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Postural control changes due to pain in the knee and leg muscles

Ph.D.-thesis by Rogerio Pessoto Hirata

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Abbreviations used in the thesis

COP	Center of Pressure
ML	Medial-lateral
AP	Anterior-posterior
RMS	Root mean square
MU	Motor Unit
BOS	Base of support
COG	Center of Gravity
COM	Center of Mass
CNS	Central Nervous System
MVC	Maximum voluntary contraction
RM-ANOVA	Repeated measures ANOVA
NK	Newman Keul's post-hoc test for multiple comparison
EMG	Electromyography
iEMG	Electromyography integral
deltaEMG	The absolute percentage difference in the integrated EMG (iEMG) between the pain and baseline condition
Total-deltaEMG	Averaged deltaEMG for all muscles across all subjects.

Preface

This Ph.D. thesis is based on the three below studies performed at Center for Sensory-Motor Interaction (SMI), Analysis Movement Laboratory, Aalborg University, Denmark, from 2007 to 2010:

Study 1: Hirata RP, Arendt-Nielsen L, Graven-Nielsen T (2010). Experimental calf muscle pain attenuates the postural stability during quiet stance and perturbation. *Clinical Biomechanics* (Bristol, Avon). 2010 Nov;25(9):931-7.

Study 2: Hirata RP, Ervilha UF, Arendt-Nielsen L, Graven-Nielsen T (2011). Experimental thigh muscle pain challenges the postural stability during quiet stance and unexpected posture perturbation. *The Journal of Pain*. 2011, Aug; 12(8): 911:919.

Study 3: Hirata RP, Arendt-Nielsen L, Shiozawa S, Graven-Nielsen T (2010). Experimental knee pain impairs the postural stability during quiet stance but not after unexpected perturbations. *The European Journal of Applied Physiology* (in press).

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1 Introduction

According to the International Association for the Study of Pain (IASP), pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. Pain significantly affects the economy worldwide (Krismer and van Tulder 2007) increasing health care expenditures (Rizzo et al. 1998) and causing patients to take time off paid work (Gronning et al. 2010). Furthermore, pain affects general quality of life, sometimes causes social isolation and potentially leads to further problems such as depression (Aguera-Ortiz et al. 2011). Given the widespread effects of pain in the population, efforts have been made to understand the causes and effects of pain.

The effect of pain is larger if associated with neurological impairments and biomechanical changes (such as bone deformation due to arthritis). The complexities of pain, combined with additional impairments such as muscle weakness and cartilage degeneration, interferes with postural control, increasing the vulnerability of pain patients to falls and injuries (Foley et al. 2006). Musculoskeletal pain (particularly widespread pain) is also related to an increased risk of falls in elderly women with disability (Leveille et al. 2002). Falls are the leading cause of morbidity and mortality in elderly people (Szabo et al. 2008) in which 30% will present with one or more falls per year (Tinetti et al. 1988; Campbell et al. 1989). Twenty-five percent of elderly people with hip fractures due to falls die within six months, and 50% never walk again (Winter 1995). Approximately 10 to 71% of elderly are afflicted with pain (McAlindon et al. 1992), relating to knee osteoarthritis: Therefore, this presents as one of the most common types of pain in this population (Felson et al. 1987; Davis 1988; Felson 1988). In addition, pain due to knee OA causes (potentially) impaired knee proprioception and postural stability (Wegener et al. 1997; Hinman et al. 2002; Messier et al. 2002), and increases the risk of falls and fractures (Campbell et al. 1989; Leveille et al. 2002; Foley et al. 2006; Blyth et al. 2007; Yagci et al. 2007).

Postural stability is achieved when the center of mass (COM) of the body is maintained within the base of support (BOS), usually delineated by the area under the feet. Muscles in the body generate

forces around the joints that produce torques. These are capable of maintaining posture and balance against the force of gravity and external perturbations. The external perturbations are defined as external forces applied to the body shifting the COM towards the BOS limits. During standing, humans are continually moving. This movement consists of small body oscillations in anterior-posterior (AP) and medial-lateral (ML) direction. When the COM migrates to the boundaries of the BOS, postural stability is reduced. Once these drifts beyond boundaries of the BOS, stability is lost and reactive strategies are required to regain balance and move the COM within the BOS. In healthy subjects, during small perturbations, these strategies are easily implemented; however, following sensory-motor impairments (such as in elderly people, neuropathic and OA patients), counter-reactions may not be optimal and the perturbation may lead to falls.

A possible explanation for the increased falls in OA patients compared to health subjects is reduced postural stability and weaker knee strength (Jones et al. 1995; Wegener et al. 1997). These changes combined with degeneration of the bone cartilage, may induce mechanical changes such as an increase in joint stiffness. In addition, pain may induce a loss of proprioception (Matre et al. 2002) and muscle strength (Graven-Nielsen et al. 2002). Altogether, these factors partly explain why the postural control in knee OA patients is highly impaired. Despite this, it is not clear to what extent the postural impairments, observed in the knee OA patients, are due to structural changes (such as the degeneration of the tibia-femur cartilage) or pain. This means that clinical treatment focusing on postural control rehabilitation may be inappropriate in this population. Therefore, an understanding of the effect of pain on postural control is critical to clarify the complex mechanisms underlying the impairment of postural control in OA patients. It is possible to study the effect of pain on postural control, and mapping the extent of pain and its affect on postural control in knee OA patients is required. Induction of experimental pain in healthy subjects generates a standard and controlled assessment of the effects of pain in a healthy system without the interference of other variables (such as those found in knee OA patients). The assessment of the effect of pain in healthy subjects might provide insight into more appropriate rehabilitation strategies (subsequently increasing the quality of life) in knee OA patients.

1.1 Aim of the Ph.D. project

To investigate, in healthy subjects, the effect of experimental calf and thigh muscle and infrapatellar fat pad (knee) pain on postural control during quiet standing and following unexpected perturbations (Figure 1).

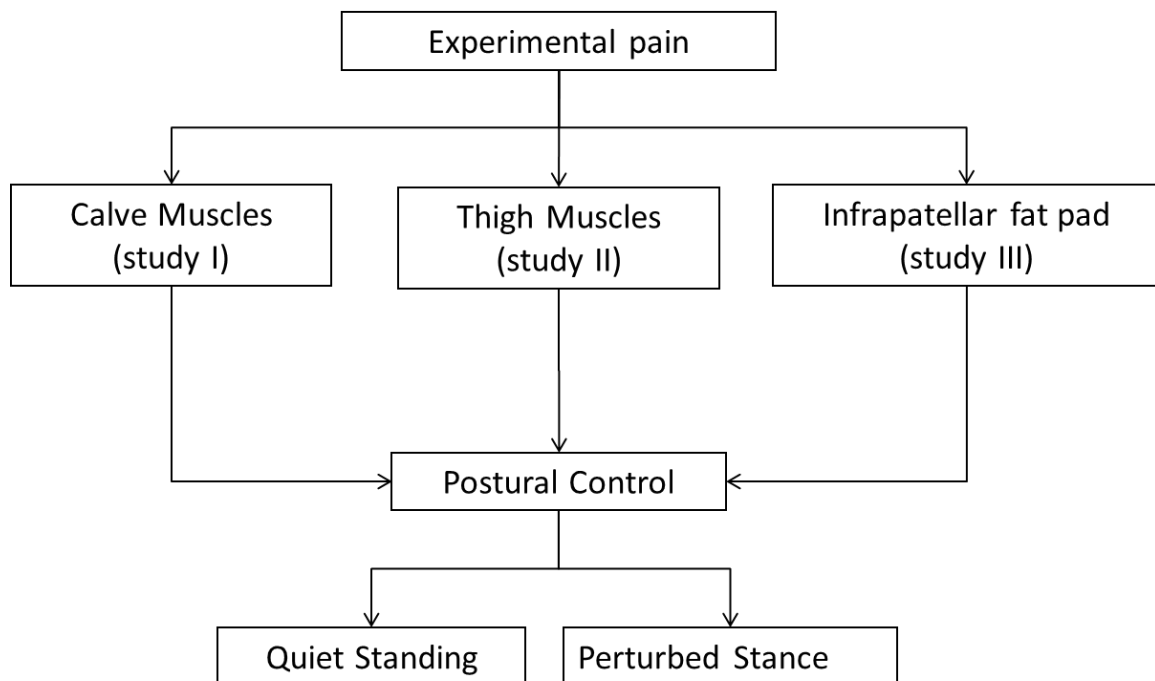


Figure 1: Model for the thesis demonstrating the effect of muscular and joint pain on postural control in healthy subjects.

2 Postural Control

A requirement for the control of posture are the perception and action systems, which must act together to control the COG. During standing, the BOS is defined by the area delineated by the feet. This can change according to the position of the feet [which will subsequently affect postural sway; ((Chiari et al. 2002)]. Moreover, previous studies have demonstrated significant differences in the postural stability according to the size of the BOS, with a more stable posture in the ML direction (Day et al. 1993) and less EMG activity, especially in the proximal muscles, in the lower limb and trunk (Henry 2001). Therefore, when the COG exceeds the boundaries of the BOS, individuals adopt responsive strategies to avoid falls (for instance, changing the BOS configuration by moving the feet) (Horak and Nashner 1986). Increased postural sway was shown in the ML direction and has been correlated to the dimensions of the BOS. In addition, the COG displacement in the ML direction was more affected than the AP direction following a reduction in the area of the BOS (Mochizuki et al. 2006).

The body has no receptors specifically sensing the position of the COG. Instead, information from sensory receptors located over the whole body is integrated to estimate its location (perception system) and send correct commands to the muscles controlling posture (action system). Together these result in forces and torques that can be measured to quantify the neuronal output during standing (Winter et al. 1996). Usually the COG and COM are used synonymously although they represent different physical variables. Nonetheless, in the human body, the COG and COM are in the same location and therefore either can be used without affecting the interpretation of the results. Therefore, in this thesis only the COG will be used to represent the average location of the body weight. The centre of pressure (COP) is the response of the body to the COG displacement. Physically, it represents the position of the ground reaction vector force, which is the resultant of all the forces acting within the body (internal and external forces). The COP is under continuous control and moves to keep the vertical projection of the COG within the BOS. The sway in the AP direction is mainly achieved by torques generated around the ankle joints, whereas ML sway is controlled by torques generated around the hip (Winter et al. 1996). As muscle stiffness alone cannot stabilize balance during quiet standing, accurate voluntary control of the

COG is crucial for postural stability, and fall avoidance (Morasso and Sanguineti 2002). Zatsiorsky and Duarte (1999) introduced the concepts of rambling and trembling which represents the differing control of quiet stance. The rambling component refers to the motion of the moving reference point used for equilibrium control (Gurfinkel et al. 1995). The trembling component of the COP trace reflects oscillations of the body around the reference point trajectory, governed by quasi-elastic forces (Zatsiorsky and Duarte 1999).

Due to the complexities of the postural control system and its deterioration and associated complications due to different pathologies, research is required to establish the mechanisms underlying postural control. Previous studies have shown that psychological factors, such as fear of falling and perception of safety (Pai et al. 2000) affect balance. COP (mainly measured by force platforms), pressure insoles, electromyography and kinematic parameters have been widely used to quantify postural stability (Table 1). Piirtola (2006) stated that alterations to the ML body sway, measured by force platforms, would be a better predictor of falls among elderly people as there is a good correlation between increased postural sway in the ML direction and likelihood of falling. Table 1 shows studies that have developed the methods used in this thesis to quantify postural stability during quiet standing and following perturbations. In general, the results suggest impaired postural control in the presence of pain. Increased COP displacement and speed in both ML and AP direction have been reported in patient groups and healthy subjects. In particular, knee OA patients present with impaired muscle strength, sensorimotor deficits, decreased postural stability and deterioration of performance during functional activities.

2.1 *Visual, vestibular and somatosensory information and postural control*

In order to restore the position of the body, the generation and application of forces and effective postural control are required so that forces are applied precisely and in the correct way. Therefore, it is necessary for the central nervous system (CNS) to accurately identify the position of the body in space. Three major systems are involved in postural control (Figure 2): (i) visual, (ii) vestibular and (iii) somatosensory (Winter 1995). These provide information for constructing an internal body model that represents the

different body segments relative to the surrounding environment. Muscle stiffness assists in the stabilization of joints; however, muscle stiffness alone cannot stabilize balance during quiet standing. Hence, it is necessary to determine the interaction between sensory input (provided by the three systems mentioned above) and motor output to maintain the COM within the BOS (Morasso 2002).

In the presence of pain, the system can reorganize the gain of each sensor and re-weight the sensory strategy to optimize postural control in altered sensory environments (Oie et al. 2002). Since pain may induce loss of proprioception (Djupsjobacka et al. 1995b; Matre et al. 2002) the re-weighting strategy may increase the gain of information from the non-affected areas providing correct information with regards to the position of the body in relation to the surroundings (therefore, maintaining the balance).

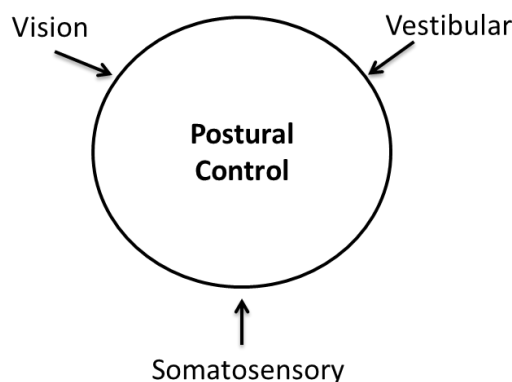


Figure 2: The sensory systems involved in postural control which together, provide information for constructing an internal body model that represents the different body segments relative to the surrounding environment.

Visual input has been widely studied during postural control and influences the amount of postural sway. When subjects stand with their closed eyes the postural sway increases, although balance is still maintained (Sundermier et al. 2001). Vision is a source of information that indicates head position and movement in relation to the external environment. Experiments using the “moving room” paradigm (room in which the subjects stand on fixed ground with the surrounding walls moving back and forth; (Lee and Aronson 1974) showed that the movement of the wall induced synchronous involuntary body oscillations in the subjects, matching the rooms oscillations. Therefore, visual information is used as a reference and adjusts the body position over time (Duarte and Zatsiorsky 2002).

Somatosensory input from the whole body is important in controlling posture. When ischemia was applied at the level of the ankle and thigh, increased body sway in the ML (Magnusson et al. 1990b) and AP directions (Magnusson et al. 1990a) were reported, indicating that proprioceptive input from skin, pressure and joint receptors of the foot do not contribute for the reactive strategy against sinusoidal low frequency floor translations. Despite this, ischemia produced an abnormal body tremor (1Hz) while standing (Diener et al. 1984). Haptic receptors from the tip of the fingers also have a role in the stabilization of the body (Jeka and Lackner 1994; Jeka and Lackner 1995). Light touch (less than a 1 Newton force) to the finger tips, with subjects standing on a stable platform, reduced the sway amplitude by 50% when compared to the 'no touch' conditions (Jeka and Lackner 1995). As the intensity of the contact force was below the intensity capable of directly destabilizing the body, the reduced body sway was probably due to the stimulation of haptic sensors. The haptic and proprioceptive information (from the body) is combined, and used to provide information of the position of the body over time. The combination of information allows the muscles to act more effectively to reduce the body sway amplitude (Jeka and Lackner 1995). Similar results were shown in diabetic patients with impaired proprioception to the soles of the feet. In these patients, light touch reduced postural sway (Dickstein et al. 2001).

In cats, the activity of vestibular neurons were directly recorded, with connections cut from the cerebellum (Peterson 1970), during head tilts. Twenty degrees of lateral tilting caused 149 neurons in the vestibular nuclei to change their firing rate. This may infer that the changes are triggered by afferents from the labyrinthine receptors. Furthermore, following unilateral vestibular neurotomy, baboons exhibited an asymmetrical distribution of muscular tone, reduced or absent EMG activity from the splenius muscle, head-tilt toward the operated side and rotation of the chin to the non-operated (normal) side. This indicates that information from the vestibular centers play a major role in the regulation of posture (Lacour et al. 1976) in these animals. Similar results were also found in patients with vestibular disorders, who exhibited an increased lateral deviation in the body sway measured by the COG movement (Taguchi 1979).

Altogether, it is likely that visual, vestibular and somatosensory afferent inputs are required for postural control.

2.2 *Postural control after perturbations*

Most falls occur when the body is perturbed (Winter 1995). To react precisely to an external perturbation, accurate proprioceptive information from the muscles and joints involved in the movement is crucial (Kavounoudias et al. 1999). Therefore, understanding the mechanisms behind posture in quiet standing and following unexpected perturbations may reveal how sensory systems (visual, vestibular and somatosensory) combine to avoid falls. Furthermore, pain may affect the quality of information from these sensory systems, subsequently impairing balance.

Rapid postural adjustments are most likely influenced by local mechanisms utilizing inputs from the lower limb muscle, joint and skin afferents (Nashner et al. 1979). Muscle response latencies to visual cues, following perturbations, are relatively slow (longer than 200 ms) when compared to vestibular and somatosensory information that have latencies of approximately 80-100 ms (Nashner et al. 1979). Furthermore, muscular response latencies following head displacements (which triggers the vestibular system) were shorter in comparison to those from body translations (which triggers sensory receptors) (Horak et al. 2001). Although postural muscles are activated by forward and backward displacements of the head alone (Dietz et al. 1988; Horak et al. 2001), the contribution of the vestibular system is reduced when the somatosensory information from nerve afferents predominates (Horak et al. 1994; Horak et al. 2001). The main effect of the vestibular system, following perturbations, is in the control of the final equilibrium position adopted by subjects. (Hlavacka et al. 1999).

Proprioception around the ankle seems to play an important role in the estimation of the internal representation of the body (Hlavacka 1995) as electrical vestibular stimulation combined with vibratory stimuli to the ankle muscles, changed the amplitude and direction of the body sway in healthy subjects. Further, Inglis (1995) confirmed that vestibular information has a large influence on postural control

following perturbations. In healthy subjects (under electrical vestibular stimulation) large changes during postural recovery movements following perturbations were observed. When both stimuli (vestibular and perturbations) were applied in close proximity, larger COP and COM shifts were reported, demonstrating impaired postural control following both stimuli.

To avoid losing balance, two main strategies were identified in response to postural perturbations: (i) ankle (ii) hip strategies. The ankle and hip strategies were first described by Horak and Nashner (1986). Postural perturbations (either backward or forward) were induced while the subjects were standing on a “normal” stable support surface or a shorter more unstable support surface. Subjects used mainly muscles around the ankle joint to correct the body position after the postural disturbance (while standing on a normal support surface). In this condition, the muscle activity followed a bottom-up direction, starting from the ankle joint muscles (*tibialis anterior* and *medial gastrocnemius* muscles), at a latency of 73 to 100 ms following the perturbation. This was followed by activation of the posterior or anterior thigh and finally the posterior or anterior trunk muscles (depending on the perturbation direction). If the perturbation moved the body backwards, the *tibialis anterior* muscle, knee extensors muscles and hip extensors muscles were activated; if the perturbation moved the body forward, the triceps surae muscles, knee flexors and hip extensors were activated (Horak and Nashner 1986). Interestingly, when standing on a more unstable support surface, the subjects did not show any activation of the ankle muscles in the response to similar perturbations. Additionally, the leg and trunk muscles were activated at similar latencies in a distal to proximal direction (the so called “hip strategy”), as the movements mainly occurred at the hip joint (Horak and Nashner 1986). Furthermore, if the perturbation was expected and the subjects were accustomed to the perturbation applied, the postural responses were altered and pre-reacted to the body perturbation, reflecting feedforward control and a possible learning effect (Horak et al. 1989). These automatic responses to perturbations are specific to the task (Horak and Nashner 1986; Horak et al. 1989; Burleigh et al. 1994) demonstrating that central commands may alter the neuronal excitability prior to the perturbation (Burleigh et al. 1994). These strategies were confirmed by internal torque estimations around the ankle and hip joints, where, depending on the perturbation speed, either torques around the

ankle or hip were used to react against the perturbation (Runge et al. 1999). As the perturbation speed increases, the faster the COG travels towards the BOS boundaries. Despite this, if the COG is located far from the BOS boundaries, it is still capable of destabilizing the body if the COG speed large (Pai et al. 2000). On the other hand, if the COG lies close to the BOS boundaries, low COG speed may be able to destabilize the body (Pai et al. 2000). Therefore, the postural stability is a combination of the COG position and destabilisation speed (Pai et al. 2000).

Overall, somatosensory information is probably of greater importance than the other sensory modalities (visual and vestibular) for postural control following perturbations.

3 Nociception and Motor Control

Pain sensations from the muscle are mediated by free nerve endings located in the wall of muscle arterioles and the connective tissue between the muscle fibres (Stacey 1969). Part of the free nerve endings are called nociceptors and are activated when tissue damage occurs. They have the capability of transducing chemical, mechanical and thermal stimuli to electrical signals (action potentials) carried by nerve afferents (Mense 1993). The primary afferent neurones are classified according to diameter and presence of myelin (Schwann cells) around the axon of the nerve. The faster myelinated afferent neurons are defined as “group III or A δ ”, and propagate the action potentials (Stacey 1969), with range of speeds (Simone et al. 1994; Marchettini et al. 1996) from 3.1 to 13.5 ms⁻¹. The slower unmyelinated sensory afferents, “group IV or C”, have a conduction velocity of less than 2 ms⁻¹ (0.6 – 1.2 ms⁻¹) (Simone et al. 1994; Marchettini et al. 1996).

Muscle nociceptors can be experimentally stimulated by: (i) infusion of algescic substances, (ii) thermal or (iii) electrical stimulation (Graven-Nielsen 2006) where injection of hypertonic saline is the most common model (Graven-Nielsen 2006). The hypertonic saline (typically a concentration of 6%) excites group III and IV afferents. Experimental muscle pain in healthy subjects allows a standardized assessment of the muscle pain effects on the intact nociceptive system in which all other factors [such as adaptive strategies due to the pain (as in patient populations)], are eliminated. To measure pain the VAS scale is used. An example of a typical VAS score can be seen in Figure 3.

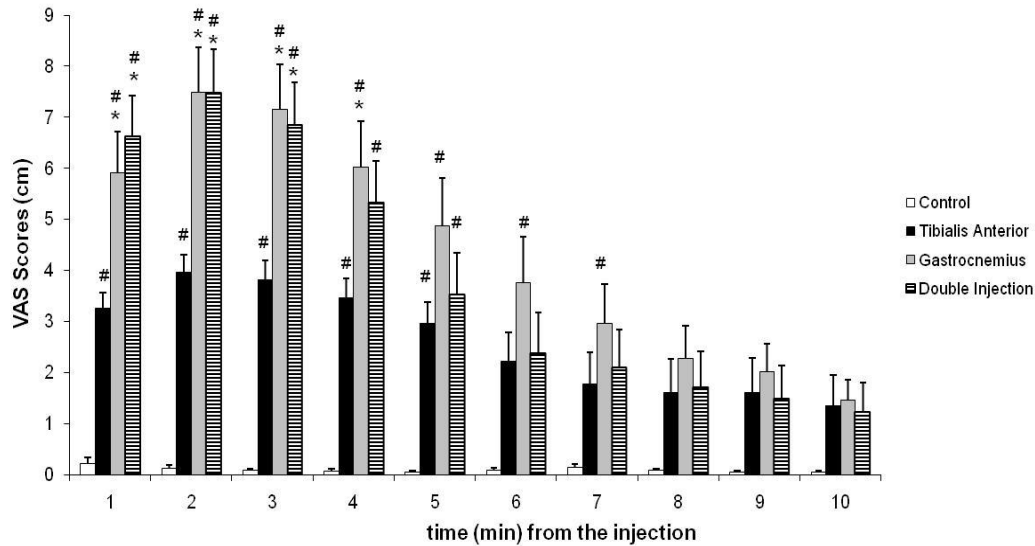


Figure 3: Mean pain intensity (VAS + SEM) following intramuscular injections of hypertonic and isotonic saline. Significantly higher than the tibialis anterior injections (*, NK; $P < 0.05$). Significantly higher than the control injection of isotonic saline (#, NK; $P < 0.05$) (Study1).

3.1 Sensory-motor interaction between pain and motor output

Group III and IV afferents are connected to the spinal cord via the dorsal horn with connections to second-order neurons situated mainly in the lamiae I and V (Mense and Prabhakar 1986; Mense and Craig 1988; Hoheisel et al. 1989). Additionally, synapses between the first and second-order neurons are found in the subnucleus caudalis of the brain stem (Sessle 2000). Finally, the second-order axons are connected to the cortical areas via the spinothalamic tract (Chung et al. 1979), which completes the pathway following painful stimuli (Foreman et al. 1975; Beall et al. 1977; Chung et al. 1979).

Nociceptive information is transmitted to higher brain centres and has an important role in muscular strategies. At the spinal cord level, afferent neurones carry nociceptive information (group III and IV) and affect the interneurons that modulate efferent activity (α -motorneurones). This links the painful sensory information to motor (muscular) output. In animal models changes in muscular responses are observed following painful stimuli (Jovanovic et al. 1990; Mense and Skeppar 1991; Djupsjobacka et al. 1995a; Djupsjobacka et al. 1995b; Capra and Ro 2000; Ro and Capra 2001)

In healthy humans, Cobb *et al* (1975) used surface electrodes on the forearm and paravertebral muscles and identified an increase in the muscle activity following an injection of 0.3 ml of hypertonic

saline. Similar results were observed by Elert *et al* (1989) in fibromyalgia patients. Despite the results of these studies, injection of hypertonic saline to the tibialis anterior muscle of healthy subjects, elicited no changes during: (i) rest (between two active maximum voluntary contractions (MVC)) (Graven-Nielsen *et al.* 1997), and (ii) when the muscle remained relaxed (Birznieks *et al.* 2008).

Previous studies showed that motor unit activation in presence of pain is altered (Falla *et al.* 2007; Hodges *et al.* 2008; Tucker *et al.* 2009; Falla *et al.* 2011). During low intensity isometric contractions, pain provoked: (i) reduced motor unit (MU) discharge rate (Sohn *et al.* 2000; Svensson *et al.* 2000; Farina *et al.* 2004; Farina *et al.* 2005a; Farina *et al.* 2005b; Farina *et al.* 2008), (ii) recruitment of new MU populations (Falla *et al.* 2007; Tucker *et al.* 2009) and (iii) derecruitment of other MUs (Falla *et al.* 2007; Tucker *et al.* 2009).

Additionally, force steadiness is altered in the presence of pain, probably due to changes in the muscle activation strategies (Bandholm *et al.* 2008) of synergist muscles groups (Graves *et al.* 2000). Likewise, force steadiness was reduced in patients with knee OA (Hortobagyi *et al.* 2004).

Experimental pain reduces endurance time (Graven-Nielsen *et al.* 1997). The presence of experimental pain in the *tibialis anterior* muscle causes a reduction of the MVC in healthy subjects with pain intensity being significantly correlated to changes in the MVC (Graven-Nielsen *et al.* 1997). As the *tibialis anterior* muscle is the main ankle dorsiflexor, an inhibitory effect to the motoneurons might be responsible for the reduction in MVC. This however can be overcome when submaximal contractions are performed, as, extra motor units may be activated to compensate the inhibitory effect (Falla *et al.* 2007; Hodges *et al.* 2008; Tucker *et al.* 2009; Falla *et al.* 2011). Similar impairments were reported in female patients suffering from neck pain, which produced a lower peak torque when compared to a matched control group (Cagnie *et al.* 2007).

In dynamic tasks, decreased EMG agonist activity has been reported in presence of experimental pain for the *masseter* muscle during chewing (Svensson *et al.* 1996), *tibialis anterior* muscle during gait (Graven-Nielsen *et al.* 1997), *vastus medialis* muscle during a forward lunge (Henriksen *et al.* 2009) and

gait (Henriksen et al. 2009), *biceps brachii* muscle during elbow flexion (Ervilha et al. 2004; Ervilha et al. 2005) and *erector spinae* muscle during trunk extension (Zedka et al. 1999). When healthy subjects ascended and descended stairs following pain to the infrapatellar fat pad (Hodges et al. 2009), the quadriceps muscle group activity was altered. In general, these studies suggest that there is a dynamic reorganization of the muscle activity in order to minimize the use of the painful muscles/structures to perform a task. Such reorganization was also observed in chronic low back pain patients during coordination exercises in which a reduced EMG activity of the *multifidus* muscle was observed (Danneels et al. 2002). This reorganization might reflect the motor redundancy in the tasks, given by numerous degrees of freedom inherent to the assessed task (Latash et al. 2007) which, in the case of pain, reorganizes the muscle activation to avoid or reduce the pain sensation.

Although the mechanisms behind the sensory-motor interaction of pain sensation and motor control components have been extensively studied in the past few decades, the contribution of pain to motor commands during functional tasks, such as postural control, is still not entirely understood. It is likely that pain affects motor and postural control, leading to an increased likelihood of injury and falls.

4 Effect of Pain on Postural Control

Patient populations suffering from pain exhibit poor postural control compared to healthy subjects. Bouche (2006) compared the postural control in patients following lumbar discectomy with matched controls and demonstrated a larger COG sway in the patient group. Interestingly, the patient group reporting pain showed a tendency for larger COG displacements in comparison with the asymptomatic patient group. Knee OA patients suffering from pain showed greater postural sway than the age-matched control group (Wegener et al. 1997), which has been previously correlated with degenerative changes in the knee (Birmingham et al. 2001; Masui et al. 2006) and pain (Hassan et al. 2001) (with pain being strongly correlated with an increased sway in the ML direction (Hinman et al. 2002)). Further, patients suffering from chronic knee pain presented with a loss of ankle and knee muscle strength resulting in an increased risk of falls (Messier et al. 2002). Patients with work-related chronic neck pain and whiplash associated disorders showed impaired postural control during standing and following perturbations (Michaelson et al. 2003), with an increased sway area when compared to healthy subjects. Furthermore, closing the eyes and altering the BOS, increased the body sway in the patient group (Michaelson et al. 2003). In whiplash patients, perturbations evoked larger sway displacements in the AP direction suggesting a major impairment in the restoration of balance. Rambling components of the COP (Zatsiorsky and Duarte 1999) were also increased in whiplash patients during quiet standing, reflecting that patient populations are usually complex, with impairments to many different body structures. Confounding factors may interact with pain and affect the postural control; e.g. structural changes in the joint (Hurley et al. 1997; Wegener et al. 1997; McChesney and Woollacott 2000; Birmingham et al. 2001; Hinman et al. 2002; Masui et al. 2006), aging (Maki et al. 1994; Shumway-Cook et al. 1997; Prado et al. 2007; Duarte and Sternad 2008) and muscular strength (Hurley et al. 1997; Messier et al. 2002), etc. Therefore understanding the isolated effect of pain on the postural control of these patients is not practical. However, addressing the effect of muscle pain in healthy subjects means the changes due to pain can be observed. The following section will discuss the effect of pain on postural control.

4.1 Quiet standing posture and pain

Although the effect of triceps surae muscle pain on postural control has not been well documented, it is relevant given the importance of these muscles in postural control (Winter et al. 1996; Woollacott et al. 1998). The ankle, knee and hip joints act as synergists to the control of posture (de Freitas et al. 2009), however the ankle and foot joints are usually investigated during upright postural control. The knee joint also plays an important role in postural control (Iqbal and Pai 2000; Aramaki et al. 2001; Gage et al. 2004) although is rarely investigated in postural control studies. The effect of pain around the knee joint may provide new knowledge about impairments in the postural control of patients with knee OA (Wegener et al. 1997; Hinman et al. 2002; Messier et al. 2002).

Experimental pain models applied in previous studies and current showed that deep tissue pain around the knee, ankle and foot joints impairs the postural control in healthy subjects primarily due to alterations in sensorimotor processes (Study1; Study2; Study3; Blouin et al. 2003; Corbeil et al. 2004; Vuillerme and Pinsault 2009; Pradels et al. 2011). Despite this, a shift in attention due to pain might cause a loss of performance in the required task.

4.1.1 Quiet standing and attentional shift due to pain

Distraction from the task may occur due to the pain, leading to increase in the postural sway (Shumway-Cook and Woollacott 2000). If pain requires large part of the attentional capacity, less attention would be used for controlling posture (distraction), hence, increasing the postural sway.

Corbeil *et al.* (2004), Hirata *et al.* (Study1; Study2; Study3) and Pradels (2011) reported that attentional shifts due to pain do not modify the postural control during quiet standing. Corbeil *et al.* (2004) administered electrical pain to the dorsum of the foot which provoked an increase in the postural sway. In this study, an electrically induced painful stimulus was also applied to the heads of the metacarpals, provoking a similar amount of pain when compared to painful stimulus on the feet. This intervention demonstrated no impairment to the postural control indicating that the disturbance in posture was due to the stimuli applied to the dorsum of the foot. Hirata *et al.* (Study1) induced experimental pain

with a unilateral injection of hypertonic saline in either the *tibialis anterior* muscle, *medial gastrocnemius* muscle or both muscles (double injection). The double injection caused major changes in postural control, increasing postural sway in predominantly the ML direction. The other injection paradigms did not alter postural control, despite the amount of pain being significant larger than the control condition (and comparable to the double injection pain scores). If pain affects the postural control, all experimental trials with pain should cause impairments in body sway. Consequently, attentional shifts do not explain the impairments observed in these studies (Study1; Corbeil et al. 2004). This was shown in Study2 and Study3 in which the pain intensity was significantly higher than the control injections and although the injections induced similar pain intensities, only certain painful injection sites/conditions were able to impair the postural control in healthy subjects. Pradels (2011) also demonstrated impaired postural control when painful electrical stimulation was applied to the plantar surface of both feet compared to painful stimuli applied to the palms of both hands. Therefore, it is unlikely that attentional shifts due to pain were responsible for the postural impairment observed in that study (Pradels *et al.* 2011).

4.1.2 Quiet standing and sensorimotor impairments due to pain

Experimental pain may impair postural control via deficits to the sensorimotor mechanisms as suggested in the current (Study1; Study2; Study3) and previous studies (Blouin et al. 2003; Corbeil et al. 2004; Vuillerme and Pinsault 2009). In knee OA patients, the presence of pain has also been associated with impaired proprioceptive acuity in the knee joint (Hassan et al. 2001; Shakoor et al. 2008; Felson et al. 2009) leading to an unstable posture when compared to healthy subjects.

Effects of experimental pain under the feet and calf region during quiet standing

Representative data for COP measurements during simultaneous pain to the *gastrocnemius medialis* and *tibialis anterior* muscles (Study1) can be seen in Figure 4. The blue line represents the COP excursion and the red line represents the ellipse fitted to the data for analysis of the sway area. Figure 4 demonstrates a larger sway during quiet standing in presence of pain, during and after the perturbation.

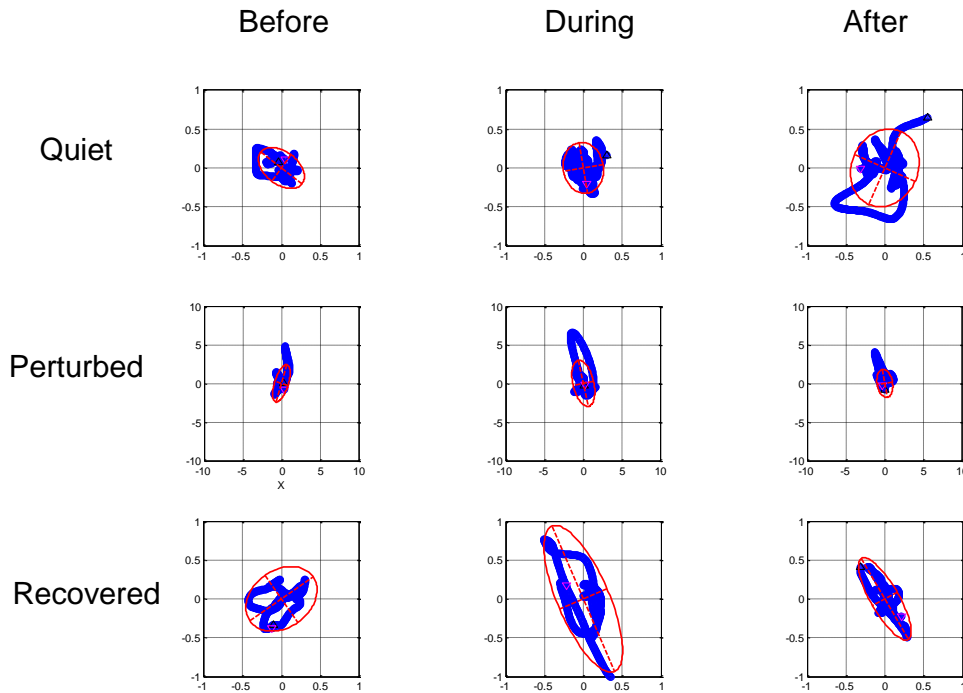


Figure 4: Representative trial of the center of pressure data (COP) for one subject before, during and after pain administered to both right *tibialis anterior* and *medial gastrocnemius* muscles. The red line represents the ellipse fitted to the data for analysis of the sway area. (Study1).

Electrical stimulation under both feet (Corbeil et al. 2004; Pradels et al. 2011) increased COP: (i) area, (ii) ML displacement, (iii) AP displacement and (iv) mean velocity when compared to baseline and control conditions. When compared to baseline and control conditions, cutaneous heat pain on both triceps surae increased COP in: (i) AP and ML oscillations and (ii) ML speed (Blouin et al. 2003). Experimental pain in the triceps surae muscles (Study1) increased the COP (i) ML speed and (ii) ML displacement. A summary of these results can be found in Figure 5.

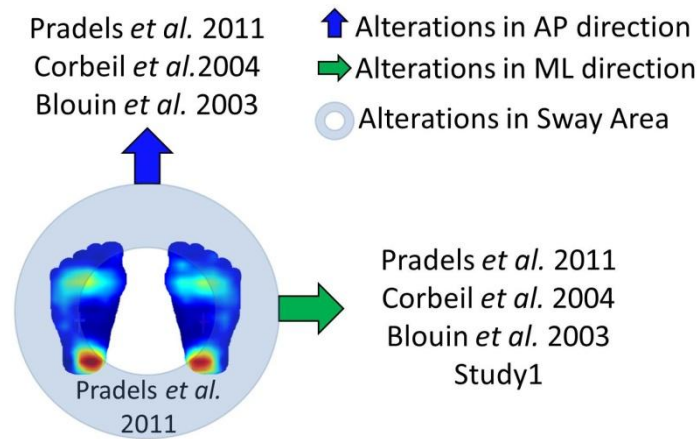


Figure 5: Summary of findings on effect of experimental pain under the feet and calf region during quiet standing. Increased sway in the anterior-posterior (AP) direction, medial-lateral (ML) direction and sway area were reported.

Study1 showed that only simultaneous injections to the *gastrocnemius medialis* and *tibialis anterior* muscles were able to impair postural control. This was demonstrated by an increased body sway speed in the ML direction with a shifting of body weight to the non-painful leg (Figure 6). Despite this, no difference in muscle activation was found during the different paradigms of calf muscle pain. An additional consequence of the asymmetrical weight-bearing was an increased pressure on different foot areas when compared to normal conditions (Study1). Figure 6 demonstrates that the pressure in the left rear foot was increased at the same time that pressure in the regions of the left foot was decreased (Figure 6). Compared to the baseline, pain in only the *tibialis anterior* muscle elicited higher pressure peaks in the rear foot region of the left foot during quiet standing (Table 2 from Study1).

This asymmetrical posture can induce compensatory musculoskeletal strategies (Sacco and Amadio 2000) and changes to the internal joint moments (Savelberg et al. 2009). This might result in alterations to the COP sway analysis as shown by a loss of postural stability.

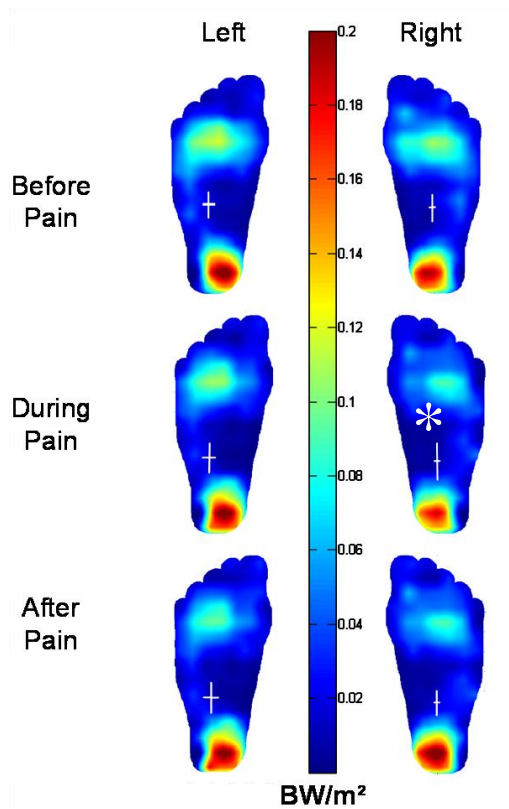


Figure 6: Mean foot pressure (n = 8) during quiet standing after the injection to the right *tibialis anterior* and *medial gastrocnemius* muscles. The mean (SEM) plantar centre of pressure position is represented by the white crosses. The pressure values were normalized to the body weight (BW) of the subject. The “*” indicates significant differences from the plantar COP position in the anterior-posterior direction in relation to the baseline condition (*, NK: P < 0.05) - (Study1).

Effects of experimental thigh muscles pain and experimental infrapatellar fat pad pain during quiet standing posture

Experimental pain around the knee muscles (Study2) and in the infrapatellar fat pad (Study3) induced larger COP sway area (Study2), greater ML COP displacement, higher COP speed in the ML direction (Study2; Study3), increased sway displacement in the AP direction (Study2) and increased sway speed in the AP direction (Study3). A summary of these results can be found in Figure 7.

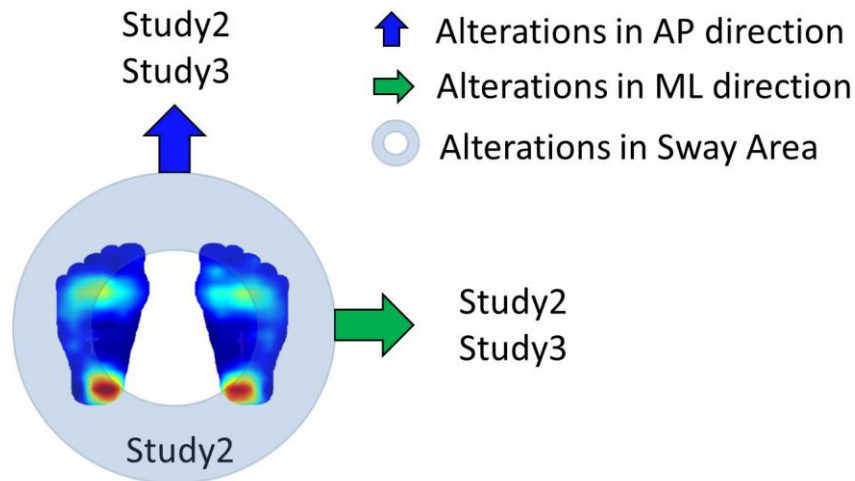


Figure 7: Summary of findings on effect of thigh muscles pain and experimental infrapatellar fat pad pain during quiet standing. Increased sway in the anterior-posterior (AP) direction, medial-lateral (ML) direction and sway area were reported.

In addition to regular EMG analysis in Study3, the absolute percentage difference in the integrated EMG (iEMG) between the pain and baseline conditions were extracted for each muscle (deltaEMG – Table2 from Study3) and were averaged for each subject (defined as total-deltaEMG - Figure 8). These indices can only distinguish between the overall difference according to the baseline condition but not an increase or decrease in the muscular activation. Simultaneous bilateral knee-related pain (Study3) inflicted larger impairments to postural control when compared to unilateral pain, with significant alterations in the EMG patterns (total-deltaEMG) of the lower limb muscles during quiet standing (Figure 8). Both *tibialis anterior* muscles showed significant changes in the deltaEMG during bilateral knee pain (Study3).

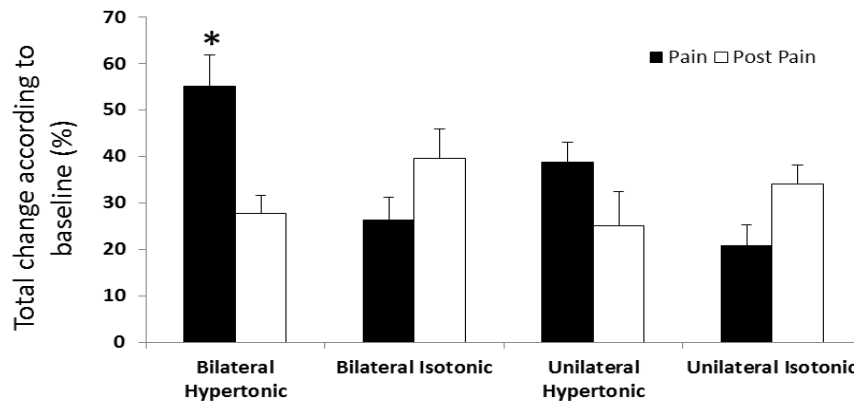


Figure 8: Mean (+ SEM, N = 9). Mean absolute muscular activation difference from baseline across all muscles during quiet standing. Bilateral knee pain inflicted larger changes in muscle activity when compared to control injection and post pain condition. Significantly different from the respective control injections (*, NK: $P < 0.01$) – (Study3). Zero % in the vertical axis indicates no difference between baseline and pain/post-pain conditions.

Unilateral pain administered to the infrapatellar fat pad induced a larger sway displacement in the medial-lateral direction (Study3). Despite this Bennell and Hinman (2005) reported no differences in the postural sway in healthy subjects with unilateral knee pain. In Study3, the subjects flexed both knees (on average, 6° for the right injected knee and 2° for the left knee) when comparing the pain and baseline sessions. Furthermore, the subjects unloaded the right knee (painful side), shown by the shift in the mean COP position in the ML direction (leading to an asymmetrical position - Figure 9). Asymmetry per se, has been shown to affect the COP amplitude and speed in both directions (Anker et al. 2008). No asymmetrical posture was reported by Bennell and Hinman (2005) which might explain the difference in the results from the current study (Study3).

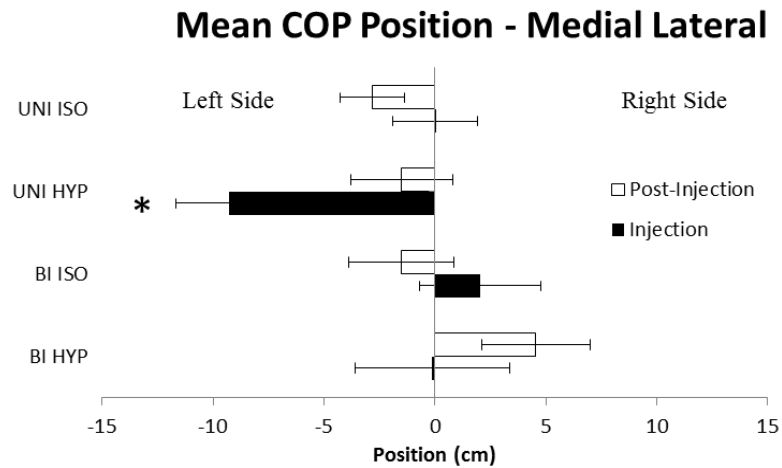


Figure 9: Mean (+ SEM, N = 12). The COP asymmetry is presented during quiet standing followed by an injection of hypertonic (HYP) and isotonic (ISO) saline in the infrapatellar unilaterally (UNI) and bilaterally (BI). Negative values demonstrate that subjects were leaning in relation to the baseline condition to the left side (and positive values to the right side). Significant differences from the respective baseline and control injections are shown (*, NK: $P < 0.01$) - (Study3).

Compensatory effects of experimental pain on postural control during quiet standing

Changes caused by painful injections (Study1; Study2; Study3) inflicted different postural impairments across subjects, which may reflect the complexity and adaptability of postural control.

The overall muscle activity changes observed in Study2 and Study3, supports the notion that the task performed (quiet standing) has multiple degrees of freedom, allowing the subjects to maintain posture using many different strategies. Altogether, the differences in muscle activation strategies indicates a complex mechanism of postural reorganization (compensatory), given the large variability in the muscular strategies used to maintain balance in the presence of pain in different structures.

For instance, complexity in the compensatory strategy was found during experimental pain in the infrapatellar fat pad (Study3), where no consistent increase or decrease in muscle activity was observed in any muscle when compared to baseline and control conditions, however, COP analysis showed greater postural sway in the ML direction with increased postural sway speed in both the AP and ML directions. In line, during quiet standing, experimentally when pain was induced in the knee extensor muscles (Study2) of the right leg caused an increased activity in the contralateral (left) *erector spinae* and in the contralateral *tibialis anterior* muscle. When absolute changes in muscle activation, in relation to the

baseline condition, were calculated (deltaEMG), significant changes in both *tibialis anterior* muscles were identified during bilateral knee-related pain (Table 2 from Study 3) where the muscle activity variation was approximately 62% for the right *tibialis anterior* muscle and 88% for the left *tibialis anterior* muscle in comparison to baseline recordings. These results show that during bilateral knee-related pain, the subjects altered both *tibialis anterior* muscle activation during quiet standing. This may be the reason that only bilateral pain affected sway in the AP direction, given that the *tibialis anterior* controls the sway in this direction (Winter 1995; Winter et al. 1996). Additionally, the subjects changed the total muscle activation (total-deltaEMG) by approximately 55% (average of all muscle changes) during the bilateral knee-related pain condition (Figure 8) in comparison to baseline values. These parameters indicate that subjects adopt different strategies in the presence of pain, however, these strategies are different across subjects as no specific trend (either increased or decreased muscle activity) was observed in any analyzed muscle (Study 3). The difference in the muscular activation may reflect different muscle strategies adopted in the presence of pain. Such strategies increased COP sway, reflecting a loss of postural stability when both knee regions are affected by pain, probably by proprioceptive impairment (Djupsjobacka et al. 1995b; Matre et al. 2002).

Another example of compensatory strategies was observed during pain in the right *tibialis anterior* (Study 1) and *biceps femoris* muscle (Study 2) during quiet standing. This demonstrated differences in peak pressure of the contralateral foot (Study 1) and increased muscle activity in the ipsilateral *vastus medialis* muscle (Study 2). Interestingly, none of these conditions affected the postural sway during quiet standing. The changes found in this situation may reflect a re-weight (compensatory) sensory strategy to optimize postural control (Oie et al. 2002) that aimed to increase the amount of information from the healthy leg and enhance the muscular output from the unimpaired leg to maintain postural control (Kuramochi et al. 2004).

In summary, postural control is probably impaired in presence of pain due to proprioceptive deficits (Djupsjobacka et al. 1995a; Djupsjobacka et al. 1995b; Matre et al. 2002). This was indicated by changes in the COP sway pattern (area, displacement and speed) when compared with baseline conditions

and control sessions. Pain altered the pressure distribution under the feet, articular positions and muscle activity. Asymmetrical posture was adopted in some painful conditions, reflecting a possible adaptation aiming to decrease the load on the painful limb. Such adaptations could explain the changes in the COP sway pattern in these particular conditions given the fact that shifting the body weight alters the COP sway pattern. The asymmetry found in these situations may partly relieve the pain, but may also reflect a re-weighting sensory strategy (compensatory) that optimizes postural control in altered sensory conditions. The re-weighting strategy enhances the gain from the proprioceptors situated in the non-painful leg, and increases the motor efficacy of the non-painful muscles. Furthermore, there are indications that pain might influence postural control due to proprioceptive deficits. The muscle control strategy during quiet standing was affected by pain across the subjects but without consistent changes in the activity of the muscles. Subjects reacted with different muscle activation patterns in the presence of pain to maintain balance. Although it was not possible to identify a unique strategy in the presence of pain, the overall motor output allowed the subjects to maintain balance. This is probably due to the large degrees of freedom inherent to the control of quiet standing, which allows many strategies to maintain balance. Another interesting finding is that applying pain closer to the knee joint reduces postural control during quiet standing. This indicates that the knee joint, and its respective muscles, may play an important role in postural control, although the majority of studies in this area focus on ankle and hip joints/muscles.

4.2 *Postural recovery after perturbations and pain*

To react precisely to an external perturbation during quiet standing, accurate proprioceptive input from the muscles and joints involved in the movement is crucial (Kavounoudias et al. 1999). Strategies to recover stability following a displacement of the COG in the sagittal plane have been previously described in the: (i) ankle and (ii) hip. These postural movement strategies are controlled by both feedforward and feedback mechanisms and enhance the postural recovery following perturbations. The feedback control causes the earliest neuronal responses to unpredictable perturbations; and the feedforward control attempts to prevent disturbance of the body prior to voluntary movements. These neuronal responses can be partly estimated by electromyography analyses, which reveal the muscle activation patterns (Figure 10). In this figure, a typical recording of the calf muscle is represented. Following the forward perturbation, the body leaned backwards. Less than 100 ms following the perturbation, the *tibialis anterior* muscle is activated to bring the body to the vertical reference position. Usually the body moves forwards, and final adjustments are necessary, therefore, the plantar flexor muscles activate, and bring the body to the vertical reference position.

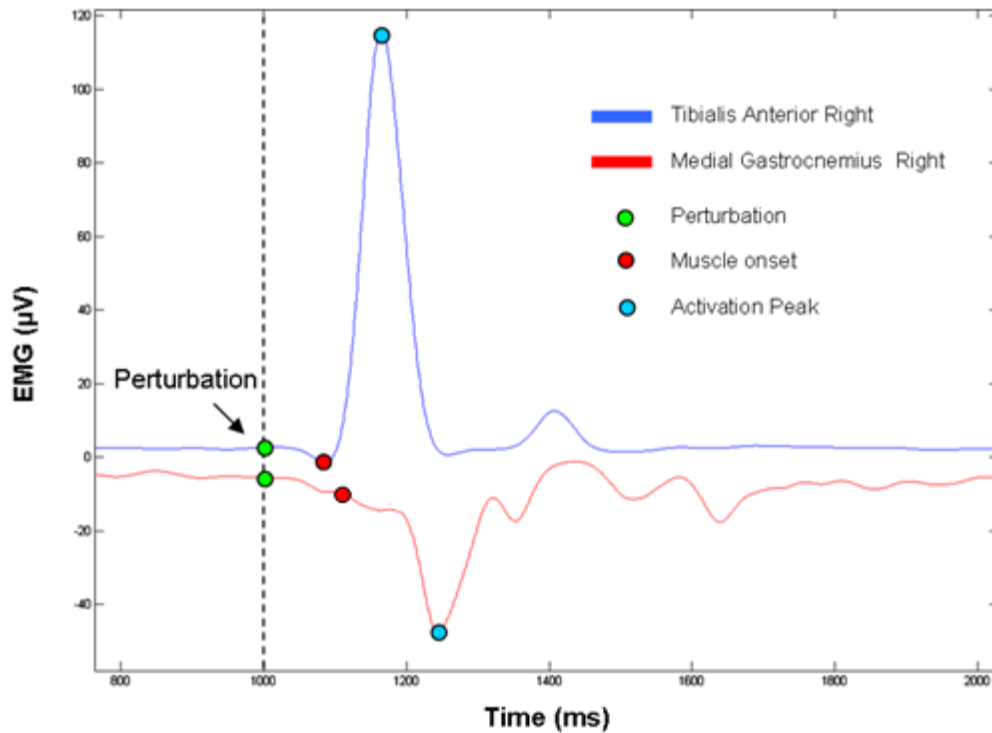


Figure 10: Illustrative EMG envelopes (band-pass filtered, full-wave rectified and low-pass filtered) during forward perturbations for *tibialis anterior* and *medial gastrocnemius* muscles of the right side for one subject. The green circles indicate the perturbation onset; red line circles indicate the onset and the blue circles represent the peak muscle activation. The onset latency and peak activation was extracted. The *medial gastrocnemius* is inverted (i.e. negative values) in this figure – (Study1).

The ankle strategy is mainly used when the perturbation is small (Horak and Nashner 1986). It is characterized by corrections in the postural alignment by movements of the ankle joint, although synergistic activation of the knee and hip muscles are fundamental for body stabilization using the ankle strategy (Horak and Nashner 1986). When the perturbations are larger and faster, the hip strategy is generally used to restore balance (Horak and Nashner 1986). The hip strategy allows for faster corrections when compared to the ankle strategy, and furthermore, it allows for larger displacements of the COG. The change in strategy is continuous and not abrupt. The subjects continue to increase the torques around the ankle joints until a critical point is achieved. Beyond this point, hip torques are generated to maintain the COG within the BOS (Horak and Nashner 1986). If these strategies are still unable to maintain balance, changes in the BOS are required, and therefore, an additional step must be taken (often called “the step strategy”). Additionally, the arms are used as a reaction against the perturbation and to maintain the COG within the BOS. If fast and small corrections are required, the arms are probably used to counteract the

perturbation rather than corrections around the ankle joint (Massion and Woollacott 2004). The momentum of inertia of the arms around the shoulder joint is reduced when compared with the momentum of inertia of the whole body around the ankle, which allows the system to execute faster corrections by moving the arms.

4.2.1 Changes in postural recovery due to floor translation and experimental pain in the lower limb

In Study1, 2 and 3, subjects stood on a movable force platform that could be translated quickly (Figure 11). At least 10 random translations of the force platform (backward and forward) were imposed with either a: (i) 2 cm displacement with a velocity of 50 cm/s (Study1), (ii), 5 cm displacement with a velocity of 50 cm/s (Study2), and (iii) 10 cm displacement with a velocity of 25 cm/s (Study3). The subjects were instructed to 'stand as quietly as possible' while looking at a fixed point (cross, 10 × 10 cm) located 4 meters in front of them. They were instructed to recover their balance as fast as possible following the perturbation, and were able to take a step if required. The smaller displacement used in the Study 1 aimed to produce adjustments mainly in the ankle joint (Horak and Nashner 1986). The displacement was increased by 3 cm in Study 2, to induce major postural adjustments at the joints closer to the pain site (knee and hip joints). In Study 3, a slower velocity and larger displacement was used in order to generate similar perturbations to those used by Bennell *et al* (2005), as injection of hypertonic saline in the infrapatellar fat pad, was also used. However, contrary to the study by Bennell *et al* (2005), bilateral injections to examine the effect of the non-painful leg on recovery of posture. The perturbation speed and translation displacement was set to provoke postural responses to better investigate the pain-related hypothesis of each study.

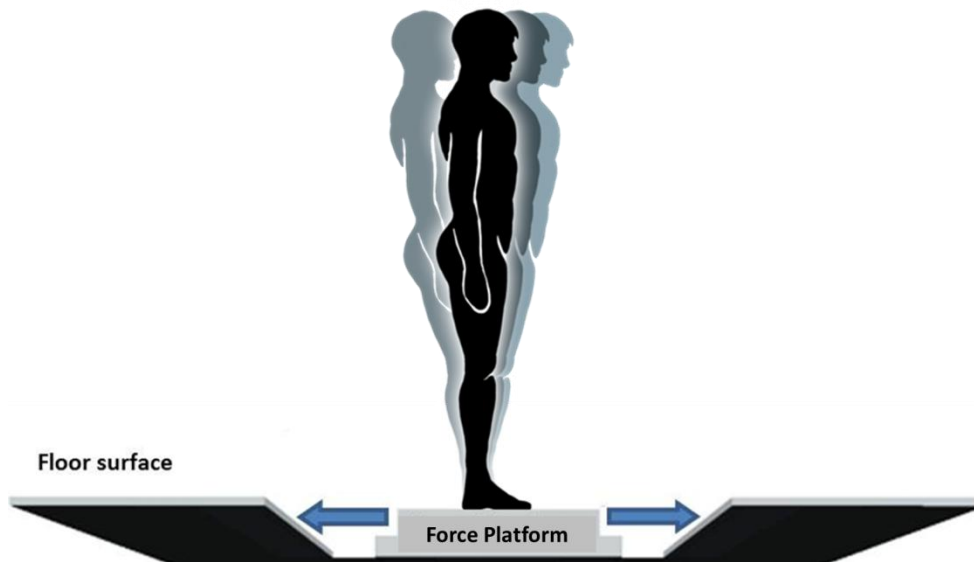


Figure 11: Experimental setup illustrating the movable force platform used to record the ground reactions forces and torques which moved randomly and unexpectedly in either the forward or backward direction (as indicated by the blue arrows).

Subjects reacted differently depending on the perturbation direction. Pain did not elicit changes in the analysed variables when the body was perturbed backwards for any of the conditions analysed in the three studies, while the reactions against forward perturbations were affected in most of the pain conditions. Simultaneous pain in both *tibialis anterior* and *lateral gastrocnemius* elicited a higher mean sway displacement in the ML direction (Study1) and a larger sway area after the body returned to the equilibrium position (Study1). The presence of pain in the *vastus medialis*, *vastus lateralis* and *biceps femoris* was associated with a longer return time to the equilibrium point during the perturbation. This might reflect an inefficient strategy compared to the one adopted in the baseline and control situations.

In line with Bennell and Hinman (2005), following floor perturbations (forward and backward), no differences were found in the postural responses during experimental knee pain (Study3). This may be due to the reduced perturbation speed applied in both studies. The high perturbation speeds applied in Study1 and Study2 showed impairments in the postural recovery in the presence of pain, indicating that the perturbation speed affects the postural responses. Furthermore, during pain, the reaction time for the

right *tibialis anterior* muscle was shorter during the painful conditions in the *vastus medialis* and *biceps femoris muscles* compared to before and after pain (during forward perturbations (Study2)).

Possible reasons for the non-significant difference in the COP data after the unexpected backward perturbation during calf muscle pain (Study1), leg muscle pain (Study2) and knee pain (infrapatellar fat pad pain) (Study3; Bennell and Hinman 2005) may be because the (i) main corrections against this perturbation occurred in muscles distant to the injection site, reflecting that the subjects adopted different strategies in the presence of pain to maintain balance, and (ii) proprioceptive information from the synergistic and antagonistic muscles from the non-painful limb, provide enough information for the central nervous system to generate accurate responses to the perturbation and/or (iii) compensatory adjustments in the non-painful muscles are more efficient against backward perturbations than forward perturbations.

Anticipatory strategies have been shown to decrease the EMG onset latency during perturbations (Koike and Yamada 2007) and reduce postural destabilization following the perturbation (Kuramochi et al. 2004). During pain in the calf muscles and infrapatellar fat pad, no differences in the muscle activation were observed. However, during forward perturbations, the reaction time for the right *tibialis anterior* muscle was reduced during painful conditions of the *vastus medialis* and *biceps femoris muscles* when compared to the before and after pain conditions (Study2). This suggests a possible strategy aiming to compensate the effects of pain in the leg muscles, enhancing the efficacy (Kuramochi et al. 2004) and decreasing the reaction time (Koike and Yamada 2007) of the *tibialis anterior* muscle (which is one of the main muscles responsible to provide postural corrections after forward perturbations (Horak and Nashner 1986)).

The presence of pain in the knee extensors (*vastus medialis* and *vastus lateralis*) and *biceps femoris* muscles increased the latency for subjects to return to the equilibrium point. This may indicate that, in presence of pain, the muscles are unable to provide the same motor output compared to when the system is pain free. Similar to the quiet standing task, it was not possible to identify a common muscular

strategy used to recover posture after the perturbation. Again, the subjects could combine different muscular strategies to restore balance, making it difficult to identify common strategies between subjects under different conditions. However, in line with the results obtained in quiet standing, pain in the muscles around the knee joint evoked more changes to parameters than those around the ankle joint. These results reinforce the importance of the knee muscles in postural control following perturbations.

Following pain to the *vastus medialis* muscle, subjects reached the maximal hip flexion earlier when compared to the other conditions during forward perturbations. The *vastus medialis* muscle is often related to the knee stability and the presence of experimental pain in the infrapatellar tissue causing an altered activation during functional tasks (Hodges et al. 2009), possibly leading to an unstable joint. The knee joint instability combined with the unexpected perturbation requires the use of the “hip strategy” over the “ankle strategy”. The reduced time for maximum hip flexion, observed in the Study2, would allow faster postural corrections after the perturbation when compared to the postural corrections obtained by torques around the ankle (Horak et al. 1989).

In summary, postural control following forward perturbations was impaired in the presence of deep-tissue pain, shown by alterations in the COP sway pattern (displacement and speed) when compared to the baseline and control sessions. No impairments in the postural sway recovery were observed following backward perturbations. Furthermore, injections within the infrapatellar fat pad did not impair the postural control following perturbations in any direction. Pain in the knee extensors altered the muscle onset latency (earlier onset), possibly reflecting an anticipatory strategy to reduce postural destabilization after the perturbation. This might demonstrate the importance of these muscles in postural stabilization. Previous studies have shown that nociceptive stimulation affects muscle activity (Travell et al. 1942; Jovanovic et al. 1990; Mense and Skeppar 1991; Djupsjobacka et al. 1995a; Djupsjobacka et al. 1995b; Matre et al. 1998; Matre et al. 1999; Capra and Ro 2000; Ro and Capra 2001; Thunberg et al. 2002; Masri et al. 2005; Birznieks et al. 2008), muscle sensitivity to stretches (Cobb et al. 1975; Elert et al. 1989; Graven-Nielsen et al. 1997; Andersen et al. 2000; Ro and Capra 2001), motor unit discharge (Sohn et al. 2000; Farina et al. 2004; Farina et al. 2005a; Farina et al. 2005b; Farina et al. 2008) and reorganization of

motor unit activation (Falla et al. 2007; Hodges et al. 2008; Tucker et al. 2009; Falla et al. 2011), which subsequently affects the desired motor output to restore balance following perturbations.

5 Proposed overall model of pain on postural control

The alteration in postural control due to pain is site and area (size of the pain area) dependent and leads to multidirectional alterations (anterior posterior and medial lateral) in all lower limb joints (ankle, knee and hip). More specifically, the knee joint and associated muscles were important in controlling postural control during both quiet standing and following perturbations.

One of the possible reactions of the system during pain is to re-weight the sensory information, increasing the gain of information and enhancing efficacy from the healthy structures and decreasing the information from the affected areas.

Not all pain conditions presented induced postural impairments. However, postural control seems to be more affected by pain in knee extensor muscles and infrapatellar fat pad than pain around the *medial gastrocnemius* muscle and *tibialis anterior* muscle, which demonstrates the importance of the knee joint in postural control. Despite this, currently models mainly focus on the ankle and hip joint, hence, models accounting for all lower limb joints would provide a better understanding of the mechanisms underlying the postural control in an altered sensory environment. Therefore, a reasonable next model in postural studies and pain would be to increase the understanding of the contribution of the knee structure to postural control (joint displacement, and internal forces and torques), especially after perturbations.

6 Future Perspectives

The experimental pain model applied in this thesis demonstrates unique findings by isolating the effect of pain in different structures in relation to control and baseline conditions (since it was applied in healthy subjects with no other impairments) during quiet standing and following unexpected perturbations. It provides a well-controlled design to evaluate the effects of pain during motor control. However, translational studies linking the experimental findings with real patients are necessary.

A straightforward translational study based on the results of this thesis is the evaluation of knee OA patients, which despite the localized pain around the knee joint, show alterations in muscle strength, structural changes in the bone and impaired muscular coordination, which combined with aging effects, possibly increases the likelihood of falling (subsequently decreasing life quality).

One important hypothesis raised based on this thesis, is the possibility that the healthy system is able to re-weight the sensory information during postural control. Stimulation of group III and IV afferents might affect proprioception, which may inaccurately inform the position of the segment in pain. Given that standing is a static task, it would be desirable to suppress the impaired information from the side/region of pain, as it may provide inaccurate proprioceptive information, and enhance the gain of information from the structures without pain.

The interactions of the sensory system (visual, somatosensory and vestibular) in knee pain patients are still controversial in the literature. After identifying how these patients use sensory information, it is worth to investigating the possibility of reeducating these patients by re-weighting the sensory information from healthy structures through appropriate training/rehabilitation programs aiming to increase muscle coordination and gain. For example, a systematic review by van Grinsven (2011) concluded that rehabilitation approaches in patients following anterior cruciate ligament rupture (where the part of the proprioceptive information coming from the ruptured ligament is lost), should include coordination (neuromuscular control) exercises. Neuromuscular control exercises applied in the

rehabilitation process could enhance the coordination between the lower limb muscles, increase stability in the joint and decrease the likelihood of further injuries to the knee (van Grinsven et al. 2011)

Similar interventions would make it possible to evaluate the postural control in knee OA patients, helping clinicians to improve training/rehabilitation procedures, enhance postural control and decrease the related injuries/problems caused by (for example) falls.

7 Conclusion

A large painful area from the calf muscles resulted in reduced postural stability in predominantly the ML direction, increased the foot pressure on the non-painful side, and provoked displacements of the plantar foot pressure below the ipsilateral foot. The postural sway during quiet standing and the postural recovery after perturbations were both impaired by the presence of calf muscle pain. The results also support the importance of knee joint movement during postural control in the presence of pain. Pain in the knee extensor muscles impaired postural sway during: (i) quiet standing (larger and faster postural sway, higher activation on non-painful limb muscles), and (ii) unexpected forward perturbations (longer time to reach an equilibrium position). Additionally, the results obtained from the infrapatellar fat pad pain model support the importance of information from the non-painful knee joint in the control of quiet standing in the presence of pain.

Together, these results suggest that pain in the lower limb reduces postural stability and potentially increases the likelihood of falling. A better understanding of these pain related adaptive strategies has important clinical implications as these strategies increase the likelihood of implementing inadequate motor control strategies which may lead to further damage/injuries. Generally, the results suggest that clinical approaches to reduce pain may lead to improvements in balance, especially in people with knee pathologies, such as OA.

8 Summary

Pain around the knee joint is one of the most common pain conditions in the elderly. This potentially causes impaired knee proprioception and postural stability which consequently leads to an increased risk of falls. However, the effect of pain on postural control is not well understood in patients as it is a complex system with many confounding factors (apart from the pain itself).

The confounding factors cannot be experimentally excluded in these populations. However, knowledge about the effect of pain on postural control in this population is required given that this knowledge would improve the actual training/rehabilitation programs applied in this population.

Experimental pain applied to healthy subjects allows understanding of the effect of pain without the interference from confounding factors present in the patient populations. In the present work, experimental pain was applied in different regions on the lower leg of healthy subjects, and the behavior during quiet standing and reactions after unexpected perturbations were evaluated.

A summary of the results can be found in Figure 12. Injection of hypertonic saline was applied to the calf muscles (Study 1), leg muscles (close to the knee joint, Study 2) and infrapatellar fat pad (Study 3) of healthy subjects who were asked to keep as quiet as possible looking at a target 4 meters ahead. The subjects were asked to recover their upright posture as fast as possible after receiving the perturbation and could take a step if required. A movable force platform was used to measure the center of pressure excursions (COP) and to provide random forward or backward perturbations. Bipolar surface EMG electrodes were used bilaterally to measure the muscle activity from the lower limb muscles and estimate the muscle response onset latencies following the perturbations. Plantar pressure insoles were used to estimate the plantar pressure beneath the feet (Study 1 and 2) and kinematic data from the lower limb segments was acquired to quantify the angular position, displacement and velocity (Study 2 and 3).

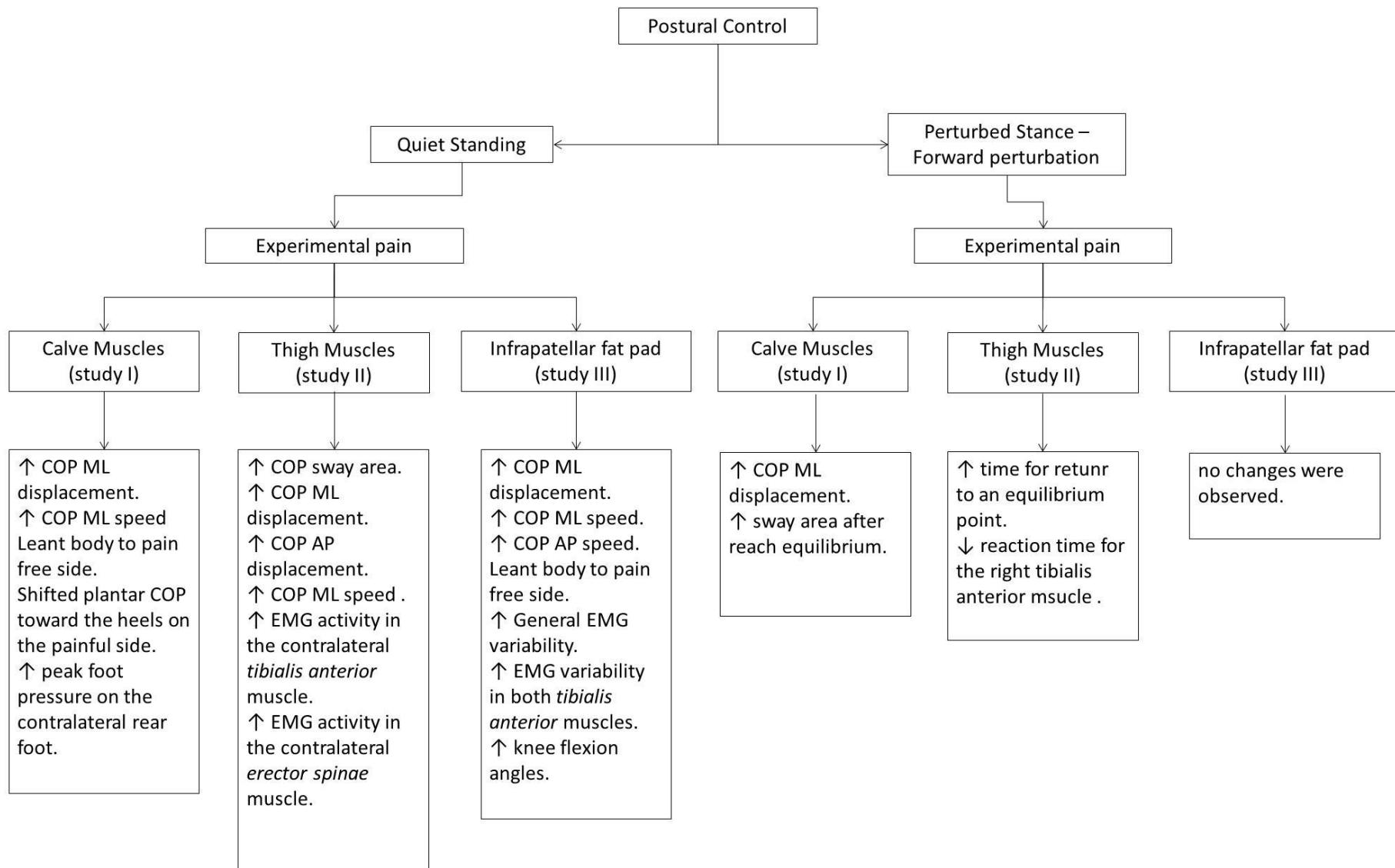


Figure 12: Summary of the effect of pain on postural control during quiet standing and after forward perturbations. Changes in the center of pressure (COP) parameters in both medial-lateral (ML) and anterior-posterior (AP) direction were identified in the presence of pain, with changes in electromyography (EMG).

Pain around the ankle joint (Study1) increased the COP speed and displacement in the ML direction, shifted the body weight to the non-painful leg, changed the plantar COP under the ipsilateral foot and increased the peak foot pressure on the ipsilateral rear foot. Experimental pain in the muscles around the knee (Study2) and infrapatellar fat pad (Study3) induced larger COP sway area (Study2), greater ML COP displacement (Study2; Study3), higher COP speed (Study2; Study3), increased sway displacement in the AP direction (Study2), increased EMG activity for left *tibialis anterior* and left *erector spinae* muscles (Study2), increased overall variability in the muscle activity (Study3) and increased knee flexion angles (Study3).

Analysis of postural strategies after perturbations, showed that simultaneous pain in the *tibialis anterior* and *lateral gastrocnemius* elicited higher mean sway displacements in the ML direction (Study1) when compared to baseline and control conditions. In addition, the presence of pain in the *vastus medialis*, *vastus lateralis* and *biceps femoris* was associated with a longer return time to the equilibrium point during the perturbation (Study2) which reflects an inefficient strategy compared to the one adopted in the baseline and control conditions.

The results suggest that pain in the lower limb decreases postural stability during quiet standing and after perturbations. Such instability may increase the likelihood of falling by the deleterious effect of nociception on the movements responsible to maintain stability. Increased speed and displacement of the COP suggest that the body sway is larger and faster when compared to non-painful conditions both during quiet standing and after perturbations. The closer the pain to the knee joint, the greater the influence the pain had on the postural stability, suggesting that the knee joint may play an important role in controlling posture. Larger variability in muscle activation patterns was identified, indicating that the subjects used different strategies during pain. Despite this they continued to maintain balance in all conditions demonstrating a possible redundancy in the postural system. However, the impairments observed in presence of pain indicate that the muscle strategies used cannot provide the same stability as the strategies adopted prior to pain. Such non-optimal strategies used in the presence of pain, probably increase the likelihood of destabilization of the body, which may lead to further damage/injuries and subsequent pain.

Hence, clinical approaches to reduce pain may lead to improvements in balance especially for people with knee pathologies such as OA.

9 Dansk Sammenfatning

Smerte omkring knæleddet er en af de mest almindelige smertetilstande hos den ældre befolkning. Dette medfører blandt andet nedsat proprioception i knæet og nedsat holdningsstabilitet, hvilket kan give en øget risiko for at falde. Smertens indflydelse på patienternes positur er dog ikke velbeskrevet fordi der er tale om et komplekst system med mange influerende faktorer (udover selve smerten). Alle de påvirkende faktorer kan ikke beskrives ved patientundersøgelser. Specifik viden om smertens indflydelse på postural kontrol er nødvendig for at kunne forbedre trænings/rehabiliterings-programmer for disse patienter.

Ved at påfører raske personer eksperimentel smerte er det muligt at undersøge effekten af smerte uden sammenblanding med de øvrige influerende faktorer hos patienterne. I de indeværende studier påførtes eksperimentel smerte i forskellige regioner af underbenet hos raske forsøgspersoner, og efterfølgende evalueredes effekten på den posturale kontrol når forsøgspersonerne stod stille samt efter uventede påvirkninger (perturbering).

En sammenfatning af resultaterne kan ses i Figur 10. Hypertont saltvand blev injiceret i lægmusklerne (Studie 1), lårmusklerne (tæt ved knæleddet, Studie 2), og i den infrapatellære fedtpude (Studie 3) hos raske forsøgspersoner der blev instrueret i at stå så stille som muligt mens de fastholdt visuel kontakt på et punkt 4 meter foran dem. Forsøgspersonerne blev desuden bedt om at holde balancen og finde tilbage til deres opretstående position hurtigst muligt efter perturbationerne. En bevægelig kraftplatform blev anvendt til at måle ændringer i trykcenteret (COP), og til at påfører perturbationer tilfældigt (frem eller tilbage). Bipolære overfladeelektroder blev brugt til at måle muskelaktiviteten på begge ben, og til at estimere forsinkelsen i muskelresponsen efter perturbationerne. Trykindlæg under fødderne blev anvendt til at estimere plantartrykket under fødderne (Studie 1 og 2) og kinematiske data blev opsamlet fra segmenter af underbenene for at kvantificerer vinkelposition, forskydning, og hastighed (Studie 2 og 3).

Smerte omkring knæleddet (Studie 1) forøgede COP hastighed og forskydningen i medial-lateral retning, forskød kropsvægten til det ikke-smertefulde ben, ændrede plantar COP under foden på det

smertefulde ben, og øgede det maksimale tryk under hælen på det smertefulde ben. Eksperimentel smerte i musklerne omkring knæet (Studie 2) og i den infrapatellære fedtpude (Studie 3) medførte et større COP svajningsområde (Studie 2), større medial-lateral COP forskydning (Studie 2; Studie 3), højere COP hastighed (Studie 2; Studie 3), øget anterior-posterior svajningsforskydning (Studie 2), øget aktivitet i venstre tibialis anterior og erector spinae muskler (Studie 2), øget absolut variation i muskelaktiviteten (Studie 3), og øget knæledsvinkler (Studie 3).

Analyse af forsøgspersonernes posturale strategier efter perturbation viste at samtidig smerte i tibialis anterior og lateral gastrocnemius musklerne medførte en forøget medial-lateral svajningsforskydning (Studie 1) i forhold til ikke smertefulde kontrolmålinger. Muskelsmerte i vastus medialis, vastus lateralis, og biceps femoris var desuden forbundet med en forøget tid som forsøgspersonerne brugte til at vende tilbage til udgangspositionen efter perturbationerne (Studie 2), indikerende en ineffektiv strategi sammenlignet med den som avendes før påvirkningen af smerte samt under kontrolmålingerne.

Resultaterne antyder at smerte i benet medfører nedsat postural stabilitet ved opretholdelsen af en stillestående position og efter perturbation. Denne ustabilitet kan øge risikoen for at falde på grund af smertens (nociceptiones) påvirkning af de bevægelser, som er ansvarlige for at vedligeholde stabilitet. Den øgede hastighed og forskydning af COP tyder på at kroppen svajer mere og hurtigere end under ikke-smertefulde tilstande, både når personen står stille og når vedkommende udsættes for uventede perturbationer. Jo tættere smerten var på knæleddet desto større indflydelse havde smerten på den posturale stabilitet, hvilket tyder på at knæleddet spiller en vigtig rolle for kontrollen af kropsholdning. Der blev fundet større variation i muskelaktiveringsmønstrene under smerte, hvilket indikerer at forsøgspersonerne anvendte andre strategier under smerte. På trods af dette bevarede forsøgspersonerne balancen under alle tilstande, hvilket viser en redundans i det posturale system. Forringelserne af den posturale stabilitet, som blev observeret under smerte, tyder dog på at de ændrede muskelstrategier ikke kan sikre samme stabilitet, som de strategier der anvendes, når forsøgspersonerne ikke føler smerte. Sådanne ikke-optimale strategier i forbindelse med smerte øger formentligt sandsynligheden for at

destabilisere kroppen, hvilket kan føre til yderligere skader/uheld og deraf følgende smerte. Det er derfor sandsynligt at smertebehandling af patienter (f.eks. OA knæ) kan forbedre deres balance evne og stabilitet.

10 Table

The studies presented in the Table 1 have developed methods used in this thesis to quantify the postural stability and motor control strategies during quiet standing and following perturbations using force plates, electrical goniometers, EMG and plantar pressure insoles. Table 1a shows experiments performed on healthy subjects in which different approaches were used to analyze the postural control and the effect of different sensory information on the control of postural sway during quiet standing and after perturbations. Table 1b demonstrates studies applying the methods in Table 1a using different patients groups, addressing the effect of specific diseases on postural control, such as osteoarthritis, parkinson and diabetics patients. In addition, studies on elderly people and people with total knee replacement have been included in the Table 1c is a composite of the studies available in PubMed (www.pubmed.com) dating from February 2011 regarding the effect of experimental pain on quiet standing and the recovery of posture following perturbations in healthy subjects. In general, the results suggest impaired postural control in presence of pain. Increased COP displacement and speed in both medial-lateral and anterior-posterior direction has been reported in patient groups and healthy subjects exposed to experimental pain. In particular, knee OA patients presented with impaired muscle strength, sensorimotor deficit, decreased postural stability and deterioration of performance during functional activities.

Table 1: Postural control studies in the literature based on knee OA, pain, perturbation, EMG, kinetic and kinematic parameters

Table 1a (Healthy Subjects)

Reference	Parameters	Population	Pain Protocol	Perturbation	Main Finding
Horak and Nashner (1986)	- Muscle activity - kinematics - kinetics	Healthy		√	Identification of ankle and hip strategies. Characterization of ankle and hip strategies.
Horak et al (1989)	- Muscle activity - kinematics - kinetics	Healthy		√	Effect of expectation on ankle torques prior to perturbation. Experience affected postural responses.
Burleigh et al (1994)	- Muscle activity - kinematics - kinetics	Healthy		√	Automatic responses to perturbation is not general, but specific to the task. Central commands may alter neuronal excitability prior pert.
Hlavacka et al (1995)	-kinetics	Healthy		√	Proprioception from muscles around the ankle and vestibular information play important roles in the estimation of the internal representation of the body, therefore altering posture
Inglis et al (1995)	-kinetics - kinematics	Healthy		√	Vestibular information: has a large influence on postural control following perturbations.
Winter et al (1996)	-kinetics	Healthy			Ankle torques are primarily responsible for controlling sway in the A/P direction and hip torques in the M/L.

Hlavacka et al (1999)	-kinetics	Healthy		√	Vestibular information may be more involved in interpreting sensory information during body movement, than triggering postural responses.
Runge et al (1999)	- Muscle activity - kinematics - kinetics	Healthy		√	Ankle and hip strategies were confirmed by internal joint torque estimation. Different perturbation velocities induced different motor responses.
Zatsiorsky and Duarte (1999)	- kinetics	Healthy			The concepts of instant equilibrium point (IEP), rambling and trembling were introduced, which represents different Control of quiet posture.
Pai et al (2000)	- kinetics - kinematics	Healthy		√	Correlation between postural stability is and COM position and velocity in relation to the BOS
Henry et al (2001)	- Muscle activity - kinematics - kinetics	Healthy		√	- no difference in latency between narrow and wide stance - wide stance showed less EMG activity - greater hip and sway displacement with a larger stance width
Duarte and Zatsiorsky (2002)	- kinetics	Healthy			- Increased sway area and frequency when subjects leant the body - Visual information is used to control the reference position and to adjust the body over time
Oie et al (2002)	-kinematics	Healthy		√	- sensory re-weighting is a dynamic variable dependent upon stimulus amplitude that enhances balance under conditions where sensory information are impaired
Latash et al (2003)	- kinetics	Healthy			- Larger ML sway during voluntary COP shift than AP sway.
Duarte and Freitas (2005)	- kinetics	Healthy			accuracy of fast voluntary postural movements is reduced due to the variability of sway during standing.

Mochizuki et al (2006)	- kinetics	Healthy			- increased postural sway in the ML direction was related to the dimensions of the support area. Impairments in the ML direction was larger than in the AP direction.
Duarte and Latash (2007)	- kinetics	Healthy			- speed-accuracy trade-off in a tasks with postural adjustments originates at the movement planning level
de Freitas et al (2009)	-kinematics -kinetics	Healthy			- increased sway in both ML and AP direction during immobilization of lower limb joints. - Inverted pendulum model not applied.

Table 1b – Patient groups

Kantner et al (1991)	- kinetics	Patients with dizzines			Eyes open + foam condition elicited greater sway displacement in the anterior/posterior direction.
Maki et al (1994)	-kinetics	Elderly		√	Lateral stability was significantly different between fallers and non-fallers, indicating possible biomarkers for risk of falling.
Mitchell et al (1995)	-kinetics	Parkinson			Parkinson patients have impaired postural sway in the medial-lateral direction.
Hurley et al (1997)	- kinematics -kinetics	Knee OA patients			Quadriceps sensorimotor deficits, decreased postural stability and the deterioration of functional performance.
Shumway-Cook et al (1997)	-kinetics	Elderly fallers			Cognitive tasks impaired postural control in elderly fallers, indicating the attentional demand in this population during quiet standing posture.
Wegener et al (1997)	-kinetics	Knee OA patients		√	Greater postural sway in the patient group, indicating an impaired postural control in patients suffering from knee OA.
Immisch et al (1999)	-kinematics	Parkinson		√	Parkinson patients showed increased hip sway during unpredictable perturbations, reflecting an impaired reactive response in these patients.
McChesney and Woollacott (2000)	- kinetics - threshold joint position sense (TJPS)	Total knee replacement		√	Poor TJPS for both knee and ankle was associated with poor balance.

Birmingham et al (2001)	- knee proprioception - kinetics - Radiographic	Knee OA patients			Balance was correlated with degenerative changes. No correlation between knee proprioception and degenerative changes/ standing balance control.
Dickstein et al (2001)	- kinetics	Diabetic patients			Fingertip light touch reduced postural sway in diabetic patients. Reduction was associated with the force of touch.
Hassan et al (2001)	- knee proprioception - Quadriceps strength - kinetics	Knee OA patients			Subjects with knee OA sway more in both AP and ML directions, Reduced proprioception and extension force. Pain and MVC/body weight are predictors of impaired sway
Horak and Hlavacka (2001)	- kinetics - kinematics	Diabetic patients		√	- patients showed larger sway after galvanic stimulation - stimulation affected the trunk segment primarily, suggesting that the vestibular system may control postural orientation via trunk
Hinman et al (2002)	- swaymeter - step test	Knee OA patients			- Increased total sway in OA group, increase AP sway in OA while eyes closed, greater ML sway with eyes open and less steps in 15 seconds. Pain was associated with increased ML sway.
Messier et al (2002)	- knee/ankle strength - kinetics	Chronic knee pain			- after 30 months, weaker knee patients had larger sway impairments - knee and ankle strength declined after a 30 month period. - increased risk of falling
Hlavacka and Horak (2006)	- kinetics - kinematics	Diabetic patients		√	- Somatosensory loss due to diabetic neuropathy and alteration of somatosensory input during stance on translating support surface resulted in increased vestibulospinal sensitivity.

Masui et al (2006)	- Radiographic - kinetics	knee OA patients			- Radiographic OA was correlated with increased postural sway. - OA group showed greater postural sway than control groups
Prado et al (2007)	- kinetics	Elderly			- decreased postural control with aging, with increased postural sway in the AP direction with eyes closed.
Anker et al (2008)	- kinetics	middle-aged			- Voluntary asymmetry increased sway in the ML direction.
Duarte and Sternad (2008)	- kinetics	Older Adults			- higher sway complexity in older adults
Madeleine et al (2010)	-kinetics	Whiplash			- increased sway amplitude and decreased complexity

Table 1c – Healthy Subjects and Experimental Pain

Blouin et al (2003)	- kinematics	Healthy	√	√	- heat pain and vibration stimuli were applied in the calf muscles - impairments in both directions was observed - vision did not improved balance
Corbeil et al (2004)	- kinetics	Healthy	√		- increased body sway with increased pain intensity. - pain locus importance
Bennell and Hinman (2005)	- kinetics	Healthy	√	√	- no impairment after experimental pain.
Vuillerme and Pinsault (2009)	-kinetics	Healthy	√		- sway impairment in both directions following painful Electrical stimuli in the trapezius muscle.
Pradels et al (2011)	-kinetics	Healthy	√		- Negative effect of bilateral electrical stimuli under the feet. - increased COP displacement.

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