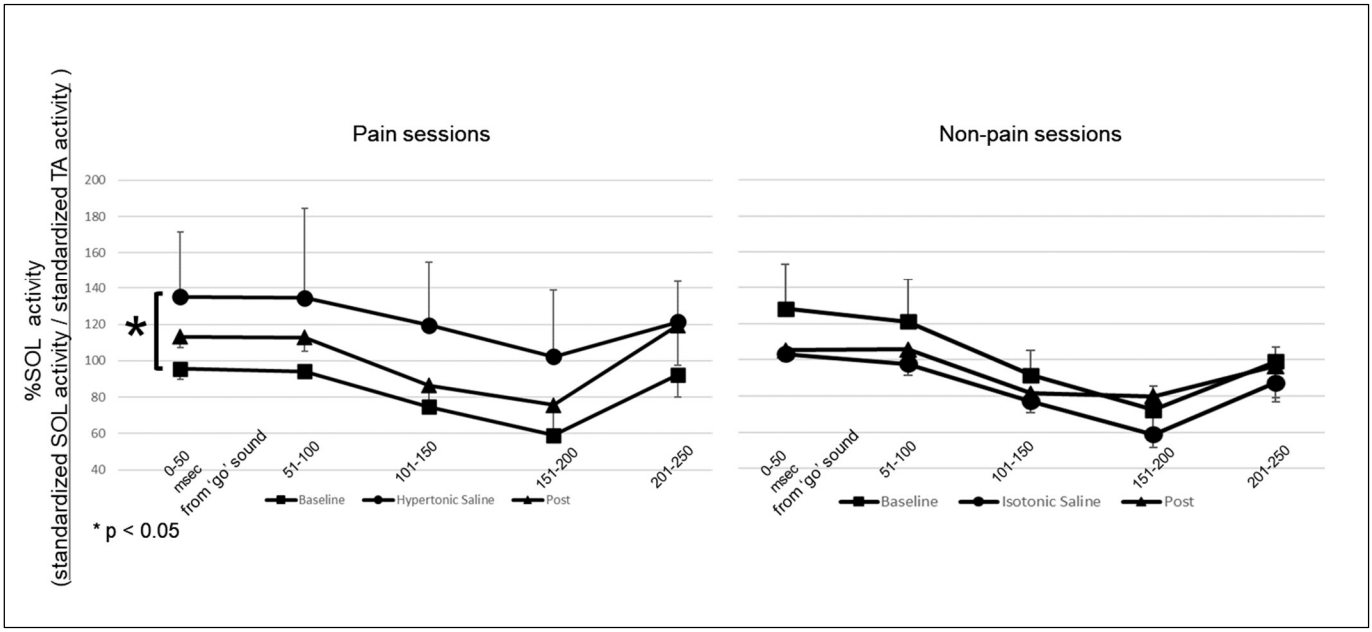

Figure 7: Mean and standard error of %SOL activity. Association between knee-related pain and leg muscle modulation. In TA pain condition, decrease of relative SOL activity during the APA is not evoked (left figure and circle). A three-way RM-ANOVA (***Session*** [3] ****Saline type*** [2] ****Epoch*** [5]) is used to investigate the effect of TA pain during the APA. Interaction between session and saline type is significant. In the post-hoc test, %SOL activity during the hypertonic saline session is significantly increased compared with a baseline value.

4.7 Effect of infrapatellar fat pad pain during APAs based on EMG data

In the bilateral heel lift task, a significant interaction between saline type, time, and side was demonstrated (RM-ANOVA: $F(2,22) = 14.93$; $p < 0.01$ for VM, $F(2,22) = 8.66$; $p < 0.01$ for VL, and $F(2,22) = 9.65$; $p < 0.01$ for TA). Post-hoc analysis indicated that the relative onset of VM, VL, and TA activity in the ipsilateral side during the pain condition was significantly delayed compared with the non-pain condition (Figure 8A–C; $p < 0.01$). Moreover, a significantly earlier activation onset of the VM and VL was indicated in the contralateral side during the pain condition than in the non-pain condition (Figure 8A, B; $p < 0.05$ for VM and $p = 0.05$ for VL). The relative onset of activation of the postural muscles

during shoulder flexion remained unaffected by experimental pain. In the bilateral heel lift task, a significant interaction was found between saline type, time, and epoch. Pain reduced the muscle activity (normalized RMS EMG) in the last six epochs (from 201 ms to 500 ms after the 'go' signal) for the ipsilateral VM and VL during the bilateral heel raise task compared with all other non-pain sessions (Figure 9; RM-ANOVA: $F(18,198) = 2.56$, NK: $p < 0.01$). In addition, the muscle activity of epochs 5–7 in the ipsilateral TA (from 201 ms to 350 ms after the 'go' signal) was significantly lower than that in the same epochs in all other non-pain conditions (Figure 9; RM-ANOVA: $F(18,198) = 3.59$; $p < 0.01$, NK: $p \leq 0.01$). During the heel lift task, the muscle activity between the 'go' signal and 200 ms was not significantly changed compared with the non-pain conditions. Experimental pain did not affect the muscle activation pattern of the postural muscles during the shoulder flexion task.

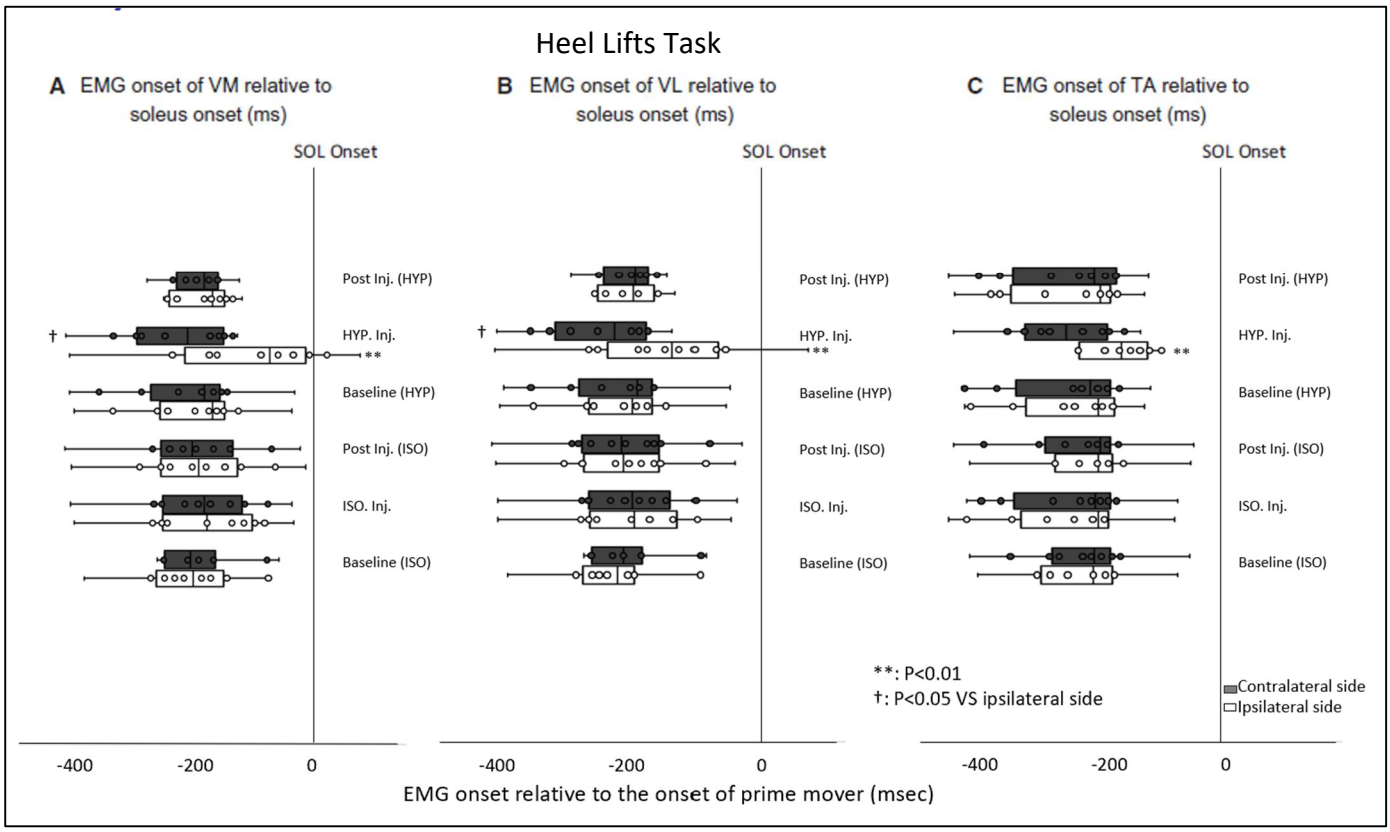

***Figure 8*:** Boxplots with minimum, lower quatile, median, upper quartile, and maximum for electromyography reaction time of bilateral VM (A), VL (B), and TA (C) (bilateral heel raise task) at baseline, injection, and post-injection. Significantly delayed onset compared with the other sessions is illustrated (*, NK: $p < 0.01$). Significantly early onset compared with the isotonic saline session is illustrated (†, NK: $p \leq 0.05$). Ipsilateral side (open symbols). Contralateral side (solid symbols).

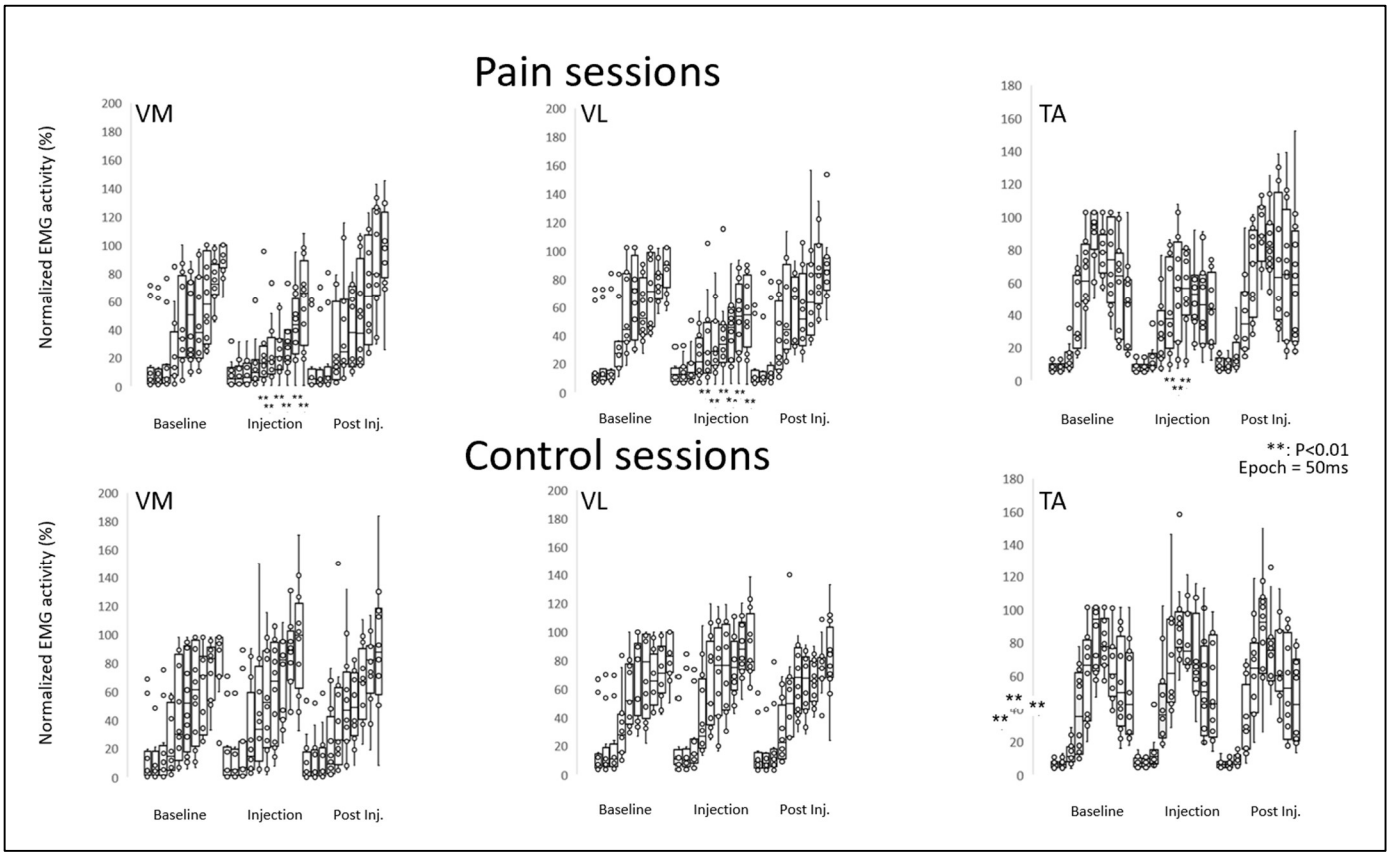

***Figure 9*:** Boxplots with minimum, lower quatile, median, upper quartile, and maximum for electromyography epoch data of bilateral VM (A), VL (B), and TA (C) during bilateral heel lift at baseline, injection, and post-injection. Each normalized muscle activity is calculated by the peak muscle activity of two baseline sessions. The upper and lower panels illustrate the hypertonic and isotonic saline injection sessions, respectively. The ipsilateral VM, VL, and TA activity in the pain condition during the heel lift task is significantly decreased compared with the same epoch of other sessions (*NK: $p \leq 0.01$).

A neuromuscular approach to examine whether infrapatellar fat pad pain affected APAs on the painful and non-painful sides in healthy participants was used in Study 3. In clinical research, anterior knee pain problems are key issues for both older adults and young athletes because it is often the chief complaint in knee OA and sports injuries (Yoshimura et al., 2009; Iwamoto et al., 2008). Decreasing pain threshold on anterior aspect of knee joint is one reason for knee pain in older adults with knee OA (Arendt-Nielsen., 2015). Another reason is because the pain threshold of infrapatellar fat pad is lower than that of the other knee joint tissues (Dye et al., 1998). Moreover, the volume of infrapatellar fat pad increases during aging, especially in knee OA in older adults (Chuckpaiwong et al., 2010). Hence, the association between anterior knee pain and infrapatellar fat pad is important for pain management in older adults. In Study 3, experimental infrapatellar fat pad pain was used to investigate the effect of knee-related pain during

APAs. Hypertonic saline injection-induced infrapatellar fat pad pain caused earlier activation onset (relative time from the onset of the target muscle movement) of the contralateral VM during a bilateral heel lift task than that in the no-pain condition. Moreover, pain induced a longer delay in activation onset of the ipsilateral VM, VL, and TA than that in the no-pain condition in the same task. Furthermore, pain reduced the muscle activity level (muscle activity between the 'go' signal and 500 ms was isolated for each 50 ms and was evaluated by RMS) in the aforementioned muscles during the same task compared with the no-pain condition. Early activation onset of postural muscles during APAs occurred on the non-painful side, while delayed activation onset and reduced activity level of the postural muscles were observed on the painful side during APAs. Nevertheless, the activation onset of the bilateral SOL, and the bilateral peak angle and peak angular velocity remained unchanged during the bilateral heel lift task in the pain condition. Reorganization of APAs due to infrapatellar fat pad pain was observed in the non-painful limbs, which indicated a compensatory function to maintain posture, while that in the painful limbs indicated an adaptive strategy to protect the painful joint and limb. Furthermore, early activation onset of postural muscles on the non-painful side during APAs involved one quadriceps femoris muscle, while the delayed activation onset and reduced muscle activity in painful limbs involved three muscles of the lower limb. Notably, reorganization of APAs due to infrapatellar fat pad pain had several different effects (early and delayed activation onsets and reduced activity levels) in bilateral limbs and different spreading effects (early activation onset in a thigh muscle and reduced activity levels in the leg and thigh muscles) in the painful and non-painful limbs (Study 3). Similar changes in postural muscle activity were observed in Studies 1 and 3. The APA mechanisms involved multiple adaptations to the pain stimuli locations in knee-related pain conditions in bilateral limbs. Thus, non-painful muscles on the non-painful side, painful muscles on the painful side, and painful muscles' synergistic muscles were involved in the reorganization of APAs.

A previous study investigated the effect of musculoskeletal pain during APA and reported inhibition of both muscle activation onset and activity levels. The effects of knee-related pain during APAs (Studies 1 and 3) suggested the possibility of inducing specific neuromuscular modulations for postural muscles,

that is, inhibition of muscle activation onset and muscle activity and facilitation of muscle activation onset as well. The effects of knee-related pain during APAs may be important for both intact voluntary target movement and modulated APAs. Furthermore, this neuromuscular modulation during APAs is lower extremity-specific because bilateral separation of the spine is not possible for neck pain and LBP. Knee pain was experimentally induced at three locations via hypertonic saline injection in the three studies comprising this thesis. Infrapatellar fat pad pain and knee-related muscle pain were good models for clinical knee pain, such as knee OA. Hence, Studies 1 and 3 possibly indicate that similar effects occur in knee OA pain. Therefore, modulation of APA mechanisms by knee OA should be investigated in future.

Asymmetrical muscle activities during APAs were demonstrated in the baseline sessions. Unilateral shoulder movement induced an asymmetrical muscle activity profile in the bilateral BF during APAs, consistent with the first report on APA research (Belen'kii et al., 1967). However, the asymmetry of the bilateral BF was maintained in the presence of infrapatellar fat pad pain. Hence, robust APA mechanisms were demonstrated during shoulder flexion, although infrapatellar fat pad pain induced early and delayed activation onsets and reduced muscle activity levels.

4.8 Effect of knee-related muscle pain during APAs based on CoP data

During the unilateral shoulder flexion task, a significant interaction between saline type and time was found for the normalised ipsilateral AP CoP displacement; it was reduced during the painful condition compared with the non-painful condition (Figure 10C, RM-ANOVA: $F(2,16) = 5.90$, $p < 0.05$; NK: $p < 0.01$). Moreover, a significant interaction between saline type, time, and painful muscle was found for the normalised ML net CoP displacement; it was reduced during the TA pain condition compared with the non-painful condition (Figure 10E, RM-ANOVA: $F(2,16) = 3.67$, $p < 0.05$; NK: $p < 0.05$).

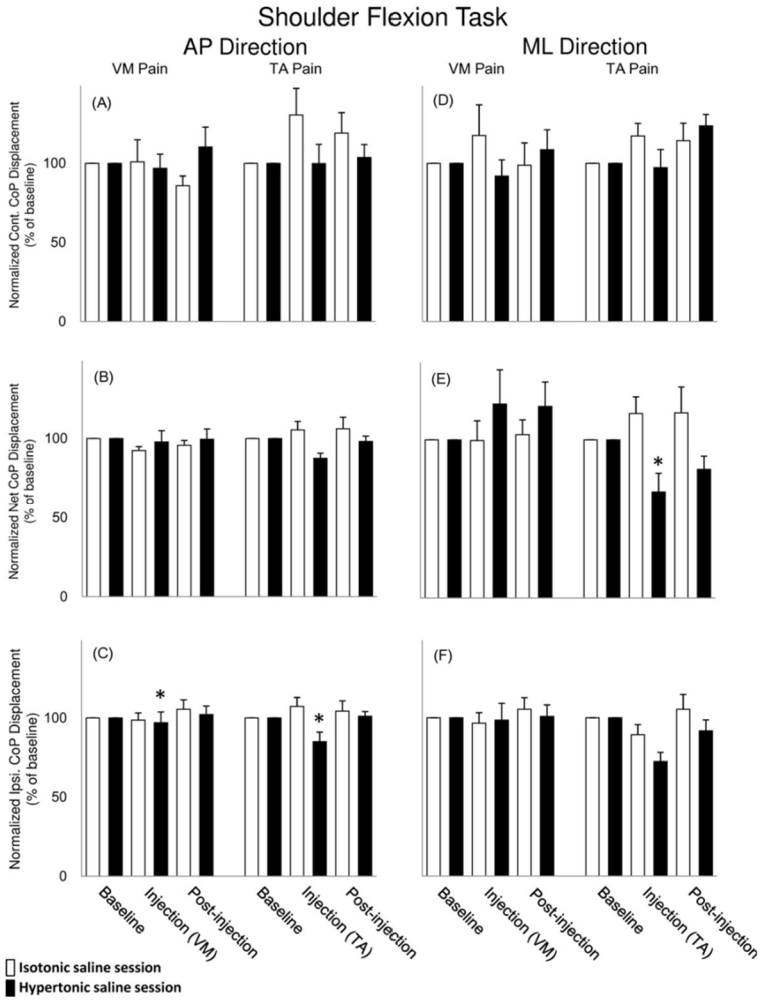

***Figure 10*:** Mean and standard error of normalised peak-to-peak displacement in the anterior-posterior (AP) (A-C) and medial-lateral (ML) CoP directions (D-F) during unilateral shoulder flexion task. The data are illustrated for the ipsilateral (Ipsi.) displacement, net CoP, and contralateral (Cont.) displacement during baseline, injection, and post-injection sessions. The CoP displacement in isotonic (open bar) and hypertonic (solid) saline injections into the VM and TA are illustrated. The * indicates significant smaller displacement compared with non-pain condition.

Although EMG studies provide a good overview of muscle contraction strategies, direct inference of postural stability may not be possible. However, balance problems due to knee-related pain can be estimated by using CoP in a biomechanical approach. The CoP parameters enable the understanding of clinical perspectives. In this thesis, three CoP parameters (ipsilateral and contralateral sides and net CoPs) were used to clarify changes in standing posture during APAs. During painful standing, these CoP parameters indicate the painful side, non-painful side, and centre of gravity, respectively. In previous

studies, biomechanical parameters based on a motion capture system and force-reaction forces were used to investigate the effects of LBP, hip pain, and knee pain during APAs (Table 1). These studies found changes in postural control strategies under painful conditions (Mouchnino et al., 2005; Mok et al., 2011; Tateuchi et al., 2011). Parameters of CoP are widely used to quantify postural control reorganization strategies during knee pain. A knee OA study which investigated APA characteristics while climbing stairs reported that the amount of time required during a step-down task was greater in post-operative patients with knee OA with reduced pain than in pre-operative patients with knee OA and control participants (Mouchnino et al., 2005). During a reaching task, the CoP displacement between patients with knee OA and older adult controls was not significantly different (Venema and Karst, 2012). However, whether knee pain affects postural stability during APAs remains unknown. Additionally, investigating the contribution of the painful and non-painful limbs to the overall postural stability is necessary because pain induces different muscular activities in either limbs during APAs. The biomechanical approach used in this project may contribute to the knowledge on the impact of pain on each side, and on overall postural control, during APAs. Furthermore, this approach is essential for understanding the relationship between pain-induced reorganization of neuromuscular function and postural control. The CoP under the ipsilateral and contralateral feet were measured, and the net CoP was calculated (Winter, 1995) after the ground reaction forces were recorded. Ipsilateral and contralateral CoPs were calculated in each base of support. The net CoP calculated from both aforementioned CoPs was the mean value of the bilateral CoPs as well. The net CoP during static standing indicated the CoM trajectory. Moreover, the three CoP displacements were split into AP and ML directions, which allowed the evaluation of ankle and hip strategies in balance maintenance (Winter, 1995; Winter et al. 1996; Winter et al. 2003). These strategies represent the functional roles for antigravity postural control. The AP and ML directions indicate the use of ankle and hip strategies (Winter, 1995) and include the effect of mental condition such as when a fear of fall is experienced (Yiou et at, 2011). Furthermore, ankle and hip strategies are near the ground surface and CoM controls, respectively. Hypertonic saline injection-induced TA pain was found to reduce the net ML CoP displacement between the first and second peak

values during APAs in a shoulder flexion task compared with the no-pain condition. Hence, maximum ML CoP displacement direction during APAs was reduced. In addition, muscle pain reduced AP CoP displacement on the ipsilateral side in the pain condition compared with the no-pain condition; however, CoP displacement on the contralateral side during the same task remained unchanged. The onset time of arm movement during shoulder flexion in the pain condition remained unchanged compared with the no-pain condition. Reorganization of APAs due to knee-related muscle pain indicated that reduced CoP displacement occurred on the painful side and net CoP, which might have reduced the capacity for postural control under RT tasks. Thus, the area available for postural control during APAs within the base of support decreased with pain. Notably, CoP displacement was maintained during the shoulder flexion task with VM pain. Similarly, CoP was maintained during the bilateral heel lift task under pain conditions in the VM and TA (Study 2). These biomechanical changes in postural control demonstrated the relationship between APAs and knee-related muscle pain and the findings suggested the impact of knee pain on APAs. The three conditions of VM pain, TA pain, and infrapatellar fat pad pain demonstrated that neuromuscular function was reorganized during APAs, which indicated a possible compensatory relationship between neural and biomechanical reorganization of APAs. Neural reorganization due to knee-related pain during APA is required for maintenance of normal postural control. The relationship between ML net CoP displacement during injection sessions and pain intensity was demonstrated (Figure 11). Pain intensity reduced the net CoP displacement during the shoulder flexion task, although the relationship between each side's CoP displacements and pain intensity was not significantly correlated.

Hence, ML net CoP displacement during APAs may have a sensitive response to pain intensity. This was a reasonable response for postural control because it indicated integrated postural control. Notably, VM pain did not induce changes in the net CoP, which indicated a possible dependence on pain area because the TA causes referred pain to the ankle joint.

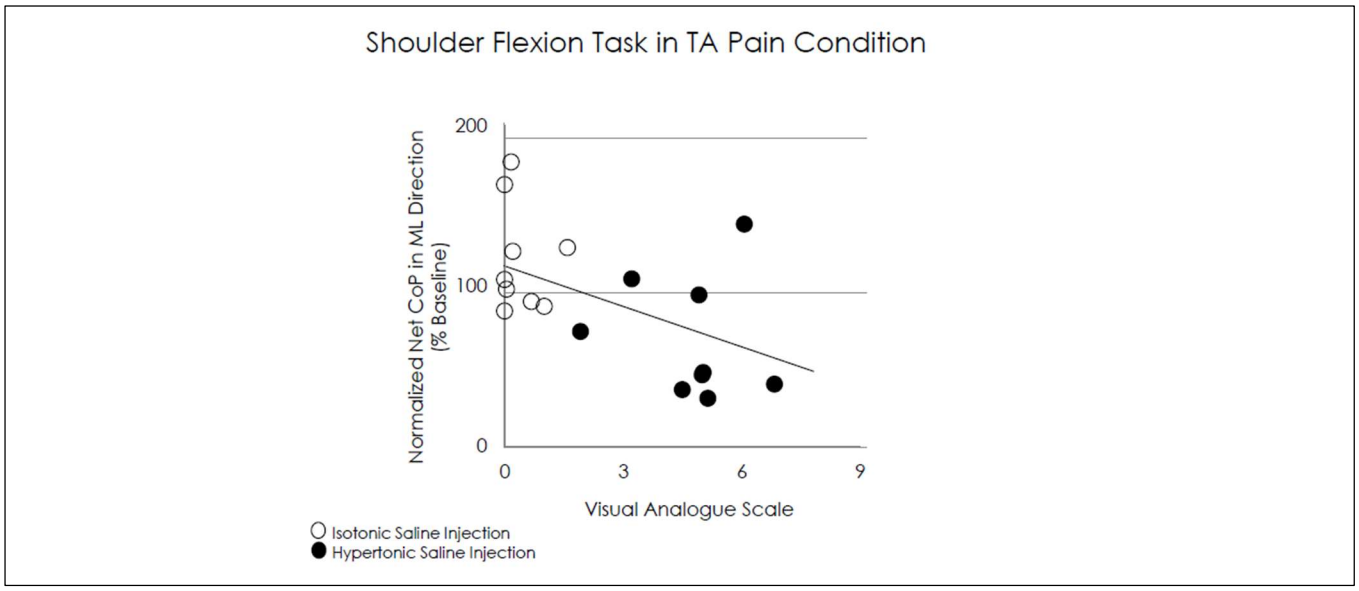

Figure 11: Relationship between pain intensity and normalized ML net CoP displacement. Net CoP displacement is estimated between the first and second peak of the net CoP in each injection session. A visual analogue scale (VAS) reveals that maximum pain intensity is present throughout all trials in each injection session. The white and black circles indicate isotonic and hypertonic saline injections, respectively. The ML net CoP displacement and VAS score were significantly negatively correlated (Correlation coefficient = -0.58; $p < 0.05$).

Asymmetrical CoP was observed in the baseline sessions between the ipsilateral and contralateral sides during APAs. This indicated that unilateral shoulder movement induced an asymmetrical CoP displacement and time-related CoP parameters between the ipsilateral and contralateral side. This was expected because biomechanical studies of APAs have indicated asymmetrical biomechanics during unilateral shoulder movement (Bouisset & Zattara, 1987). Unilateral shoulder flexion movement while standing requires cancellation of perturbation via rapid arm elevation. Postural instability under perturbation during an RT task might be suppressed effectively by APAs because APA asymmetry begins before unilateral shoulder flexion movement (Bouisset & Zattara, 1987). Notably, in knee-related muscle pain, the asymmetry of bilateral CoPs was maintained, indicating a robust APA mechanism, although in the same condition, earlier activation onset in the postural muscles was observed (Studies 1 or 2). In summary, participants were able to maintain a standing posture by reorganising APAs during knee-related pain, which was demonstrated on both the painful and non-painful sides and in the net postural control. Reorganization of muscle activation onset and muscle activity level during APAs indicated complex modulation of APA mechanisms under knee pain conditions (Studies 1 and 3). Reorganized CoP

displacement due to knee-related muscle pain during APAs affects ipsilateral and net CoP except for the effect of contralateral CoP (Study 2). In addition, bilateral delayed activation onset of SOL and heel movement during the bilateral heel lift task should be considered for comprehending reorganized APAs due to knee-related pain. Hence, during a bilateral heel lift task, delayed onset helps avoid an unstable posture. Moreover, CoP parameters during the bilateral heel lift task were maintained due to the delayed onset of bilateral heel movement together with the reorganization of postural muscle activities, which indicated that reorganized APAs and bilateral delayed target movement contribute to maintaining stable posture. Conversely, no reorganized APAs were observed during the shoulder flexion task under TA pain conditions which altered ipsilateral side and net CoP displacements; however, contralateral CoP displacement was maintained (Study 2).

5 Impact of affected APAs due to knee-related pain

Changes in the APA mechanisms due to knee-related pain are determined by pain location and are motor task-dependent. Notably, APA changes generate a protective effect which can avoid secondary damage to painful and synergistic muscles. Moreover, APAs are reorganized to maintain a standing posture by modulating either the non-painful side or the muscle because postural control under knee-related pain condition is needed for both a protective effect and to maintain an antigravity standing posture. Inhibition of muscle activity in both the painful limb and the painful location generates protective effects (Studies 1 and 3). Conversely, postural control may reduce inhibition of muscle activity. Therefore, pain exerts two effects (facilitation and inhibition) on postural muscle activity during APA. These pain effects might be induced by the CNS.

This thesis posits the protective and compensatory reorganization of postural muscles due to knee-related pain during RT tasks. Additional motor tasks must be used in translational studies that aim to clarify the influence of knee pain on postural control. Regarding knee OA, differences between the RT and self-paced trigger tasks in terms of postural control may be an important issue. Older adults' responses in daily living do not consist of RT task responses alone; hence, their responses to traffic signals or to being called by another person are classified as a self-paced trigger tasks. If both RT and self-paced trigger responses are investigated, the risk of pain-induced falls in older adults may be clarified. The effect of self-paced trigger responses on postural control in healthy adults are characterised by different postural muscle kinetics than that in RT tasks in terms of APA mechanisms (Benvenuti et al., 1997; Klous et al., 2011). Self-paced trigger responses under experimental pain conditions may exhibit modulation of various postural control strategies in addition to RT tasks. Hence, self-paced trigger responses under knee pain conditions might involve a larger CNS contribution for maintaining posture than RT tasks. Furthermore, neuromuscular function assessment and biomechanics may be reasonable parameters for detecting reorganization of APAs due to modulation by the brain. However, the influence of knee-related pain on the self-paced APA mechanisms in healthy adults and older adults needs clarification.

6 Summary

Knee-related pain is a common issue in clinical practice. Pain resulting from knee-related deep tissues may increase an individual's risk of falls.

Knee-related deep tissue pain induced a reduction in muscle activity levels and delayed activation onset of postural muscles on the painful side and caused an early activation onset of postural muscles on the non-painful side, during APAs. These results suggest the importance of APAs for maintaining a standing posture during RT tasks and imply that the mechanism of postural control provides reasonable compensation for APAs. Notably, APA achieves the following during knee-related deep tissue pain: 1) protection of painful or related tissues or joints from secondary damage, as a pain-adaptation strategy; 2) maintenance of a standing posture, using a compensatory strategy; and 3) avoidance of falls and an unstable standing posture. Furthermore, bilateral CoP and net CoP displacement are reasonable biomechanical parameters for detecting the effect of knee-related pain during APAs.

Overall, these results suggest that pain in knee-related deep tissues reorganises APAs and induces an altered postural control strategy during RT tasks. These effects have clinical implications because pain can generate a new strategy or a lack of standing balance automatically.

Collectively, these studies revealed that musculoskeletal pain without pathological degeneration factors affects the activation onset and muscle activity levels of painful and non-painful muscles during APAs.

Early and delayed activation onsets and reduced activity levels in postural muscles were caused by pain (Studies 1 and 3). Displacement of the net CoP and ipsilateral CoP was reduced due to knee-related muscle pain (Study 2). As summarised in Figure 6, CoP displacement was maintained by reorganized muscle activation onset and muscle activity levels during APAs for both RT tasks. Conversely, reduced net CoP displacement during APAs was not indicated by changes in EMG parameters. Hence, reorganized neuromuscular function and reduced CoP displacement due to knee-related pain during APAs suggest that the neuromuscular and biomechanical reorganizations during APAs under pain conditions should be investigated under other varied conditions because only limited conditions were used in Studies

1–3. Neuromuscular reorganization in a knee-related pain condition indicates changes in neuromuscular function during APAs, whereas biomechanical reorganization during knee-related muscle pain indicates whole body balance.

Neuromuscular reorganization due to knee-related pain maintains CoP displacement, whereas its absence might induce reorganization of CoP displacement. Furthermore, the delay in target movement in the bilateral heel movement task may indicate the possibility of contributing to reorganization of APAs because these are prepared by the onset and intensity of target movements. Moreover, VM pain in knee-related muscles (Study 1) reduced the peak activity of painful and co-active muscles during a bilateral heel lift task, and induced earlier activation onset of non-painful muscles during a shoulder flexion task than that under a no-pain condition. Compared with the no-pain condition, TA pain (Studies 1 and 2) reduced the peak activity of painful and co-active muscles and led to an earlier onset activation of non-painful muscles during the bilateral heel lift task. Additionally, it reduced ML CoP displacement during the shoulder flexion task. Infrapatellar fat pad pain (Study 3) delayed muscle activation onset, reduced muscle activity in the painful side, and led to an early muscle activation onset in the non-painful side during the bilateral heel lift task.

Furthermore, VM and TA pain (Study 1) during a bilateral heel-lift task induced bilateral delayed onset of target movement. Delayed onset of the bilateral SOL was detected in the bilateral heel lift task (Study 1). However, VM, TA, and infrapatellar fat pad pain conditions did not affect the RT of shoulder flexion. Furthermore, peak performance of target movement kinematics during shoulder flexion and bilateral heel lift was maintained compared with the no-pain condition.

The results of this project have demonstrated that knee-related pain, including muscle and infrapatellar fat pad pain, alters APAs during RT tasks. Such changes contribute to standing posture control, while protecting painful tissues. Altered activation onset and reduced muscle activity levels of postural muscles indicate that knee pain influences APAs, even when it involves reactive voluntary movements and not knee movement. Moreover, knee-related deep tissue pain effects, including pain in the VM, TA, and infrapatellar fat pad, indicate that new strategies may be used for automatic and predictive postural

control. Hence, the pain caused by clinical knee conditions might affect APAs if the peak performance of target movements is maintained.

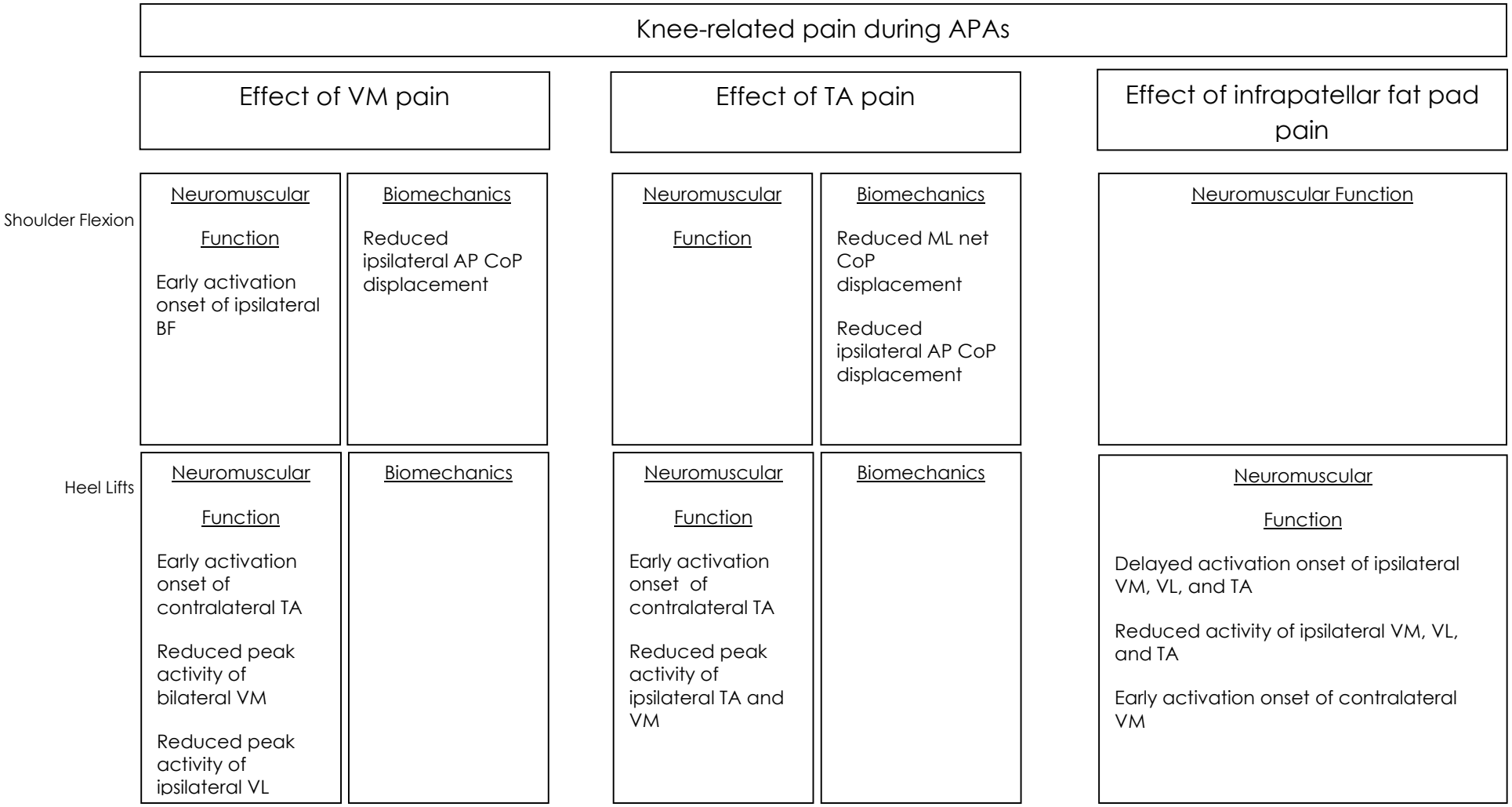

***Figure 12**:* Summary of the effects of knee-related pain during APAs for knee protection and posture maintenance. Altered muscle activation onset and postural muscle activity levels on the painful and non-painful sides are identified, together with reduced CoP displacement. Percentage of CoP data is not pain muscle-specific, although AP CoP displacement is reduced due to pain.

7 Japanese Summary

膝関節に関連する疼痛がいくつかの運動制御に及ぼす影響について神経筋機能とバイオメカニクス的アプローチから検討した。

膝関節関連の疼痛は運動制御に影響を及ぼすことは、臨床的あるいは実験的に先行研究でも示されている。膝関節関連の疼痛は随意的膝関節伸展時に脊髄運動ニューロン興奮性に影響を与えるだけでなく、最大随意性収縮時や動的運動時の筋活動量も低下させる。また、歩行や前方への踏み込み動作、急速な前進運動など、膝関節動作時の関節角度や関節モーメントを抑制し、膝関節伸展時の安定した力発揮を阻害する。

膝関節に関連する疼痛と運動制御の関係は、膝関節疼痛を有する高齢者の転倒リスクが高いという研究結果に対して運動制御の側面からエビデンスを説明することになる。これは、膝関節の疼痛による運動制御の障害が日常生活における姿勢の不安定さを誘発するためと考えられる。

高齢者に多い変形性膝関節症患者では、フィードフォワード制御による姿勢に関する運動制御の再組織化が行われていることが実証されている。前方への踏み込み動作およびリーチング動作において、膝関節疾患ではフィードフォワード制御下に姿勢筋の筋活動量低下を誘発した。しかし、膝関節疼痛がフィードフォワードの姿勢制御メカニズムに対してどのような影響を与えるか、これまでの変形性膝関節症患者の臨床研究では、痛みの影響と他の病的要因の両方が含まれていることから、まだ明確な結論にはいたっていなかった。

そこで、本プロジェクトでは、実験的に膝関節関連疼痛を誘発し、フィードフォワード姿勢制御の関係について具体的に検討した。

本研究ではまず、膝関節に関連する実験的筋痛がフィードフォワード姿勢制御に及ぼす影響を、神経筋機能のアプローチにより検討した。片側の肩関節屈曲時に内側広筋に疼痛が生じると、姿勢筋活動量が減少することが明らかになった。両側踵上げ時の内側広筋と前脛骨筋の疼痛は、疼痛側の姿勢筋と共働筋の筋活動量を低下させた。

次に、膝関節に関連する実験的筋痛がフィードフォワード姿勢制御に及ぼす影響について、CoP（centre-of-pressure）測定を用いて検討した。片側の肩関節屈曲時に前脛骨筋に疼痛があると、疼痛側の内側及び外側方向への変位が減少し、正味の CoP 測定値も減少することが明らかになった。

最後に、膝蓋下脂肪体の疼痛がフィードフォワード姿勢制御に及ぼす影響について、神経筋機能的なアプローチで検討した。両側踵上げ時の膝蓋下脂肪体疼痛により、姿勢筋の筋活動開始時期が早期及び遅延し、さらに筋活動量が低下した。疼痛側と反対側では筋活動開始タイミング早期化が観察され、疼痛側では開始タイミングが遅延化していることが明らかになった。

膝関節に関連する実験的疼痛とフィードフォワード姿勢制御の関係を健常者により調べたところ、疼痛によって姿勢制御の再組織化が示された。この姿勢制御の変化は、膝関節疼痛によるフィードフォワード姿勢制御への影響が、疼痛筋やその周辺部位を保護するため疼痛側だけに出現するのではなく、姿勢を維持するために疼痛側と反対側にも生じていることを示している。

Table 1: Anticipatory postural adjustment studies in the literature based on clinical musculoskeletal and experimental pain

References	Parameters	Participants	Experimental Pain	Type of Motor Task	Main Findings on APAs
Hodges & Richardson, 1996 *Spine*	Muscle activation onset Target movement velocity	Patients with low back pain (LBP) (n = 15) and control participants (n = 15)		Shoulder flexion, abduction, and extension	The activation onset of the transversus abdominis during all shoulder movements was delayed in patients with LBP compared with control participants. The activation onset of the internal and external oblique abdominis during shoulder flexion was more delayed in patients with LBP than in control participants. The activation onset of the lumbar multifidus during shoulder abduction was more delayed in patients with LBP than in control participants. Delayed activation onset of trunk muscles indicated a motor control deficit, which was hypothesised to result in inefficient muscular stabilisation of the spine.

Hodges & Richardson, 1998 *J Spinal Disord Tech*	Muscle activation onset Target movement velocity	Patients with LBP (n = 15) and control participants (n = 15)		Hip flexion, abduction, and extension	The activation onset of the transversus abdominis during all hip movements was delayed in patients with LBP compared with control participants. The activation onset of the rectus abdominis, internal oblique abdominis, and erector spinae muscles (ERE) during hip flexion was more delayed in patients with LBP than in control participants. The activation onset of the ERE during hip extension was more delayed in patients with LBP than in control participants. A change in the postural control of the trunk in people with LBP was indicated.
Hodges, 2001 *Exp Brain Res*	Muscle activation onset	Patients with LBP (n = 14) vs healthy participants (n = 14)		Shoulder flexion and abduction during different preparation conditions	The activation onset of the transversus abdominis during different preparation conditions of shoulder flexion was delayed in patients with LBP compared with control participants. The electromyography reaction time EMG RT from the 'go' signal of the transversus, internal oblique, external oblique, and rectus abdominis during incorrect condition of shoulder flexion was more delayed than that during correct condition in patients with LBP. While inhibition of the descending motor command could not be excluded, the change in recruitment of the trunk muscle could have

					represented a more complex change in organisation of the postural response.
Leinonen et al., 2001 *Spine*	Muscle activation onset Muscle activity duration	Patients with LBP (n = 20) vs healthy participants (n = 15)		Impact loading on the upper extremity	The activation onset the back muscles during impact loading was not changed by an expectation condition in patients with LBP compared with control participants. Feedforward control of the lumbar muscles was impaired in patients with sciatica.
Cowan et al., 2002 *Arch Phys Med Reha*	Muscle activation onset	Patients with patellofemoral pain syndrome (n = 37) vs healthy participants (n = 37)		Heel and toe while standing	The simultaneous recruitment of the vastus medialis (VM) and vastus lateralis (VL) during ankle movements was altered in patients with patellofemoral pain syndrome compared with control participants.
Cowan et al., 2003 *J Orthop Res*	Muscle activation onset	Patients with patellofemoral pain syndrome (n = 40)		Heel and toe lifts while standing	Impaired simultaneous recruitment of the VM and VL during ankle movements was improved in the post-physiotherapy intervention compared with the pre-intervention status.
Hodges et al., 2003 *Exp Brain Res*	Muscle activation onset Muscle amplitude Joint angle of target movement	Healthy participants (n = 7)	Saline injections into lower back muscles	Shoulder flexion	The activation onset of the transversus abdominis and the deep spinal muscles during shoulder flexion was delayed in an experimental LBP condition compared with a non-pain condition. The amplitude and frequency spectrum of the transversus abdominis during shoulder flexion were lower than that in a non-pain condition.

					Acute experimentally-induced pain may affect the feedforward postural activity of the trunk muscles. Although the response was variable, pain produced differential changes in the motor control of the trunk muscles.
Leinonen et al., 2003 *Spine*	Muscle activation onset Centre-point of force velocity while standing	Patients with LBP before and after surgery (n = 20) vs healthy participants (n = 15)		Impact loading on the upper extremity	The activation onset of the ERE after impact loading during an expectation condition was earlier in post-micro discectomy patients than in pre-micro discectomy patients. During short-term postoperative follow-up, postural control did not apparently change; however, impaired lumbar proprioception and feed-forward control of paraspinal muscles appeared to recover.
Falla et al., 2004 *Exp Brain Res*	Muscle activation onset Muscle amplitude	Patients with bilateral neck pain (n = 10) vs healthy participants (n = 12)		Shoulder flexion and extension	The activation onset of deep cervical flexors, the sternocleidomastoid and scalenus anterior during shoulder flexion was delayed in patients with neck pain compared with control participants. The activation onset of the sternocleidomastoid and scalenus anterior during shoulder extension was more delayed in patients with neck pain than in control participants. The amplitude of the deep cervical flexors and scalenus anterior during shoulder flexion was more reduced in patients with neck pain than in control participants.

					The amplitude of the scalenus anterior during shoulder extension was more reduced in patients with neck pain than in control participants. Delay in neck muscle activity associated with arm movement in patients with neck pain indicated a significant deficit in the feedforward control of the cervical spine.
Moseley et al., 2004 *Brain*	Muscle activation onset Muscle activity	Healthy participants (n = 8)	Electrical stimulation to lower back and elbow	Shoulder flexion	The activation onset of the transversus abdominis and deep multifidus during shoulder flexion were delayed in the LBP condition compared with the control condition. The activity of the transversus abdominis and deep multifidus during shoulder flexion was delayed in the LBP condition compared with the control condition. The activity of the superficial multifidus and external oblique abdominis during shoulder flexion was greater in the LBP condition than in the control condition. Anticipation of experimental back pain evoked a protective postural strategy which stiffened the spine.
Moseley et al., 2004 *Exp Brain Res*	Muscle activation onset Muscle activity	Healthy participants (n = 8)	Saline injection into lower back muscles	Shoulder flexion	The activation onset of the transversus abdominis during shoulder flexion was delayed in the pain condition compared with the non-pain condition. The activation onset of the transversus abdominis and deep multifidus was earlier in an attention-

					demanding condition than in the non-pain condition. The activity of the transversus abdominis was more reduced in the pain condition than in the non-pain condition. The activity of the multifidus and external oblique abdominis was greater in the pain condition than in the non-pain condition. Although postural activity of deep trunk muscles was not affected when central nervous system resources are limited, it was delayed when the individual was stressed.
Moseley & Hodges, 2005 *Clin J Pain*	Muscle activation onset	Patients with LBP (n = 16)	Electrical stimulation to lower back	Shoulder flexion while sitting	The activation onset of the transversus abdominis during shoulder flexion was delayed in the pain condition compared with the non-pain condition. The activation onset of the external oblique abdominis activation onset during shoulder flexion was earlier in the pain condition than in the non-pain condition. Altered postural adjustments of the trunk muscles during pain were not caused by pain interference; however, they indicated the possible development and adoption of an alternate postural adjustment strategy, which may serve to limit the amplitude and velocity of trunk excursion caused by arm movement.

Mouchnino et al., 2005 *BMC Musculoskelet Disord*	Force reaction Joint angle Muscle activation onset Muscle activity	Patients with knee osteoarthritis (OA) before and after total knee replacement (n = 11) vs healthy participants (n = 14)		While descending the stairs	Amount of time during a step-down task was greater in postoperative patients with knee OA than in preoperative patients and control participants. The activation onset of the VL during the step-down task was earlier on the painful side than on the non-painful side. The strategy change used when supporting the arthritic and painful limb could have resulted from the action of nociceptors, which led to increased proprioceptor thresholds, thus gating the proprioceptive inputs, which may have been the critical afferents in controlling the coordination timing between balance and control of movement initiation.
Tsao et al., 2008 *Brain*	Muscle activation onset Motor cortical map	Patients with LBP (n = 11) and healthy participants (n = 11)		Shoulder flexion or extension	The activation onset of the bilateral transversus abdominis during shoulder flexion and extension was delayed in patients with LBP compared with control participants. A differential relationship between the activation onset of the transversus abdominis and the motor cortex map location was demonstrated in patients with LBP compared with control participants. A differential relationship between the activation onset of the transversus abdominis and motor cortex map volume was demonstrated in patients with LBP compared with control participants.

					These findings provided preliminary evidence of reorganization of trunk muscle representation in the motor cortex in individuals with recurrent LBP and suggested that this reorganization is associated with postural control deficits.
Tsao & Hodges, 2008 *J Electromyogr Kinesiol*	Muscle activation onset Arm acceleration	Patients with LBP (n = 9)		Shoulder flexion or extension	The LBP-induced delayed activation onset of the transversus abdominis during shoulder flexion and extension after training was shorter than that at the baseline evaluation. Variation of the activation onset of the transversus abdominis in individual patients during shoulder flexion and extension after training was smaller than that at baseline evaluation. A linear relationship between the improved activation onset of the transversus abdominis during shoulder flexion and extension and improved trunk muscle training performance was demonstrated.
Hodges et al., 2009 *Arthritis Rheum*	Muscle activation onset Muscle activity	Healthy participants (n = 10)	Saline injection into the infrapatellar fat pad and electrical stimulation to the patella	Ascending and descending the stairs	Simultaneous timing of activation of the VM and VL while climbing the stairs was altered in a pain condition compared with a no-pain condition. Activity level of the VL while climbing stairs was more reduced in a pain condition than in a no-pain condition.

					Alterations in coordination of knee muscle activity can be caused by pain, even pain of non-muscle origin.
Jacobs et al., 2009 *Behav Neurosci*	Variability of muscle activation onset	Patients with LBP (n = 10) vs healthy participants (n = 10)		Shoulder flexion and abduction while sitting	Variability of the bilateral internal oblique during shoulder movement was reduced in LBP patients compared with control participants. Patients with chronic LBP may be less capable of adapting their APAs to ensure postural stability during movement.
MacDonald et al., 2009 *Pain*	Muscle activation onset Joint angle	Patients with LBP (n = 15) vs healthy participants (n = 19)		Shoulder flexion and extension	Difference in activation onset between short and long fibres of the multifidus disappeared in patients with LBP compared with control participants. The activity of the deep back muscles is different in people with a recurrent unilateral LBP, despite symptom resolution.
Silfies et al., 2009 *Arch Phys Med Rehabil*	Muscle activity pattern	Patients with LBP with spinal instability (n = 25) vs those with LBP without mechanical instability (n = 18) vs healthy participants (n = 39)		Shoulder flexion	Pattern of activity onset of the contralateral external oblique abdominis, ERE, multifidus, and ipsilateral abdominal muscles during shoulder flexion differed between patients with LBP and control participants. Pattern of activity onset of the ERE and multifidus during shoulder flexion was different between patients with LBP with and without mechanical instability. Activation timing was more impaired in patients with LBP with mechanical instability than in those without such instability.

Jacobs et al., 2010 *Clin Neurophysiol*	Muscle activation onset Brain activity	Patients with LBP (n = 10) vs healthy participants (n = 10)		Shoulder flexion during sitting	The relationship between brain activity amplitude and trunk muscles activation onset during shoulder flexion was negatively correlated in patients with LBP. Altered central motor neurophysiology is associated with LBP; thus, rehabilitation strategies should address these neuromotor impairments.
MacDonald et al., 2010 *Spine*	Muscle activity	Patients with LBP (n = 13) vs healthy participants (n = 14)		Impact on the upper extremity	The activity of the deep multifidus was reduced during a predictive impact condition in patients with LBP compared with control participants.
Mok et al., 2011 *Gait Posture*	Motion analysis CoP displacement	Patients with LBP (n = 13) vs healthy participants (n = 13)		Bilateral shoulder flexion	Time required to return to a basic position during bilateral shoulder flexion was longer in patients with LBP than in control participants. The anterior-posterior (AP) sway for postural stability was greater during shoulder movement in patients with LBP than in control participants. While the centre of pressure (CoP) is tightly controlled during postural recovery, the fine-tuning of the control equilibrium is compromised in patients with LBP. Hence, postural control dysfunctions should be considered in the management of chronic LBP.
Tateuchi et al., 2011 *J Appl Biomech*	CoP CoM Motion analysis	Patients with hip OA (n = 18) vs healthy participants (n = 10)		Lateral stepping	Anticipatory phase was longer during lateral stepping in patients with hip OA than in control participants.

					The centre of mass (CoM) movement on the supporting and stepping sides was lesser during stepping in patients with hip OA than in control participants. The CoP support phase was longer during lateral stepping in patients with hip OA than in control participants. Counter movement of acromion was greater during stepping in patients with hip OA than in control participants. These movement characteristics might contribute to achieving protection of the affected hip joint and swiftness in the subsequent lateral step in patients with hip OA.
Venema & Karst, 2012 *J Geriatr Phys Ther*	Muscle activation onset Muscle activity CoP displacement	Patients with TKA patients (n = 10) vs healthy participants (n = 10)		Easy and far reaching tasks	The leg muscle activity onset was earlier during the reaching movements in patients with TKA than in control participants. The activity of the VL and biceps femoris (BF) was more reduced during the reaching movements in patients with TKA than in control participants. Potential contributors to the differences in EMG amplitudes, such as impaired neural activation or efforts to reduce stress on the involved knee joint, in patients with TKA compared with controls, require further investigation.

Brooks et al., 2012 *Spine*	Muscle activation onset	Patients with LBP (n = 64)		Shoulder flexion	The activation onset of the bilateral rectus abdominis occurred later during shoulder flexion after training than before training. The activation onset of the contralateral transversus and internal oblique abdominis occurred later during shoulder flexion after training than before training. The activation onset of the ipsilateral ERE occurred later during shoulder flexion after training than before training. Trunk muscle activation onset during rapid limb movement was apparently not a valid mechanism of action for specific trunk exercise rehabilitation programs.
Mannion et al., 2012 *Eur Spine J*	Muscle activation onset	Patients with LBP (n = 32)		Shoulder flexion, abduction, and extension	The activation onset of the transversus abdominis was unchanged during shoulder movement tasks after training compared with before training parameters.
Massé-Alarie et al., 2012 *Exp Brain Res*	Muscle activation onset Brain activity	Patients with LBP (n = 13) vs healthy participants (n = 9)		Shoulder flexion	The activation onset of the ipsilateral transversus and internal oblique abdominis was delayed during shoulder flexion in patients with LBP compared with control participants. The anticipatory activation of the transversus and internal oblique abdominis occurred more rapidly during shoulder flexion in patients with LBP than in control participants.

					The co-activation time duration of bilateral abdominal muscles during shoulder flexion was shorter in patients with LBP than in control participants. Patients with LBP demonstrated an important change in the control of spine stability, which can be explained by altered mechanisms of M1 motor programming.
Larivière et al., 2013 *Clin J Pain*	Muscle activation onset	Patients with LBP (n = 59)		Shoulder flexion	The activation onset of the Postural muscles during shoulder flexion was affected by several cognitive conditions. Patients with LBP who are characterised by higher scores on some pain-related variables, reacted favourably to protect the spine from further pain and injuries; however, they were at a greater risk of injury when performing a complex physical task with a higher attention demand.
Hedayati et al., 2014 *J Back Musculoskelet Rehabil*	Muscle activation onset	Patients with LBP (n = 21) vs healthy participants (n = 21)		Shoulder flexion	Variability of the postural muscles (transversus abdominis/internal oblique abdominis) responses in patients with LBP decreased during a shoulder flexion task. Restoring variability in postural control responses might be a goal for rehabilitating these patients.
Hwang et al., 2014 *J Phys Ther Sci*	Muscle activation onset	Patients with LBP (n = 14) vs healthy participants (n = 7)		Shoulder flexion	By using the intervention program with sensorimotor training for LBP, the activation onset of transversus and external oblique abdominis was earlier during shoulder flexion in

					both standing and sitting positions than that at baseline. At baseline, the activation onset of the transversus and external oblique abdominis was delayed during shoulder flexion in both standing and sitting positions in patients with LBP compared with control participants. Sensorimotor training helps patients learn muscle adjustment, which helps alleviate pain and improve muscle performance.
Lomond et al., 2015 *Spine J*	Reaction force Muscle activity	LBP patients (n = 33) vs healthy participants (n = 15)		Leg raises in a supine position	In patients with LBP, trunk and leg muscle activities during APA were lower than that in healthy participants. Main effects of treatment did not rule out nonspecific effects of time or repeated exposure.
Marshall et al., 2014 *Exp Brain Res*	Muscle activity Muscle activation onset	Healthy participants (n = 26)		Shoulder flexion and extension in pre- and post-standing conditions.	Trunk muscle activity during APA under a shoulder flexion task in the post-standing condition was reduced compared with the pre-standing condition. Experimental LBP reduced APA amplitudes, and extended findings did not affect compensatory postural adjustments.
Shiozawa et al., (2013) *Study 1*	Muscle activation onset Muscle activity	Healthy participants (n = 9)	Saline injection into VM and tibialis anterior (TA)	Shoulder flexion and bilateral heel lifts	The activation onset of the BF on the ipsilateral side was earlier during shoulder flexion in participants with VM pain condition than in those with a no-pain condition.

					The activation onset of the TA was earlier on the contralateral side during bilateral heel lifts in the VM and TA pain conditions than in the no-pain condition. Peak activity of the bilateral VM and ipsilateral VL was more reduced during bilateral heel lifts in a VM pain condition than in a no-pain condition. Peak activity of the ipsilateral VM and TA during bilateral heel lifts was more reduced in a TA pain condition than in a no-pain condition. Knee-related muscle pain induced both inhibition and facilitation effects in neuromuscular function during APAs.
Shiozawa et al., (2015) *Study 2*	CoP displacement Time-to-peak of CoP displacement Velocity of CoP displacement	Healthy participants (n = 9)	Saline injection into the VM and TA	Shoulder flexion and bilateral heel raises	Displacement of the medial-lateral net CoP during a shoulder flexion task was reduced in a TA pain condition compared with a no-pain condition. Displacement of the ipsilateral AP CoP during a shoulder flexion task was reduced in the muscle pain condition compared with a no-pain condition. Knee-related muscle pain induced biomechanical postural changes during APAs.
Shiozawa et al., (2014)	Muscle activation onset	Healthy participants (n = 12)	Saline injection into the infrapatellar fat pad	Shoulder flexion and bilateral heel raises	The activation onset of the contralateral VM and VL was earlier during bilateral heel lifts in a pain condition than in a no-pain condition.

Study 3	Muscle activity				The activation onset of the VM, VL, and TA was delayed on the ipsilateral side during bilateral heel lifts in a pain condition compared with a no-pain condition. Muscle activity levels of the VM, VL, and TA were reduced on the ipsilateral side during bilateral heel lifts in a pain condition compared with a no-pain condition. Knee-related pain induced both inhibition and facilitation effects in neuromuscular function during APAs.

References

Arendt-Nielsen L, Graven-Nielsen T (2008) Muscle pain: sensory implications and interaction with motor control. Clin J Pain 24:291–298

Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, Graven-Nielsen T (2010) Sensitization in patients with painful knee osteoarthritis. Pain 149:573–581

Arendt-Nielsen L, Egsgaard LL, Petersen KK, Eskehave TN, Graven- Nielsen T, Hoeck HC, Simonsen O (2015) A mechanism-based pain sensitivity index to characterize knee osteoarthritis patients with different disease stages and pain levels. Eur J Pain 19:1406-1417

Aruin AS, Shiratori T (2004) The effect of the amplitude of motor action on anticipatory postural adjustments. J Electromyogr Kinesiol 14:455–462

Aruin AS (2006) The effect of asymmetry of posture on anticipatory postural adjustments. Neurosci Lett 401:150–153

Bank PJM, Peper CE, Marinus J, Beek PJ, Van Hilten JJ (2013) Motor consequences of experimentally induced limb pain: a systematic review. Eur J Pain 17:145–157

Belen'kii V, Gurfinkel V, Pal'tsev E (1967) Control elements of voluntary movements. Biofizika 12:135–141

Benvenuti F, Stanhope SJ, Thomas SL, Panzer VP, Hallett M (1997) Flexibility of anticipatory postural adjustments revealed by self-paced and reaction-time arm movements. Brain Res 761:59–70

Bouisset S, Zattara M (1981) A sequence of postural movements precedes voluntary movement. Neurosci Lett 22:263–270

Bouisset S, Zattara M (1987) Biomechanical study of the programming of anticipatory postural adjustments associated with voluntary movement. J Biomech 20:735–742

Brooks C, Kennedy S, Marshall PWM (2012) Specific trunk and general exercise elicit similar changes in anticipatory postural adjustments in patients with chronic low back pain: a randomized controlled trial. Spine 37:E1543–E1550

Cecchi F, Mannoni A, Molino-Lova R, Ceppatelli S, Benvenuti E, Bandinelli S, Lauretani F (2008) Epidemiology of hip and knee pain in a community based sample of Italian persons aged 65 and older. Osteoarthritis Cartilage 16:1039–1046

Chabran E, Fourment A, Maton B, Ribreau C (1999) Chronology of upper limb anticipatory postural adjustments associated with voluntary wrist flexions and extensions in humans. Neurosci Lett 268:13–16

Chiou SY, Gottardi SE, Hodges PW, Strutton PH (2016) Corticospinal excitability of trunk muscles during different postural tasks. PLoS One 25(11):e0147650

Chuckpaiwong B, Charles HC, Kraus VB, Guilak F, Nunley JA (2010) Age-associated increases in the size of the infrapatellar fat pad in knee osteoarthritis as Measured by 3T MRI. J Orthop Res 28:1149–1154

Courtney CA, Lewek MD, Witte PO, Chmell SJ, Hornby TG (2009) Heightened flexor withdrawal responses in subjects with knee osteoarthritis. J Pain 10:1242–1249

Cowan S, Hodges P, Bennell K (2001) Anticipatory activity of vastus lateralis and vastus medialis obliquus occurs simultaneously in voluntary heel and toe raises. Phys Ther Sport 2:71–79

Cowan S, Hodges P, Bennell K, Crossley K (2002) Altered vastii recruitment when people with patellofemoral pain syndrome complete a postural task. Arch Phys Med Rehabil 83:989–995

Cowan S, Bennell K, Hodges PW, Crossley KM, McConnell J (2003) Simultaneous feedforward recruitment of the vasti in untrained postural tasks can be restored by physical therapy. J Orthop Res 21:553–558

De Wolf S, Slijper H, Latach ML (1998) Anticipatory postural adjustments during self-paced and reaction time movements. Exp Brain Res 121:7–19

Dye SF, Vaupel GL, Dye CC (1998) Conscious neurosensory mapping of the internal structures of the human knee without intraarticular anesthesia. Am J Sports Med. 26:773–777

Falla D, Jull G, Hodges PW (2004) Feedforward activity of the cervical flexor muscles during voluntary arm movements is delayed in chronic neck pain. Exp Brain Res 157:43–48

Ferrans CE, Zerwic JJ, Wilbur JE, Larson JL (2005) Conceptual model of health-related quality of life. J Nurs Scholarsh 37:336–342

Fink B, Egl M, Singer J, Fuerst M, Bubenheim M, Neuen-Jacob E (2007) Morphologic changes in the vastus medialis muscle in patients with osteoarthritis of the knee. Arthritis Rheum 56:3626–3633

Foley SJ, Lord SR, Srikanth V, Cooley H, Jones G (2006) Falls risk is associated with pain and dysfunction but not radiographic osteoarthritis in older adults: Tasmanian Older Adult Cohort study. Osteoarthritis Cartilage 14:533–539

Forget R, Lamarre Y (1990) Anticipatory postural adjustment in the absence of normal peripheral feedback. Brain Res 508:176–179

Girolami GL, Shiratori T, Aruin AS (2010) Anticipatory postural adjustments in children with typical motor development. Exp Brain Res 205:153–165

Graven-Nielsen T, Lund H, Arendt-Nielsen L, Danneskiold-Samsøe B, Bliddal H (2002) Inhibition of maximal voluntary contraction force by experimental muscle pain: a centrally mediated mechanism. Muscle Nerve 26:708–712

Guccione A, Felson D, Anderson J, Anthony J, Zhang Y, Wilson P, Kelly-Hayes M (1993) The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health 84:351–358

Hassan BS, Mockett S, Doherty M (2001) Static postural sway, proprioception, and maximal voluntary quadriceps contraction in patients with knee osteoarthritis and normal control subjects. Ann Rheum Dis 60:612–618

Hatfield GL, Morrison A, Wenman M, Hammond CA, Hunt MA (2016) Clinical tests of standing balance in the knee osteoarthritis population: systematic review and meta-analysis. Phys Ther 96:324–337

Hatton AL, Crossley KM, Hug F, Bouma J, Ha B, Spaulding KL, Tucker K (2015) Acute experimental hip muscle pain alters single-leg squat balance in healthy young adults. Gait Posture 41:871–876

Hedayati R, Kahrizi S, Parnianpour M, Bahrami F, Kazemnejad A, Mobini B (2014) The study of the variability of anticipatory postural adjustments in patients with recurrent non-specific low back pain. J Back Musculoskeletal Rehabil 27:33–40

Henriksen M, Alkjær T, Lund H, Simonsen EB, Graven-Nielsen T, Danneskiold-samsøe B, Bliddal H (2007) Experimental quadriceps muscle pain impairs knee joint control during walking. J Appl Physiol 103:132–139

Henriksen M, Alkjaer T, Simonsen EB, Bliddal H (2009) Experimental muscle pain during a forward lunge--the effects on knee joint dynamics and electromyographic activity. Br J Sports Med 43:503–507

Henriksen M, Graven-Nielsen T, AaboeJ, Andriacchi T, Bliddal H (2010) Gait change in patients with osteoarthritis are replicated by experimental knee pain. Arthris Care Res 62:501–509

Henriksen M, Rosager S, Aaboe J, Graven-Nielsen T, Bliddal H (2011) Experimental knee pain reduces muscle strength. J Pain 12:460–467

Hermens HJ, Freriks B, Disselhorst-Klug C, Rau G (2000) Development of recommendations for SEMG sensors and sensor placement procedures. J Electromyogr Kinesiol 10:361–374.

Hirata RP, Arendt-Nielsen L, Graven-Nielsen T (2010) Experimental calf muscle pain attenuates the postural stability during quiet stance and perturbation. Clin Biomech (Bristol, Avon) 25:931–937

Hirata RP, Erviha UF, Arendt-Nielsen L, Graven-Nielsen T (2011) Experimental muscle pain challenges the postural stability during quiet stance and unexpected posture perturbation. J Pain 12:911–919

Hirata RP, Arendt-Nielsen L, Shiozawa S, Graven-Nielsen T (2012) Experimental knee pain impairs postural stability during quiet stance but not after perturbations. Eur J Appl Physiol 112:2511–2521

Hirata RP, Jørgensen TS, Rosager, Arendt-Nielsen, Bliddal, Henriksen M, Graven-Nielsen T (2013) Altered visual and feet proprioceptive feedbacks during quiet standing increase postural sway in patients with severe knee osteoarthritis. PloS One 22:e71253

Hodges PW, Richardson CA (1996) Inefficient muscle stabilization of the lumbar spine associated with low back pain: a motor control evaluation of transversus abdominis. Spine 21:2640–2650

Hodges PW, Richardson CA (1998) Delayed postural contraction of transversus abdominis in low back pain associated with movement of the lower limb. J Spinal Disord Tech 11:46–56

Hodges PW (2001) Changes in motor planning of feedforward postural responses of the trunk muscles in low back pain. Exp Brain Res 141:261–266

Hodges PW, Moseley GL, Gabrielsson A, Gandevia SC (2003) Experimental muscle pain changes feedforward postural responses of the trunk muscles. Exp Brain Res 151:262–271

Hodges PW, Mellor R, Crossley K, Bennell K (2009) Pain induced by injection of hypertonic saline into the infrapatellar fat pad and effect on coordination of the quadriceps muscles. Arthritis Rheum 61:70–77

Hodges PW, Tucker K. (2011) Moving differently in pain: a new theory to explain the adaptation to pain. Pain 152:S90-98

Horak FB, Nashner LM (1989) Influence of central set on human. J Neurophysiol 62:841–853.

Horak FB (2006) Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? Age Ageing 35-S2:H7–H11

Hwang JA, Bae SH, Kim GD, Kim KY (2014) The effects of sensorimotor training on anticipatory postural adjustment of the trunk in chronic low back pain patients. J Phys Ther Sci 25:1189–1192

Jacobs JV, Henry SM, Nagle KJ (2009) People with chronic low back pain exhibit decreased variability in the timing of their anticipatory postural adjustments. Behav Neurosci 123:455–458

Jacobs JV, Henry SM, Nagle KJ (2010) Low back pain associates with altered activity of the cerebral cortex prior to arm movements that require postural adjustment. Clin Neurophysiol 121:431–440

Jørgensen KT, Pedersen BV, Nielsen NM, Hansen AV, Jacobsen S, Frisch M (2011) Socio-demographic factors, reproductive history and risk of osteoarthritis in a cohort of 4.6 million Danish women and men. Osteoarthritis Cartilage 19:1176–1182

Julius D, Basbaum AI (2001) Molecular mechanisms of nociception. Nature 413:203–210

Kellgren JH, Lawrence JS (1957) Radiological assessment of osteo-arthrosis. Ann Rheum 16:494–503

Kim IJ, Kim HA, Seo Y-I, Jung YO, Song YW, Jeong JY, Kim DH (2011) Prevalence of knee pain and its influence on quality of life and physical function in the Korean elderly population: a community based cross-sectional study. J Korean Med Sci 26:1140–1146

Klous M, Mikulic P, Latash ML (2011) Two aspects of feedforward postural control: anticipatory postural adjustments and anticipatory synergy adjustments. J Neurophysiol 105:2275–2288

Knutson GA (2000) The role of the gamma-motor system in increasing muscle tone and muscle pain syndromes: a review of the Johansson/Sojka hypothesis. J Manipulative Physiol Ther 23: 564–572

Komiyama T, Kasai T (1997) Changes in the H-reflexes of ankle extensor and flexor muscles at the initiation of a stepping movement in humans. Brain Res 766:227–235

Koshino T, Machida J (1993) Grading system of articular cartilage degeneration in osteoarthritis of the knee. Bulletin (Hospital for Joint Diseases (New York, N.Y.)) 53:41–46

Larivière C, Butler H, Sullivan MJL, Fung J (2013) An exploratory study on the effect of pain interference and attentional interference on neuromuscular responses during rapid arm flexion movements. Clin J Pain 29:265–275

Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S (2008) Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 58:26–35

Lee RG, Tonolli E, Viallet F, Aurenty R, Massion J (1995) Preparatory postural adjustments in Parkinsonian patients with postural instability. Can J Neurol Sci 22:126–135

Leinonen V, Kankaanpää M, Luukkonen M, Hänninen O, Airaksinen O, Taimela S (2001) Disc herniation-related back pain impairs feed-forward control of paraspinal muscles. Spine 26:E367–E372

Leinonen V, Kankaanpää M, Luukkonen M, Kansanen M, Hänninen O, Airaksinen O, Taimela S (2003) Lumbar paraspinal muscle function, perception of lumbar position, and postural control in disc herniation-related back pain. Spine 28:842–848

Lomond KV, Jacobs JV, Hitt JR, DeSarno MJ, Bunn JY, Henry SM (2015) Effects of low back pain stabilization or movement system impairment treatments on voluntary postural adjustments: a randomized controlled trial. Spine J 15:596-606

Lyytinen T, Liikavainio T, Bragge T, Hakkarainen M, Karjalainen PA, Arokoski JPA (2010) Postural control and thigh muscle activity in men with knee osteoarthritis. J Electromyogr Kinesiol 20:1066–1074

MacDonald D, Moseley GL, Hodges PW (2009) Why do some patients keep hurting their back? evidence of ongoing back muscle dysfunction during remission from recurrent back pain. Pain 142:183–188

MacDonald D, Moseley GL, Hodges PW (2010) People with recurrent low back pain respond differently to trunk loading despite remission from symptoms. Spine 35:818–824

Mannion AF, Caporaso F, Pulkovski N, Sprott H (2012) Spine stabilisation exercises in the treatment of chronic low back pain: a good clinical outcome is not associated with improved abdominal muscle function. Eur Spine J 21:1301–1310

Marshall PWM, Romero R, Brooks C (2014) Pain reported during prolonged standing is associated with reduced anticipatory postural adjustments of the deep abdominals. Exp Brain Res 232:3515–3524

Massé-Alarie H, Flamand VH, Moffet H, Schneider C (2012) Corticomotor control of deep abdominal muscles in chronic low back pain and anticipatory postural adjustments. Exp Brain Res 218:99–109

Massé-Alarie H, Neige C, Bouyer LJ, Mercier C (2018) Modulation of corticospinal excitability of trunk muscles in preparation of rapid arm movement. Neuroscience 15:231–241

Massion J, Ioffe M, Schmitz C, Viallet F, Gantcheva R (1999) Acquisition of anticipatory postural adjustments in a bimanual load-lifting task: normal and pathological aspects. Exp Brain Res 128:229–235

Masui T, Hasegawa Y, Yamaguchi J, Kanoh T, Ishiguro N, Suzuki S (2006) Increasing postural sway in rural-community-dwelling elderly persons with knee osteoarthritis. J Orthop Sci 11: 353–358

Mense S, Stahnke M (1983) Responses in muscle afferent fibres of slow conduction. J Physiol 342:383–397

Mergner T, Rosemeier T (1998) Interaction of vestibular, somatosensory and visual signals for postural control and motion perception under terrestrial and microgravity conditions--a conceptual model. Brain Res Brain Res Rev 28:118–135

Mezaour M, Yiou E, Le Bozec S (2010) Effect of lower limb muscle fatigue on anticipatory postural adjustments associated with bilateral-forward reach in the unipedal dominant and non-dominant stance. Eur J Appl Physiol 110:1187–1197

Mok NW, Brauer SG, Hodges PW (2011) Postural recovery following voluntary arm movement is impaired in people with chronic low back pain. Gait Posture 34:97–102

Moseley GL, Nicholas MK, Hodges PW (2004a) Does anticipation of back pain predispose to back trouble? Brain 127:2339–2347

Moseley GL, Nicholas MK, Hodges PW (2004b) Pain differs from non-painful attention-demanding or stressful tasks in its effect on postural control patterns of trunk muscles. Exp Brain Res 156:64–71

Moseley GL, Hodges PW (2005) Are the changes in postural control associated with low back pain caused by pain interference? Clin J Pain 21:323–329

Mouchnino L, Gueguen N, Blanchard C, Boulay C, Gimet G, Viton J, Franceschi J (2005) Sensori-motor adaptation to knee osteoarthritis during stepping-down before and after total knee replacement. BMC Musculoskelet Disord 6:1–11

Moyne-Bressand, S, Dhieux C, Decherchi P, Dousset E (2017) Effectiveness of foot biomechanical orthoses to relieve patients' knee pain: changes in neural strategy after 9 weeks of treatment. J Foot Ankle Surg 56:1194–1204

Muirden KD (2005) Community oriented program for the control of rheumatic diseases: studies of rheumatic diseases in the developing world. Curr Opin Rheumatol 17:153–156

Nakamura K (2008) A “super-aged” society and the “locomotive syndrome”. J Orthop Sci 13:1–2

Petrella M, Gramani-Say K, Serrão PR, Lessi GC, Barela JA, Carvalho RP, Mattiello SM (2017) Measuring postural control during mini-squat posture in men with early knee osteoarthritis. Hum Mov Sci 52:108–116

Pradels A, Pradon D, Vuillerme N (2011) Effects of experimentally induced pain of the plantar soles on centre of foot pressure displacements during unperturbed upright stance. Clin Biomech (Bristol, Avon) 26:424–428

Poortvliet PC, Tucker KJ, Finnigan S, Scott D, Hodges PW (2019) Experimental pain decreases corticomuscular coherence in a force- but not a position- control task. J Pain 20:192–200

Reinert A, Kaske A, Mense S (1998) Inflammation-induced increase in the density of neuropeptide-immunoreactive nerve endings in rat skeletal muscle. Exp Brain Res 121: 174–180

Salomoni SE, Graven-Nielsen T (2012) Experimental muscle pain increases normalized variability of multidirectional forces during isometric contractions. Eur J Appl Physiol 112:3607–3617

Schmidt RF, Thews G (1989) Human Physiology 2nd Edition :82–113

Senna ÉR, De Barros ALP, Silva EO, Costa IF, Pereira LVB, Ciconelli RM, Ferraz MB (2004) Prevalence of rheumatic diseases in Brazil: a study using the COPCORD approach. J Rheumatol 31:594–597

Sharma L, Kapoor D, Issa S (2006) Epidemiology of osteoarthritis: an update. Curr Opin Rheumatol 18:147–156

Silfies SP, Mehta R, Smith SS, Karduna AR (2009) Differences in feedforward trunk muscle activity in subgroups of patients with mechanical low back pain. Arch Phys Med Rehabil 90:1159–1169

Slemenda C, Heilman DK, Brandt KD, Katz BP, Mazzuca SA, Braunstein EM, Byrd D (1998) Reduced quadriceps strength relative to body weight: a risk factor for knee osteoarthritis in women? Arthritis Rheum 41:1951–1959

Stacey MJ (1969) Free nerve endings in skeletal muscle of the cat. J Anat 105:231–254

Study 1 Reorganised anticipatory postural adjustments due to experimental lower extremity muscle pain. Shiozawa S, Hirata RP, Graven-Nielsen T

Study 2 Center of pressure displacement of standing posture during reaction time tasks is reorganised due to experimental lower extremity muscle pain. Shiozawa S, Hirata RP, Graven-Nielsen T

Study 3 Impaired anticipatory postural adjustments due to experimental infrapatellar fat pad pain. Shiozawa S, Hirata PR, Jeppesen JB, Graven-Nielsen T

Tang X, Wang S, Zhan S, Niu J, Tao K, Zhang Y, Lin J (2016) The prevalence of symptomatic knee osteoarthritis in China results from the China Health and Retirement Longitudinal Study. Arthritis Rheumatol 68:648–653

Tateuchi H, Ichihashi N, Shinya M, Oda S (2011) Anticipatory postural adjustments during lateral step motion in patients with hip osteoarthritis. J Appl Biomech 27:32–39

Taylor JL (2005) Independent control of voluntary movements and associated anticipatory postural responses in a bimanual task. Clin Neurophysiol 116:2083–2090

Tennant A, Fear J, Pickering A, Hillman M, Cutts A, MA Chamberlain (1995) Prevalence of knee problems in the population aged 55 years and over: identifying the need for knee arthroplasty. BMJ 310:1291–1293

Tsao H, Galea MP, Hodges PW (2008a) Reorganization of the motor cortex is associated with postural control deficits in recurrent low back pain. Brain 131:2161–2171

Tsao H, Hodges PW (2008b) Persistence of improvements in postural strategies following motor control training in people with recurrent low back pain. J Electromyogr Kinesiol 18:559–567

Tucker KJ, Hodges PW (2009) Motoneurone recruitment is altered with pain induced in non-muscular tissue. Pain 141:151–155

Tucker KJ, Hodges PW (2010) Changes in motor unit recruitment strategy during pain alters force direction. Eur J Pain 14:932–938

Vasseljen O, Dahl HH, Mork PJ, Torp HG (2006) Muscle activity onset in the lumbar multifidus muscle recorded simultaneously by ultrasound imaging and intramuscular electromyography. Clin Biomech (Bristol, Avon) 21:905–913

Vasseljen O, Fladmark AM, Westad C, Torp HG (2009) Onset in abdominal muscles recorded simultaneously by ultrasound imaging and intramuscular electromyography. J Electromyogr Kinesiol 19:e23–31

Venema DM, Karst M (2012) Individuals with total knee arthroplasty demonstrate altered anticipatory postural adjustments compared with healthy control subjects. J Geriatr Phys Ther 35:62–72

Vedula S, Kearney RE, Wagner R, Stapley PJ (2010) Decoupling of stretch reflex and background muscle activity during anticipatory postural adjustments in humans. Exp Brain Res 205:205–213

Viallet F, Massion J, Massarino R, Khalil R (1992) Coordination between posture and movement in a bimanual load lifting task: putative role of a medial frontal region including the supplementary motor area. Exp Brain Res 88:674–684

Voight ML, Wieder DL (1991) Comparative reflex response times of vastus medialis obliquus and vastus lateralis in normal subjects and subjects with extensor mechanism dysfunction: an electromyographic study. Am J Sports Med 19:131–137

Watanabe H, Urabe K, Takahira N, Ikeda N, Fujita M, Obara S, Hendona T (2010) Quality of life, knee function, and physical activity in Japanese elderly women with early-stage knee osteoarthritis. J Orthop Surg (Hong Kong) 18:31–34

Wegener L, Kisner C, Nichols D (1997) Static and dynamic balance responses in persons with bilateral knee osteoarthritis. J Orthop Sports Phys Ther 25:13–18

Willis (1995) Neurobiology; Cold, pain and the brain. Nature 373:19–20

Wilson I, Cleary P (1995) Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 273:59–65

Winter D (1995a) Human balance and posture control during standing and walking. Gait Posture 3:193–214.

Winter D (1995b) A.B.C. (anatomy, biomechanics and control) of balance during standing and walking. Walterloo Biomehcanics

Winter D, Prince F, Frank JS, Powell C, Zabjek KF (1996) Unified theory regarding A/P and M/L balance in quiet stance. J Neurophysiol 75:2334–2343

Winter D, Patla AE, Ishac M, Gage WH (2003) Motor mechanisms of balance during quiet standing. J Electromyogr Kinesiol 13:49–56

Woollacott MH, Bonnet M, Yabe K (1984) Preparatory process for anticipatory postural adjustments: Modulation of leg muscles reflex pathway during preparation for arm movements in standing man. Exp Brain Res 55:263–271

Yiou E, Deroche T, Do MC, Woodman T (2011) Influence of fear of falling on anticipatory postural control of medio-lateral stability during rapid leg flexion. Eur J Appl Physiol 111: 611–620

Yoshimura N, Muraki S, Oka H, Mabuchi A, En-Yo Y, Yoshida M, Saika A (2009) Prevalence of knee osteoarthritis, lumbar spondylosis, and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study. J Bone Miner Metab 27:620–628

Zhang Y, Xu L, Nevitt MC, Aliabadi P, Yu W, Qin M, Lui LY (2001) Comparison of the prevalence of knee osteoarthritis between the elderly Chinese population in Beijing and whites in the United States: the Beijing Osteoarthritis Study. Arthritis Rheum 44:2065–2071