

Patellofemoral Pain Syndrome

*Studies on a treatment modality, somatosensory function,
pain and psychological parameters*

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Doctoral thesis

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Foreword:

“While the individual man is an absolute puzzle, in the aggregate he becomes a mathematical certainty. You can, for example, never foretell what any one man will do, but you can say with precision what an average number will be up to. Individuals vary, but percentages remain constant.”

Ref: Sherlock Holmes, in The Sign of Four

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Abstract

Patellofemoral pain syndrome (PFPS) is characterized by long-term diffuse peripatellar and retropatellar localized pain in one or both knees, which worsens during walking uphill or downhill, squatting, kneeling, or prolonged sitting with flexed knees. There is no consensus in the medical literature concerning the definition, aetiology or diagnosis of PFPS. In this thesis PFPS is described as anterior knee pain excluding intra-articular pathology, peripatellar tendonitis and bursitis. Clinical tests used to diagnose PFPS lack acceptable reliability and validity, and radiographic findings in diagnosing PFPS are inconclusive. These limitations need to be addressed given that PFPS is a common musculoskeletal complaint, especially among adolescents and young active adults. The main purpose of the studies described in this thesis was to determine possible pain mechanisms in PFPS patients and to suggest a suitable treatment modality.

The first study reported in the thesis was a randomized clinical trial involving the treatment of 36 PFPS patients with sensory stimulation by 8 acupuncture treatments. The control group consisting of 34 PFPS subjects did not receive any treatment. The two groups did not differ at baseline. The Cincinnati Rating System questionnaire was used as the main outcome measure. The results show that the Numbers Necessary to Treat (NNT) was 3.2 to achieve *no pain* or *occasional pain to strenuous sports* at the 12-month follow-up, and 3.7 to achieve *no functional limitations* or *some limitations to heavy labour*, in favour of the acupuncture group. Hence, sensory stimulation by acupuncture is recommended as a treatment modality to improve pain and function in PFPS patients.

The second study assessed the mental status of 25 PFPS patients and related this to pain and function. The health status was significantly lower and mental distress was significantly higher in PFPS patients than in a comparable group comprising 23 healthy subjects. Further, the level of mental distress increased and the health status deteriorated with increased intensity of pain and impairment of knee function. We hypothesize that pain and reduced function produce mental distress in PFPS patients, and that this influences their experience of pain.

The third study measured somatosensory functions related to the painful area using thermal and tactile quantitative sensory testing (QST) and bedside neurological tests in 25 PFPS patients. The results were compared to those obtained in 23 healthy controls. We found that QST can be used to detect sensory dysfunctions in patients with PFPS. Patients suffering from unilateral PFPS demonstrated dysfunction of sensory pathways related to the painful and contralateral areas, which might indicate a pathophysiological basis for pain in PFPS.

The fourth study assessed if a subgroup of PFPS patients experienced neuropathic pain related to the painful knee by characterizing the somatosensory phenotype and analysing the sensory and clinical patterns related to the knees. A total of 91 subjects with unilateral PFPS and a comparable group of 23 healthy subjects were included in this study with a case–control design. The degree of knee function and intensity of knee pain were assessed. Somatosensory assessments were carried out by bedside neurological tests and by assessing thermal, tactile and vibration thresholds. There was considerable heterogeneity and overlap in the degree and type of aberrations of the nervous system. However, no subgroup of subjects with neuropathic pain or clustering of features related to neuropathic pain was identified.

Conclusions from this thesis:

- Somatosensory stimulation by acupuncture is recommended as a treatment modality for PFPS.
- Quantitative sensory testing combined with clinical neurological tests can be used to detect altered somatosensory function in PFPS subjects. Sensory assessments of PFPS patients indicate that the pain can have a pathophysiological component.
- Somatosensory dysfunctions related to the painful and contralateral areas indicate modulations of central neural mechanisms.
- Ample signs of sensory aberrations related to the painful area were found but a clear subgroup of subjects with neuropathic pain could not be identified.
- Mental distress is higher and self-perceived health is lower in PFPS patients than in healthy controls. Further, the intensity of knee pain and degree of knee function are strongly correlated with the degree of mental distress.

List of original papers

The thesis is based on four papers, referred to by their roman numerals:

Paper I

Acupuncture treatment of the patellofemoral pain syndrome

Roar Jensen, Øystein Gøthesen, Knut Liseth, Anders Baerheim

J Altern Complement Med 1999;5:521-527

Paper II

Knee function and pain related to psychological variables in patients with long-term Patellofemoral Pain Syndrome.

Roar Jensen, Torill Hystad, Anders Baerheim

J Orthop Sports Phys Ther 2005;35:594-600

Paper III

Quantitative Sensory Testing of patients with long lasting Patellofemoral Pain Syndrome.

Roar Jensen, Torill Hystad, Alice Kvale, Anders Baerheim

Eur J Pain 2007;11:665-676

Paper IV

Is pain in Patellofemoral Pain Syndrome neuropathic?

Roar Jensen, Alice Kvale, Anders Baerheim

Clin J Pain 2008;24:384-394

Abbreviations

CDT	Cold detection threshold
CNS	Central nervous system
DNIC	Diffuse noxious inhibitory control
DRG	Dorsal root ganglion
IASP	International Association for the Study of Pain
NeuP SIG	Neuropathic pain special interest group, of IASP
NNT	Numbers Necessary to Treat
NSAIDs	Non-steroidal-anti-inflammatory drugs
PFPS	Patellofemoral pain syndrome
QST	Quantitative sensory testing
RCT	Randomized controlled trials
TCM	Traditional Chinese medicine
WDT	Warm detection threshold

1 Introduction

1.1 Patellofemoral pain syndrome

Patellofemoral pain syndrome (PFPS) is a descriptive diagnosis characterized by long-term anterior knee pain. The pain is not constant, instead varying with the type and level of activity. Several names have been used to denote the syndrome, including chronic anterior knee pain, idiopathic anterior knee pain, patellalgia, patellofemoral malalignment, patella compression syndrome and chondromalacia patella (Naslund 2006), however, PFPS is the term used by most authors (Arroll et al. 1997;Heintjes et al. 2003).

1.2 Incidence of patellofemoral pain syndrome

Many authors claim that PFPS is one of the most common musculoskeletal disorders (Lindberg et al. 1986;Milgrom et al. 1991;Kannus et al. 1999;Bergman et al. 2001;Tallay et al. 2004), and that it tends to affect active young people (Saxena and Haddad 2003) and adolescents (James 1979). Others state that the condition is more common among active females (Sathe et al. 2002) and athletes (Earl et al. 2004). Many authors have reported on the occurrence of PFPS in a given population, with several authors reporting its occurrence in one-fourth of the general or sporting population (McConnell 1996;Brechtler and Powers 2002;Anderson and Herrington 2003;Ireland et al. 2003;Witvrouw et al. 2003). However, the reported prevalence is often based on unclear original data sources. A recent study claims that the estimated incidence or prevalence of PFPS in the adult general population is based almost entirely from source data from sports-medicine or military settings, and hence that the incidence of PFPS in the general population is not known (Callaghan and Selfe 2007).

1.3 Symptoms and signs of patellofemoral pain syndrome

There is no consensus in the medical literature concerning the definition, aetiology, and diagnosis of PFPS (Arroll et al. 1997;Wilk et al. 1998;Blond and Hansen 1998). Most studies describe symptoms of insidious onset, such as diffuse peripatellar and retropatellar localized pain in one or both knees that is aggravated by walking uphill or downhill, squatting, kneeling, or by prolonged sitting with flexed knees (Reid 1993;Arroll et al. 1997;Bizzini et al.

2003). There is reportedly no correlation between the pain intensity and the range of knee extension or flexion, femoral rotation, or quadriceps angle (Galanty et al. 1994). Clinical tests used to assess patients with PFPS have been shown to lack reliability and validity (Caylor et al. 1993; Fitzgerald and McClure 1995; Watson et al. 1999; Powers et al. 1999). Radiographic findings are inconclusive in diagnosing PFPS, but they can be used in a differential diagnosis (Haim et al. 2006). Here we define PFPS as a descriptive diagnosis characterized as anterior knee pain excluding intra-articular pathology, peripatellar tendonitis and bursitis (Reid 1993).

1.4 Aetiology of patellofemoral pain syndrome

Research into the aetiology of pain in PFPS has concentrated on finding biomechanical causes. However, several observations indicate an involvement of the peripheral nervous system around the patellae (Fulkerson et al. 1985; Mori et al. 1991). Increased levels of substance P are found near the patella, and histological samples have shown that involvement of the nervous system is strongly correlated with the pain experienced (Yaksh 1988; Wojtys et al. 1990; Sanchis-Alfonso et al. 1998; Witonski and Wagrowska-Danielewicz 1999). Baker et al. (2002) reported abnormal knee-joint position sensing in individuals with PFPS, which might reflect dysfunction of the neuromuscular system. Differences found in skin temperature between painful and normal knees might indicate involvement of the sympathetic nervous system (Ben-Eliyahu 1992), a notion supported by a significant correlation between reduced bone mineral density and reduced strength of the quadriceps in the same leg (Leppala et al. 1998). Reduced patellar pulsatile blood flow (Naslund et al. 2007) and increased diffuse uptake on bone scintigrams (Naslund et al. 2005) might also be indicative of dysfunction of the sympathetic system. The presence of long-lasting anterior knee pain appears to be correlated with reduced strength of and altered recruitment pattern in the quadriceps in the same leg (Natri et al. 1998; Cowan et al. 2001). This could be related to the neurological-based flexion reflex involving reciprocal inhibition of the extension muscles (i.e. the quadriceps) in the leg (Stokes and Young 1984a; Stokes and Young 1984b; Leroux et al. 1995; Andersen et al. 2000). These reports indicate a possible neurophysiologic substrate for clinical signs and symptoms evident in PFPS. Few studies have assessed the relationship between sensory function and knee pain. Such assessments can utilize quantitative sensory testing (QST), a psychophysical method widely

accepted in evaluating the function of small nerve fibres (Fruhstorfer et al. 1976; Claus et al. 1987; Yarnitsky and Ochoa 1991; Dyck et al. 1993; Yarnitsky et al. 1995; Yarnitsky 1997; Shy et al. 2003). Conventional EMG and neurographic investigations test the conduction of nerve signals in thicker myelinated nerves, and can therefore not be used to assess the function of small-diameter pain-conducting fibres such as C and A δ (delta) fibres. However, interpretations of the results from the QST must consider the limitations of subjective evaluation of sensation (Shy et al. 2003).

1.5 Treatment of patellofemoral pain syndrome

Few controlled trials have investigated the treatment of PFPS. The review by Arroll et al. (1997) found only five studies meeting their criteria. Two controlled trials administering intraarticular or intramuscular injection of glycosaminoglycan gave conflicting results (Raatikainen et al. 1990; Kannus et al. 1992). Eng and Pierrynowski (1993) found that insoles with hindfoot and forefoot wedging were superior to flat insoles in reducing knee pain after 8 weeks of use, and Finestone et al. (1993) found that an elastic knee sleeve had no effect. A later review of non-surgical and non-pharmacological interventions concluded that there is only weak evidence that physical interventions are effective in managing PFPS (Crossley et al. 2001). The evidence that exercise therapy is more effective than no exercise at reducing pain is weak and conflicts with observed functional improvements (Heintjes et al. 2003). Moreover, there is little evidence of the effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs) for short-term pain reduction in PFPS (Heintjes et al. 2004), or supporting the use of braces or surgery (Dixit et al. 2007). The most recent systematic review by Bizzini et al. (2003) used a grading scale to judge the quality of randomized clinical trials of non-operative treatments for PFPS. This review gave Paper I of this thesis the highest score based on the quality of methodology, and the assessment of outcomes favoured acupuncture as a treatment modality in PFPS.

1.6 Sensory considerations

There is reportedly marked variability in the distribution and consistency of several articular nerves to the knee. Kennedy et al. (1982) described two consistently distinct groups of afferent articular nerves: (1) a posterior group including the posterior articular and obturator nerves and (2) an anterior group consisting of articular branches of the femoral (L1–4),

common peroneal (L4–S2) and saphenous nerves, and which supplies the anteriomedial and anteriolateral capsules and associated ligaments. These nerves are located deep to the medial and lateral retinaculum. Three articular afferents form the terminal branches of the femoral nerve supplying the quadriceps muscle. The lateral articular and recurrent peroneal nerves originate from the common peroneal nerve and supply the inferior portion of the lateral capsule and ligament. The infrapatellar branch of the saphenous nerve supplies the inferomedial portion of the capsule, patellar tendon and the skin overlying the medial aspect of the knee (Kennedy et al. 1982). Two cutaneous nerves coursing within the substance of the vastus medialis and lateralis reach the patella at the superomedial and superolateral edges to innervate the skin covering the patella (Maralcan et al. 2005; Nahabedian 2006) (see Figure 1). The cutaneous sensory innervation of the medial aspect of the knee includes – in addition to the infrapatellar branch of the saphenous nerve – the medial and anterior cutaneous nerve of the thigh. The lateral aspect of the knee includes the tibiofibular branch of the peroneal nerve and the lateral femoral cutaneous nerve. The superficial nerves are located in the subcutaneous fat (Nahabedian and Johnson 2001).

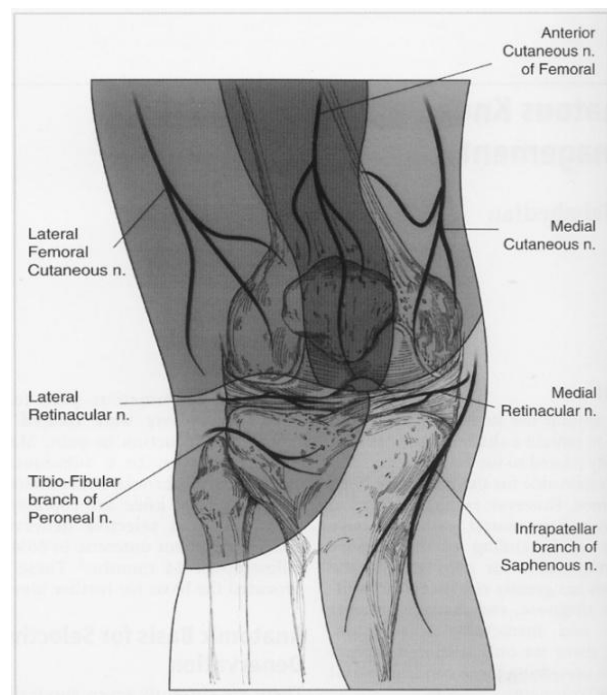


Figure 1. Sensory nerves (Nahabedian 2006, p.364, Fig. 23.1)

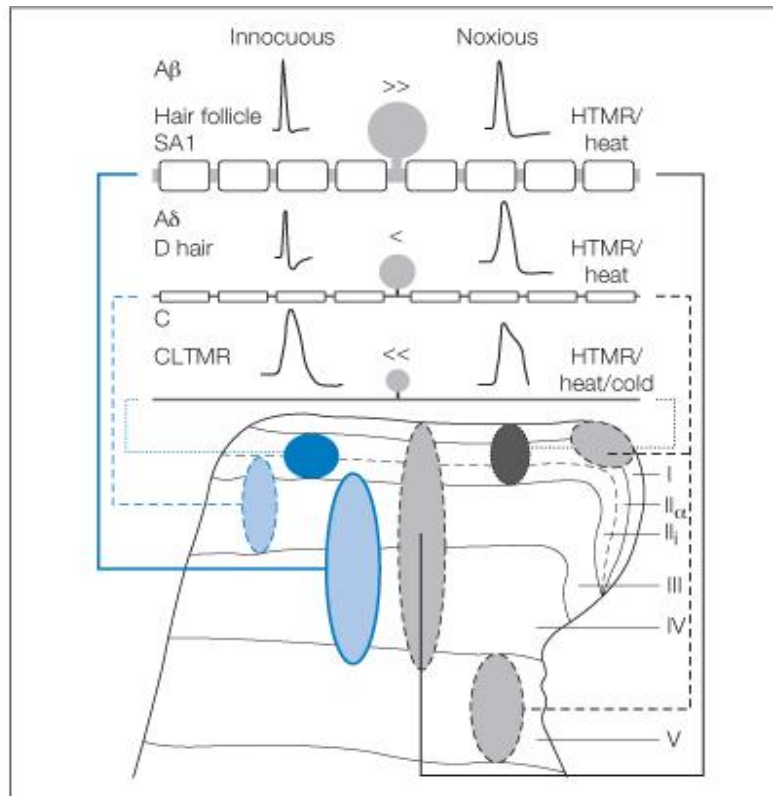
1.7 Anatomical and physiological aspects of pain

Nociceptors are defined as sensory receptors signalling ongoing tissue damage or that injury is about to occur (Sherrington 1906). Nociceptive fibres for perceiving pain are in this thesis categorized according to fibre type (C and A δ) and responsiveness to thermal and mechanical stimuli. Myelinated nociceptive A-fibres are responsible for sharp, pricking, first pain and are mainly A δ fibres with a conduction velocity of 2–30 m/sec (Adriaensen et al. 1983; Meyer et al. 2006). Sustained burning pain and second pain sensation are mainly conveyed by thin unmyelinated C-fibre nociceptors, with a conduction velocity of <2m/sec

(Meyer et al. 2006). The A β (beta) sensory fibres are cutaneous mechanoreceptors and convey innocuous information about touch and vibration (Campbell et al. 1979; Bromm and Treede 1991).

The dorsal part of the spinal cord is the sensory component receiving terminal central rootlets of the primary afferent fibres from the periphery. (see Figure 2). The grey matter of

Figure 2. Sensory fibres in dorsal horn.



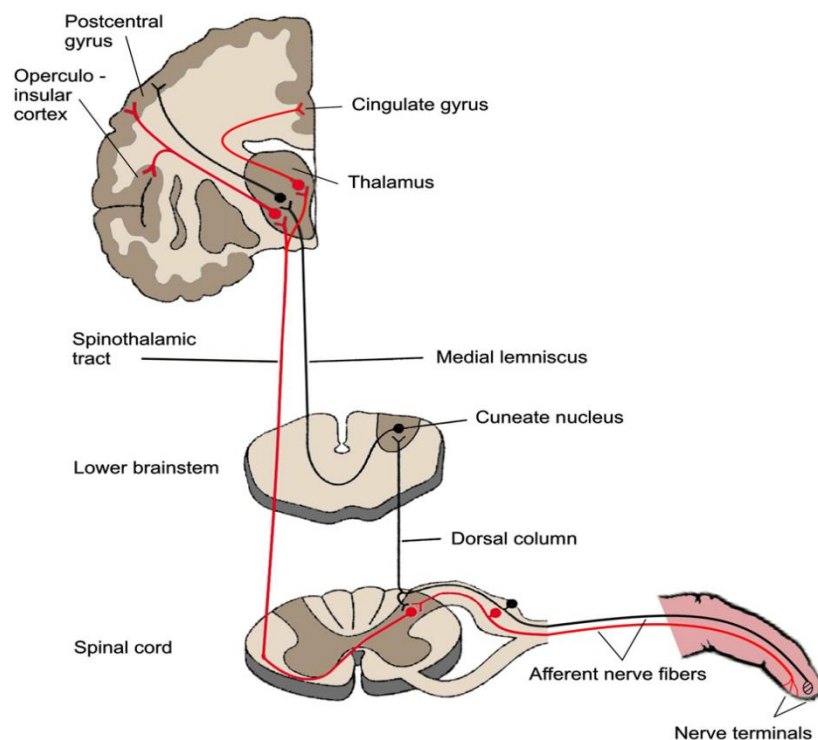
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Schematic representation of the general properties of cutaneous afferent fibres. Inequality signs denote the relative numbers of afferent fibres within a conduction pathway that respond to innocuous (blue) or noxious (grey) stimuli. The density of the terminals of each type of fibre is indicated by the degree of stippling within each projection zone. Note that not all C fibres are nociceptors, and not all A β fibres are low-threshold mechanoreceptors (CLTMR). HTMR, high-threshold mechanoreceptors.

the dorsal horn is divided into different laminae, from lamina I (superficial) to lamina V (deepest). Primary afferent A β fibres terminate mainly in lamina III and IV, nociceptive A δ fibres terminate mainly in laminae I,II and V, and C fibres terminate mainly in lamina II (substantia gelatinosa) (Todd and Koerber 2006). The main ascending somatosensory

systems consist of the dorsal-column lemniscal system and the spinothalamic system. (see Figure 3). The thermal, tactile and vibration QST used in the studies reported in this thesis assesses function mainly in these sensory pathways. The dorsal-column lemniscal system serves mechanoreception, such as tactile recognition, detection of vibration and proprioception. The spinothalamic tract is the pathway most closely associated with thermoreception (both cold and heat), nociception and visceroreception. Nociceptive tracts found in the spinal white matter (in addition to the spinothalamic tract) are the spinomedullary, spinobulbar and spinohypothalamic tracts. Projections from high threshold nociceptive neurons in lamina I and multireceptive neurons (with a wide dynamic range) in lamina V ascend mainly via the spinothalamic tract (the extralemniscal system) to the ventral posterolateral nucleus in the thalamus. The fourth-order neurons of both systems originate in the thalamus and project into the network of somatosensory cortex areas, which include the primary and secondary somatosensory cortex, posterior parietal cortex and posterior and mid-insula and mid-cingulate cortex (Dostrovsky and Craig 2006; Treede 2007).

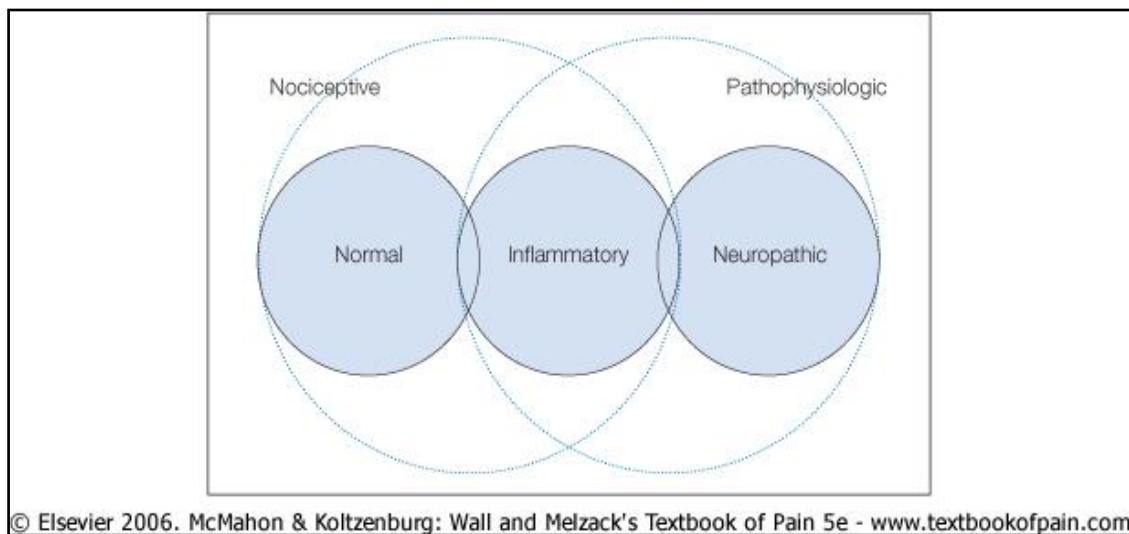
Figure 3. Sensory pathways.



1.8 Pain classification

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. Pain can be described as either nociceptive or pathophysiological (Devor 2006) (see Figure 4). Both long-term inflammation and nerve dysfunctions can give rise to pathophysiological pain. Pain generated partly or exclusively

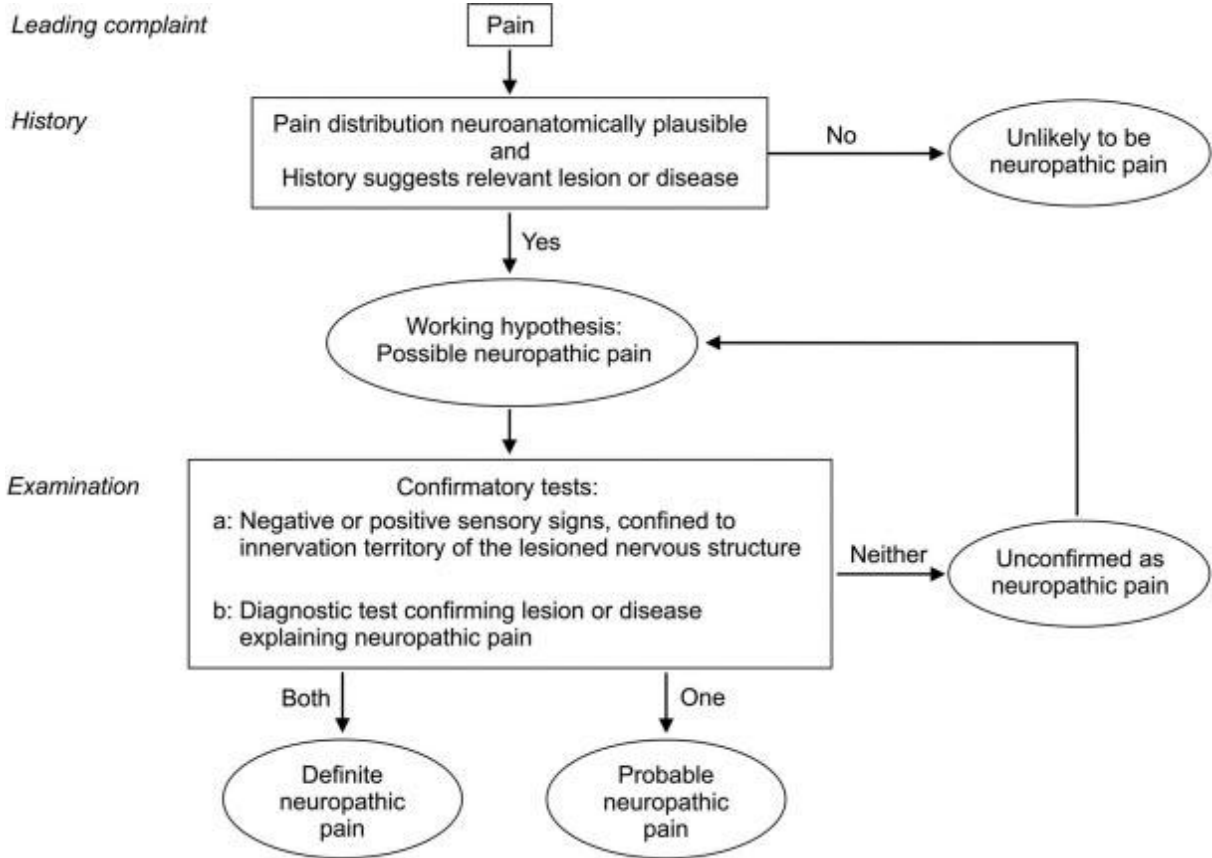
Figure 4. Classification of pain.



within the nervous system without adequate stimulation of its peripheral sensory endings has up to recently been termed neuropathic pain, and defined by the IASP as “pain initiated or caused by a primary lesion or dysfunction in the nervous system” (Merskey and Bogduk 1994). The following revised definition has recently been proposed by a group of experts from the neuropathic pain special interest group (NeuPSIG) of the IASP: “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” (Treede et al. 2007). This more-specific definition was needed to distinguish between pain due to secondary neuroplastic changes in the nociceptive system resulting from sufficiently strong nociceptive stimulation (i.e. inflammatory musculoskeletal pain) and other types of pain that arise indirectly during the course of neurological disorders. That group proposed a grading system using the following criteria: “1. Pain with a distinct neuroanatomically plausible distribution (like dermatome). 2. A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system (like polyneuropathy, apoplexia). 3.

Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory neurological clinical or laboratory test. 4. Demonstration of the relevant lesion or disease by at least one confirmatory neurological clinical or laboratory test". Gradings of definite neuropathic pain (all four criteria), probable neuropathic pain (criteria 1 and 2, plus either criterion 3 or 4), and possible neuropathic pain (criteria 1 and 2, without confirmatory evidence from criterion 3 or 4) have been proposed (see Figure 5, from Treede et al. 2007). The grade of possible neuropathic pain can only be regarded as a working hypothesis that does not exclude but does not diagnose neuropathic pain. The grades of probable neuropathic pain and definite neuropathic pain both require confirmatory evidence from additional neurological examinations.

Figure 5. Classification of neuropathic pain.



This thesis uses the revised grading system to define neuropathic pain. The term pathophysiological pain is used to describe pain that is possibly due to dysfunction or plastic changes in the nervous system (see Figure 4).

1.9 Psychological considerations

Patients with PFPS experience periods with severe and increased pain during and after activity, often without any physical findings that could explain the pain. This situation can be frustrating for both patients and therapists. The absence of physical findings that explain the pain can lead to speculation that the pain is not real or that it is psychological or exaggerated. Patients with PFPS often suffer for several years with their complaint. If patients with PFPS also suffer from depression, anxiety and somatization, or their ability to perform and adapt to their given environment is impaired, these factors should be taken into consideration when designing a treatment regime. Psychological variables and those describing self-perceived health statuses have received little attention in PFPS research, and we know of no personality or emotional characteristics that have higher prevalence rates in PFPS patients. Although clinical trials of subjects with PFPS have not assessed psychosocial aspects, four studies have addressed the mental state of patients with PFPS (Carlsson et al. 1993; Witonski 1999; Witvrouw et al. 2000; Thomee et al. 2002). These studies concluded that individuals with PFPS suffer both mentally and physically. Three of these studies included subjects suffering from long-term PFPS (Carlsson et al. 1993; Witonski 1999; Thomee et al. 2002) and one was a prospective study (Witvrouw et al. 2000). The Minnesota Multiphasic Personality Inventory (the 566-question version) and the Rorschach test were used as the main tools in two of the studies to assess the psychological state of the subjects (Carlsson et al. 1993; Witonski 1999). Analysing the data obtained with these psychological instruments requires specialized knowledge and experience, making them less useful in a normal clinical setting, which requires instruments that are easy to use and that produce results that are easy to analyse.

1.10 Somatosensory stimulation

Studies have shown that cutaneous afferent stimulation by the application of inelastic tape on the skin in the painful area induces short term pain reduction in PFPS patients (Salsich et al. 2002; Whittingham et al. 2004; Aminaka and Gribble 2005; Aminaka and Gribble 2008) and improvement in motor function of the vasti musculature of the thigh (Macgregor et al. 2005). Transcutaneous electric stimulation to the skin in the painful area also reduces pain and improve motor function in PFPS subjects (Werner et al. 1993; Callaghan and Oldham 2004; Avraham et al. 2007). The exact mechanism underlying this effect is not known.

Pain is the main symptom in PFPS; and hence its treatment modalities should reduce pain. Acupuncture treatment is increasing in popularity in mainstream health care, and is the complimentary systems that enjoys the highest credibility in the medical community (Astin et al. 1998;Kaptchuk 2002;Weidenhammer et al. 2007;Bucker et al. 2008). The original underlying therapeutic theory or conceptual framework of acupuncture differs radically from that of biomedicine, since it is based on traditional Chinese medicine (TCM). However, modern research has shown that acupuncture stimulates the nervous system by activating the A β , A δ and C afferent fibres, with the induced signals ascending mainly through the spinal ventrolateral columns to the brain. Several brain nuclei constituting a complicated network are involved in the underlying processing of acupuncture analgesia, including the nucleus raphe magnus, periaqueductal grey, locus coeruleus, arcuate nucleus, preoptic area, nucleus submedius, habenular nucleus, nucleus accumbens, caudate nucleus, septal area and the amygdala (Zhao 2008). Recent studies of the neural mechanisms underlying acupuncture analgesia have predominately focused on cellular and molecular contributions. The gate control theory of pain and the endorphin theory have been used to explain the effects of acupuncture stimulation on pain (Andersson and Lundeberg 1995;Kaptchuk 2002). Various endogenous opioids such as β endorphin, enkephalin and dynorphin have later been documented to be involved in electroacupuncture analgesia. This working hypothesis about the role of endogenous opioids in acupuncture action has been widely accepted (Han 2004). The effect of acupuncture on pain has also been explained through diffuse noxious inhibitory control (DNIC) (Le Bars D. et al. 1992).

Other possible reasons for pain relief induced by acupuncture are disassociation of the sensation of pain and the emotional distress that it normally causes, with patients being less bothered by the pain. Such psychological reactions are believed to be induced by stimulation of the limbic-paralimbic-neocortical network (Campbell 1999;Pilkington et al. 2007;Fang et al. 2008). Recent clinical studies have indicated a psychological effect of acupuncture on patients suffering from depression and anxiety (Luo et al. 1998;Pilkington et al. 2007;Leo and Ligot, Jr. 2007;Fu et al. 2008;Lu et al. 2008).

Both pain and nociceptive reflexes in the flexor muscles of the knee might be affected via the same central mechanisms (Lewith and Machin 1983;Le Bars D. et al. 1992;Mense 1993;Andersson and Lundeberg 1995). Activation of centrally modulated reflex activity has

been suggested to inhibit and disturb recruitment patterns of the vasti in the quadriceps muscle of PFPS subjects (Herrington 2001;Herrington 2004).

The above factors were addressed by the studies described in this thesis, also considering whether somatosensory stimulation by acupuncture can benefit PFPS patients by reducing pain, improve function and mental status.

2 Objectives

2.1 General aims:

This thesis aims to deepen the understanding of PFPS. The described studies focused on evaluating the effect of somatosensory stimulation by acupuncture, assess sensory function related to the painful knee, and relating mental status to function and pain in subjects with PFPS.

2.2 Aims and hypotheses:

2.2.1 Paper I

In a well-defined group of subjects with PFPS, the hypothesis in Paper I was that knee function and pain would not differ up to 12 months after eight sessions of semi-standardized acupuncture treatment compared to before treatment. We aimed to evaluate any added effect of acupuncture treatment on a defined group of patients with PFPS who had not previously improved with recommended periods of rest and traditional treatment.

2.2.2 Paper II

The hypothesis in Paper II was that mental distress and self perceived health differ between subjects with long-term PFPS and healthy controls, and that these psychological variables are related to knee pain and function. We aimed to assess the psychological and general functional state of subjects with PFPS by using the Hopkins Symptoms Checklist-25 (HSCL-25) questionnaire and COOP-Wonca charts, with the aim of identifying relationships of these psychological parameters with knee pain and function.

2.2.3 Paper III

The hypothesis in paper III was that functioning related to somatosensory pathways from the painful area differs between subjects with PFPS and healthy subjects. We aimed to use thermal and tactile QST to detect possible sensory nerve dysfunctions related to the painful area in subjects with long-term PFPS.

2.2.4 Paper IV

The hypothesis in Paper IV was that signs and symptoms clearly related to neuropathic pain are more prevalent among PFPS patients than among healthy controls. We aimed to assess if a subgroup of patients with PFPS suffers from neuropathic pain related to the painful knee based on the results of QST, bedside neurological tests and anamnestic data.

3 Methods

In the four studies that form Papers I-IV of this thesis the symptoms of PFPS were characterized as being of insidious onset, such as diffuse peripatellar and retropatellar localized pain in one or both knees that is aggravated by walking uphill or downhill, squatting, kneeling or by prolonged sitting with flexed knees (Reid 1993;Arroll et al. 1997;Bizzini et al. 2003). The materials and methods used are described in detail in the original articles, and methodological considerations are discussed in Section 8.

3.1 Subjects

3.1.1 Paper I

The sample for Study 1 (described in Paper I) consisted initially of 75 participants with PFPS. Five subjects (4 in the control group and 1 in the acupuncture group) withdrew before the first follow-up, and hence this study involved 70 subjects (sample A), comprising 41 females and 29 males aged 18 to 45 years, with a mean age of 31.0 years. Subjects were recruited from orthopaedic outpatient departments at local hospitals, from private physiotherapy clinics and by advertisements in a local newspaper in Bergen, Norway. Thirty-six and 34 patients were randomized into the treatment and control groups, respectively. Table 1 in Paper I lists the demographics background data of the participants. Subjects were included if they experienced anterior knee pain in one or both knees during activity or at rest.

Information from the medical history had to be consistent with the description of PFPS, with no other more-specific knee disorder being diagnosed or found at inclusion. Subjects who had received acupuncture within the previous 12 months or steroid treatment within the previous 3 months were excluded. Included patients had to be able to participate in the normal activities of daily life.

3.1.2 Papers II and III

Twenty-seven subjects with PFPS applied for inclusion in the studies for Papers II and III, of which 25 (16 females and 9 males) aged 19–44 years, with a mean age of 32 years, met the inclusion criteria (sample B). PFPS subjects were recruited from orthopaedic outpatient

departments at local hospitals, from private physiotherapy clinics and by advertisements in a local newspaper in Bergen, Norway. Inclusion and exclusion criteria for the PFPS group are listed in Table 1 in Paper II, and background data are presented in Table 2 in Paper II and in Table 4 in Paper III. A group of control subjects with healthy knees (sample C) consisted of 12 females and 11 males aged 18–44 years, with a mean age of 29 years. These healthy controls consisted both of colleagues of the authors and volunteers unfamiliar to the authors. Inclusion criteria for the healthy controls are presented in Table 1 in Paper II.

3.1.3 Paper IV

Study 4 included 91 subjects with unilateral PFPS (sample D), consisting of 56 males and 35 females aged 18–40 years, with a mean age of 31 years. Table 2 in Paper IV lists further background data of the PFPS subjects. Inclusion and exclusion criteria for the PFPS group are listed in Table 1 in Paper IV (see errata: Correction of age range: 18–44 years). Subjects were recruited from orthopaedic outpatient departments at local hospitals, from private physiotherapy clinics and by advertisements in a local newspaper in Bergen, Norway. The healthy control group consisted of sample C, also used as the control group in Studies 2 and 3.

3.2 Designs

3.2.1 Paper I

This study was designed as an experimental controlled trial in which the included participants were randomized into blocks of four to receive acupuncture treatment or no acupuncture treatment. Information from both the medical history and clinical examinations was used to confirm compliance with the inclusion and exclusion criteria. The study used an independent blinded tester (S.F.), and the participants were blinded for the outcome measurements. Subjects were allowed to receive normally recommended treatments other than acupuncture, but none of them did so. The acupuncture treatment was based on an individual diagnosis of each patient based on TCM criteria. The NNT was used to measure treatment efficacy. Parametric and non-parametric statistical tests were used to evaluate differences.

3.2.2 Papers II - IV

A descriptive design that including two independent samples was used in Studies 2–4. Differences between the two groups in these case–control studies were assessed using parametric and non-parametric statistical tests. The age, gender and body mass index (BMI) did not differ significantly between the groups in each study. Conclusions about the groups were based on differences and associations between variables measuring knee pain, knee function, mental state and somatosensory function. This design was chosen since it is cheaper, quicker and usually smaller than alternative epidemiological designs, such as cohort studies.

3.3 Clinical neurological examinations (Papers III and IV)

A bedside neurological assessment of the reflexes of adductors and the patella and Achilles tendons, hypo/hypraesthesia, hypo/hyperalgesia and allodynia of the skin in the knee area was performed on all PFPS subjects. Muscles identified relative to peripheral and segmental (root) nerves in the lower extremities were tested manually for strength. Positional sensations of the knee, ankle and big toe were assessed by passively flexing or extending the joints of the non-painful leg and asking the subjects to actively place the same joint in the painful leg in the same position whilst the eyes were closed. In Study 3, vibration sensation was assessed by applying a tuning fork (Hartman, 256 Hz) to the knee and ankle. A soft brush and a steel pinwheel (Wartenberger) were used to identify qualitative differences in skin sensitivity and pain perception between the painful and pain-free lower extremities. When sensation was perceived as being stronger in the non-painful knee than in the painful knee, this was recorded as hypoaesthesia of the painful knee. If the opposite was found, this was recorded as hyperaesthesia of the painful knee. An electric toothbrush (Braun) was used in attempts to provoke dynamic mechanical allodynia in the painful area (Eide and Rabben 1998).

3.4 Quadriceps atrophy (Papers I, III, IV)

Atrophy of the quadriceps muscle was assessed by using a tape measure to measure the circumference at 5 cm proximal to the superior border of the patella. A difference (reduction) between the legs of at least 2 cm was classified as atrophy (Hoppenfeld 1976).

3.5 Questionnaires

3.5.1 Cincinnati Rating System (Papers I, II and IV)

The knee function during the 2 weeks prior to the test day was assessed with the Cincinnati Rating System (CRS) self-administered questionnaire (Noyes et al. 1984). This is a numerical scale that evaluates symptoms of pain (20 points), swelling (10 points), giving-way (20 points) and function 50 points (overall activity level (20 points), walking (10 points), stairs (10 points), running activity (5 points), jumping and twisting activities (5 points), giving a maximum score in the absence of symptoms and signs of 100 points. This questionnaire has been shown to be valid in assessing patients with chronic knee pain (Barber-Westin et al. 1999;Marx et al. 2001), and has been translated into Norwegian and validated (Risberg et al. 1999).

3.5.2 COOP-Wonca charts (Paper II)

COOP-Wonca charts are designed to measure functional or self-perceived health status during the previous 2 weeks. This instrument comprises six scales that assess the level of physical fitness, feelings or emotional problems, ability to carry out daily activities, social activities, changes in health, and overall health. Scores range from 1 (best score) to 5 (worst score). The chart is commonly used in primary health care research. It has been translated into more than 20 languages, with the Norwegian version having been tested and validated (Bentsen et al. 1997;Holm et al. 2005).

3.5.3 Hopkins Symptom Check list -25 (Paper II)

The HSCL-25 questionnaire is a shorter version of the Hopkins Symptoms Checklist. It consists of 25 items measuring the degree of mental distress on a scale from 1 (none) to 4 (very high) for the previous 2 weeks. The HSCL-25 is a screening instrument designed to identify common psychiatric symptoms in the areas of anxiety and depression. The questionnaire has been found to be valid and reliable, and enables differentiation between populations comprising healthy subjects and neurotic patients (Derogatis et al. 1974;Nettelbladt et al. 1993;Rognerud et al. 2002;Strand et al. 2003). A mean score greater than 1.75 indicates a psychiatric case in need of treatment (Derogatis et al. 1974;Glass et al. 1978;Nettelbladt et al. 1993). The questionnaire has been translated into Norwegian, and applied to Norwegian subjects (Sandanger et al. 1998).

3.6 Functional tests

In addition to symptoms and signs, functional performance tests should be used when assessing individuals with PFPS. Functional performance tests specific to PFPS should include weight-bearing activities with various knee-flexion angles so as to include positions that commonly aggravate pain and require dynamic muscular control (Loudon et al. 2002). Pain experienced during testing is not measured directly, but it will influence the result of the test.

3.6.1 Stairs hopple test (Paper I)

The stairs hopple test (Risberg et al. 1995) was applied with the patients jumping on one leg up and down 12 steps, each step 17 cm high. The best leg was tested first. The time to complete the test on each leg was measured in tenths of seconds, with a lower value indicating better performance. The results of this test are strongly correlated with scores on the Lysholm scale and the CRS (Hoher et al. 1995;Risberg et al. 1995).

3.6.2 Triple jump test (Paper II)

The triple jump test has been described by Risberg et al. (1995). It was chosen for Study 2 because it is easy to perform, time efficient and needs minimal instruction and no expensive test equipment. The triple jump test is a functional test that mimics the functional demands of weight-bearing and jumping (Risberg and Ekeland 1994;Risberg et al. 1995). Standing on one foot, the subjects jumped three times on the same lower extremity along a straight line. This procedure was performed twice for each lower extremity, first on the pain-free lower extremity, and then on the lower extremity with the painful knee. The higher score of the two attempts was noted for each lower extremity. The difference between the lower extremities in the distance travelled (in centimetres) was recorded as the final score.

3.6.3 Step-down test (Paper IV)

Loudon et al. (2002) found the step down test to be the most sensitive and reliable of five assessed performance tests, with it being the only test that discriminated between PFPS patients and normal controls ($p < 0.013$). In the step down test, the subjects stand on one leg and step towards the floor from a platform 20cm higher than the floor. The down-moving limb only touches the floor with the heel and then returns to full knee extension of both legs. This counts as one repetition, and the number of repetitions the subject performed in 30 sec is recorded. Both lower extremities are tested (Loudon et al. 2002).

3.7 Pain

3.7.1 Visual analogue scale (Papers I-IV)

A visual analogue scale (VAS) consisting of a 100-mm-long horizontal line was used to measure the intensity of knee pain both during the week prior to test day and on the day of testing. The left side of the line indicates no pain (0 mm) and the far right represent intolerable pain (100 mm). The subjects indicated the intensity of pain they experienced by marking the line, from no pain (left end, 0 mm) to intolerable pain (right end, 100 mm). The VAS score was quantified as the distance in millimetres from the left end. The VAS has been documented as being both reliable and appropriate for measuring pain (Price et al. 1983), and is widely used when investigating subjects with knee pain (Chesworth et al. 1989; Flandry et al. 1991; Harrison et al. 1995). Additionally, pain was recorded and characterized according to qualities associated with neuropathic pain conditions (Hanson 1997; Bouhassira et al. 2005).

3.8 Quantitative sensory testing

QST was used to assess functioning related to A β , A δ and C-fibres and the spinothalamic and dorsal-column sensory pathways. The test procedure used is described in the methods section of Papers III and IV.

3.8.1 Tactile sensation (Papers III and IV)

Von Frey filaments were used to test low threshold mechanoreception in the painful area. Testing with von Frey monofilaments is simple in clinical practice and gives reliable and valid results (Weinstein 1962; Bell-Krotoski and Tomancik 1987; Waylett-Rendall 1988; Voerman et al. 1999; Mikkelsen et al. 2004; Keizer et al. 2007). Moreover, tactile sensation reflects the function of mechanoreceptors and myelinated A β fibres with their central connections (Hilz et al. 1995).

3.8.2 Vibration (Paper IV)

The force of the probe on the skin was calibrated to approximately 650g, with a vibration frequency of 100Hz. Results are expressed as the displacement of tissue (skin deformation) in microns. This was found to be an adequate stimulus for Pacinian corpuscles, the main type of mechanoreceptors responding to innocuous stimuli above 65Hz, and the most sensitive between 125 and 250Hz (Goldberg and Lindblom 1979; Laursen et al. 2006). Vibration

sensation reflects the function of mechanoreceptors and myelinated A β fibres with their central connections (Hilz et al. 1995).

3.8.3 Thermal sensation (Papers III and IV)

The heat detection threshold is commonly used to assess the function of unmyelinated C fibres with their central connections. The cold detection thresholds is used to assess the function of myelinated A δ fibres, and to a lesser extent that of subgroups of C fibres (Verdugo and Ochoa 1992;Campero et al. 1996). The test algorithm of the thermotesting used in this study followed that recommended by Hilz et al. (1999). The sum of heat and cold detection thresholds (limen) was also calculated (Fruhstorfer et al. 1976).

3.9 Somatosensory stimulation

3.9.1 Acupuncture (Paper I)

The acupuncture treatment was based on an individual acupuncture diagnosis from Traditional Chinese Medicine (TCM). In accordance with theories of TCM the PFPS subjects were classified into the following four diagnostic types based on the predominant symptoms and signs: Cold-Bi (painful Bi), Damp-Bi (fixed Bi), Wind-Bi (wandering Bi) and Heat-Bi (febrile Bi) (International Acupuncture Training Centre 1988). Subjects in the acupuncture group were needled locally at ST-34 and SP-10, and also at either EX-LE5 and ST-35 or SP-9 and ST-36. Other points used depending on the symptoms and signs in individual subjects were BL-17, BL-18, BL-20, BL-23; LI-4 and CV-4 (International Acupuncture Training Centre 1988). The applied manual stimulation included lifting, thrusting and rotating techniques. Five patients diagnosed as Cold-Bi with intense local knee pain received low frequency (3 Hz) electroacupuncture. Moxa stimulation was not used since it was impractical. The acupuncture treatment was repeated twice weekly for 4 weeks. Each session lasted 20-25 minutes, and the needles (sterile disposable stainless steel, gauge 0.28; Cloud & Dragon, Wujian Acupuncture Needle Factory, Jiangsu Province, China) were initially manipulated until the needling sensation described as 'De-Qi' was obtained. The insertion-depth varied from 2 to 4 cm. The operator (the candidate) is a qualified traditional acupuncturist with 25 years of clinical acupuncture experience

4 Ethical considerations

There are ethical considerations in all studies involving people. Respecting the integrity of participants is imperative, and the way an informant is approached, informed and managed throughout the research process must follow ethical considerations. The benefit of obtaining new knowledge through research must be weighed against any possible harm to the participants. Procedures used in the research process might provide few health benefits to those participating in the research. Since the focus of the researcher is normally not on improving the health of the participant, detailed information about the procedures used in the study should be given. The Helsinki Declaration makes it imperative to obtain informed consent from all participants in medical research, and care must be taken to ensure that the participants are capable of giving an informed consent. Children and senile, mentally ill or critically ill adults all require extra attention due to limitations in their ability to provide informed consent. All of the studies reported in this thesis included only persons aged 18 to 45 years with no history of mental illness.

Three dimensions related to personal integrity and consent in research are often considered when assessing the participant's right to make a decision: (1) when the participant's body is involved, (2) when material that originates from the participant's body is involved and (3) when information given by the participant is used. Written consent must be obtained from participants in research involving any of these dimensions. In my view, the need for informed consent should be graded according to which dimension of involvement the participants accept. Clearly, the need for strong rules regarding consent must be followed when the research involves invasive procedures or the use of biological material from the participants. However, the integrity of the participants is not threatened in large epidemiological studies that collect and analyse already-collected health information. In this situation low health risk and the potentially significant benefit to society mean that a lower level of consent might be acceptable. The rules of consent should be balanced between avoiding unnecessary research hindrance and ensuring the safety and integrity of the participants. In this project, the healthy control group (sample C) was recruited for Studies 2 and 3, and their data were also used as a healthy control group in Study 4.

Accepted clinical examinations related to the issues under investigation were used, and standard questionnaires and non-invasive procedures with normal stimuli were applied when assessing sensory functions. The thermotester used was controlled and tested at the Department of Medical Technology, Haukeland University Hospital, Bergen, Norway, and calibrated by the manufacturer. Acupuncture is regarded as a safe procedure for sensory stimulation with little or no side effects provided that the treatment is performed by trained practitioners (Macpherson et al. 2001; Odsberg et al. 2001; White et al. 2001a; Macpherson et al. 2004).

The literature reviews confirmed the need for more research into PFPS. Future patients will benefit if the obtained results give therapists a better understanding of the aetiology of the syndrome, resulting in more evidence-based treatments being applied. Moreover, the results obtained from the collected data might give some of the informants more knowledge about their own condition.

Ethical concerns were addressed by the written information given to the participants. Issues regarding confidentiality and the right to withdraw from the project were clearly stated. The purposes of the studies were also explained to the informants. There were no reasons to expect inconvenience or any harm to the participants either during the project or thereafter. Issues concerning PFPS are not controversial, and hence it was not necessary to invade the privacy of the informant, with only validated standard questionnaires being used. QST is an assessment that involves the application of normal non-painful stimuli. The informants were in control of the test situation throughout the procedures, and could at any time abort a particular test.

The skill and professional background of the researcher is an ethical issue when considering the likely harm or benefit to the informer. The Health Personnel Law regulates the expected conduct of health personnel when they meet with patients as therapists or researchers. Ethical issues relating to confidentiality and professional background are also regulated by this law. The data-collection processes used in this project were close to the procedures used when I assess my patients as a therapist, and I am very familiar with PFPS in my practice. My supervisors of this project are also familiar with the condition, which has provided the benefit of maintaining the professionalism of the research process.

It would be unethical to invite subjects to participate in badly designed studies, and an accurate and honest analysis and careful interpretation is needed in balancing the benefits and burdens of a project. The quality of the results was secured by data registration being controlled by co-authors of the papers. It is an ethical obligation for researchers to publish the results of completed studies to inform colleagues about the results and to be challenged by other researchers.

The studies described in this thesis complied with the latest revised edition of the Helsinki Declaration (<http://www.etikkom.no/retningslinjer/helsinkideklarasjonen>).

5 Statistics

Background data of the participants in the studies are presented as mean, standard deviation (SD), range and percentage values. Statistical tests were two-sided and at the 5% level of significance. All data were analysed using the statistical software SPSS (Windows version).

5.1 Paper I

Calculations of statistical power conducted before commencing Study 1 showed that to be able to disclose a difference of 15 in the CRS score with 80% certainty, 27 patients were needed in each group, giving an estimated SD of 20, and $\alpha=0.05$ and $\beta=0.20$. Differences in categorical scales were tested by the Mann-Whitney test. Differences in proportions were tested by chi-square tests. The CRS score, regarded as the main outcome measure, was analysed with non-parametric statistics both globally and on subscales. The results of the global scores were skewed, and the subscales were regarded as ordinal scales. Differences in continuous data, such as on the VAS, stairs hopple test and atrophy, were tested with Student's t-test for independent samples between groups, and changes within a group were tested by a paired t-test. Treatment efficacy was calculated as the NNT (Sackett et al. 1997). We chose "no pain" or "occasional pain to strenuous sports" and "no limitations" or "some limitations to heavy labour" in the CRS as cut-offs indicating a clinically significant improvement.

5.2 Paper II

Due to the skewed distribution of the obtained data in Study 2, the independent two-sample Wilcoxon test was used for the continuous variables of age and BMI. Measures on the global CRS, COOP-Wonca charts, HSCL-25 and triple jump test were normally distributed, and hence differences in means between the groups were tested with Student's t-test for independent samples. Since the outcome data had a normal distribution, Pearson's correlation coefficient (r) was used to measure relationships between the measures: functional health status (COOP-Wonca charts), mental distress (HSCL-25), pain (VAS), knee function (CRS) and triple jump test.

5.3 Paper III

Data from QST in Study 3 are presented as mean (\pm SD) values. Von Frey measurements are also presented as range and 95% confidence interval (CI) values, and we defined scores outside the range from 5–95% CI for the healthy controls as pathological (Orstavik et al. 2004). Data from QST of the healthy control group are presented as the mean score between the right and left knees. Differences between the groups were tested using the Mann-Whitney U-test for continuous variables since the distribution were skewed, and differences within groups were tested with Wilcoxon's signed-rank test. The chi-square test was used for categorical variables.

5.4 Paper IV

Data from QST in Study 4 are presented as medians, with the spread of the frequency distribution as interquartile ranges (from the 25th to the 75th percentile) in brackets. Medians were used rather than means since the data were skewed, and the cold pain thresholds of many of the participants were outside the cut-off ($<7^{\circ}\text{C}$). The uneven distribution of the QST results was tested visually on quantile–quantile plots and with the Kolmogorov-Smirnov test ($p>0.05$). Hence, differences in continuous variables between the lower extremities of the PFPS subjects and between the groups were tested with non-parametric tests. Differences between the categorical variables were tested with the chi-square test. Correlation analyses were performed with Spearman correlation analysis, and factor analysis (with Varimax) was used to identify related continuous variables. In this study we calculated the normal range of the tactile and thermal thresholds to be within the 2.5th to 97.5th percentiles of the values of the healthy controls (Wright and Royston 1999). Hence, pathological values were defined as being outside this range.

6 Results

6.1 Paper I

A randomized controlled trial (RCT) of acupuncture treatment versus no treatment of PFPS was conducted with 75 participants (41 females) aged 18–45 years, with a mean of 31 years. All of the participants reported persistent knee pain on activity (for a mean of 6.6 years) and at rest (for a mean of 4.3 years). The participants were diagnosed at baseline according to TCM as Damp-Bi (49%), Cold-Bi (41%) or Wind-Bi (10%), with none of them diagnosed as Heat-Bi. The randomized group comprising 36 patients received acupuncture treatment according to TCM eight times over a period of 4 weeks. The control group received no treatment, but were allowed to follow other previously recommended treatments, such as medication with analgesics or NSAIDs, physiotherapy or adjustment of activity level.

The demographic, diagnostic and clinical data did not differ between the groups at baseline. The pain level after performing physical tests was significantly lower in the acupuncture group at 5 months after inclusion (VAS = 17.9 mm) than at baseline (VAS = 27.8 mm, $p=0.02$) or in the controls (VAS = 33.5 mm, $p=0.007$). Participants were followed for 1 year with the CRS as the main outcome measure. At 12 months the mean CRS score was significantly higher in the acupuncture group (75.2) than in the no-treatment group (61.7, $p=0.005$). Pain and limitation of function are the main complaints in PFPS. The NNT on the defined CRS subscales (see Section 5.1) at the 12-month follow-up was 3.2 for pain and 3.7 for function.

We therefore rejected our null hypothesis, concluding that acupuncture can be a beneficial treatment modality in reducing pain and improving function in patients with PFPS.

6.2 Paper II

In addition to knee pain and function, the levels of self-perceived health and mental distress were compared between PFPS patients and healthy subjects in this cross-sectional study. The relationships of knee pain and function with these psychological variables were assessed. Two independent samples consisted of one group of 25 men and women aged 18–40 years with unilateral PFPS, and a control group ($n=23$) comprising healthy subjects with no recent history of knee pain. The CRS and triple jump test were used to assess knee

function. The intensity of knee pain was measured using a VAS. Self-perceived health and mental distress were assessed with COOP-Wonca charts and the HSCL-25 questionnaires.

In the PFPS group, the score for pain intensity on the VAS was 24(\pm 20.1) mm on the test day and had varied from 15(\pm 11.4) to 55(\pm 26.7) mm during the previous week. The score on the CRS was 57.6(\pm 15.5) in the PFPS group. The scores for the COOP-Wonca charts were 2.02(\pm 0.73) in the PFPS group and 1.20(\pm 0.53) in the controls ($p \leq 0.001$); the HSCL-25 scores were 1.46(\pm 0.47) and 1.08(\pm 0.18), respectively ($p \leq 0.001$). Correlation analysis revealed that CRS and VAS scores were significantly correlated with those for the COOP-Wonca charts and HSCL-25.

We concluded that the level of mental distress was higher while the level of self-perceived health was lower in the PFPS group than in a comparable sample of healthy subjects. Our data also indicated that the intensity of knee pain and degree of knee function were related to mental distress and self-perceived health in PFPS subjects.

6.3 Paper III

This cross-sectional case–control study attempted to assess whether patients suffering from unilateral PFPS demonstrate dysfunction of nociceptive nerve fibres with their central connections by means of QST. A total of 48 subjects participated in the study. One group consisted of 25 men and women aged 18–40 years with unilateral PFPS, and the other group consisted of a comparable group of healthy subjects with no recent history of knee pain. A thermotesting apparatus (Thermotest, Somedic, Hoerby, Sweden) was used to assess thermal perception thresholds, and thresholds of heat and cold discomfort. Von Frey filaments were used to determine tactile sensitivity. The intensity and quality of knee pain were also assessed. Symptoms and signs from orthopaedic and bedside neurological examinations were recorded. The main outcome measures were the results of the thermotesting.

Compared to the healthy controls, the mean perception threshold for “warm” was about 2° C higher ($p \leq 0.005$) in the painful knee and 1.4°C higher ($p \leq 0.01$) in the non-painful knee in the PFPS group. The perception threshold for “cold” was 1.6°C lower ($p \leq 0.01$) in the painful

knee of the PFPS group than in the control group. Reduced sensitivity to tactile stimulation was demonstrated both in the local pain area and contralaterally ($p \leq 0.001$).

This study demonstrated reduced sensibility in the local pain and homologous contralateral area. This indicates that pain in PFPS may have a pathophysiological aspect.

6.4 Paper IV

Study 4 aimed to assess if a subgroup of patients with PFPS have neuropathic pain related to the painful knee by characterizing the somatosensory phenotype and analysing the sensory and clinical patterns related to the knees. A total of 91 subjects aged 18–40 years with unilateral PFPS, and a comparable group of 23 healthy subjects aged 18–44 years were included in this study with a case–control design. The degree of knee function and intensity and quality of knee pain were assessed. Somatosensory assessments were carried out by bedside neurological tests and QST, assessing thermal, tactile and vibration thresholds.

Bedside examinations detected altered sensitivity in the painful area in 48% of the PFPS subjects, and 32% experienced pain qualities associated with neuropathic pain (i.e. burning, shooting pain, painful cold, electric shocks). Median knee pain on VAS was 20 mm on the test day with a median highest pain intensity of 41 mm during the previous week. The CRS gave a mean score of 66 (± 13.5) and the step down test gave a significant lower mean step rate compared to the non-painful extremity ($p < 0.001$). Compared to the healthy controls, the median perception threshold for “warm” was 1° C higher ($p \leq 0.01$) in the painful knee and 0.7° C higher ($p \leq 0.01$) in the non-painful knee in the PFPS group. The different detection threshold for “warm” between the painful and non-painful contralateral knee was significant ($p \leq 0.01$). The perception threshold for “cold” was 0.6° C higher ($p \leq 0.01$) in the painful knee of the PFPS group than in the control group. We calculated the upper cut-off value of normal values of warm detection threshold to be 9.0° C. Seven subject (8%) had pathological warm detection threshold values according to this definition. Reduced sensitivity to tactile stimulation was demonstrated both in the local pain area and contralaterally with median scores of 6.8 g/mm² versus 4.5 g/mm² ($p < 0.001$) in the PFPS group and 2.0 g/mm² ($p < 0.001$) in the healthy controls. The vibration threshold was significantly increased in the painful knee compared to the contralateral non-painful knee ($p = 0.003$).

We found considerable heterogeneity and overlap regarding the degree and type of functional abnormalities of the nervous system. However, no clear subgroup of PFPS subjects with neuropathic pain was identified according to the latest recommendations for diagnosing neuropathic pain.

7 General discussion

This section discusses the results from each study separately, followed by methodological limitations and finally some general reflections concerning the results.

7.1 Paper I

Study 1 evaluated the effect of acupuncture treatment in addition to recommendations normally given to PFPS patients by health practitioners. The trial had no placebo control which means that it could not measure the effect of acupuncture *per se*. The design was pragmatic, being close to the clinical setting. The acupuncture stimulation was decided according to TCM differentiation. Our differentiation of TCM syndromes related to PFPS (i.e. Bi syndrome, kidney deficiency, Qi and/ or blood stagnation) is consistent with descriptions in available TCM textbooks and research on knee complaints (International Acupuncture Training Centre 1988;Brinkhaus et al. 2007).

Concerns have been raised about using RCTs as a gold standard for assessing the outcome in complex non-pharmaceutical interventions such as physiotherapy and acupuncture (Paterson and Dieppe 2005). Important factors in these therapies are focused attention, a continuing assessment process, empathy, credibility of the intervention, patient expectation and therapeutic setting. Such factors are regarded as incidental in randomized controlled drug trials, whereas in non-pharmaceutical interventions they might be essential to a beneficial outcome. In sham-controlled acupuncture trials, the supposition is that the needling alone constitutes the treatment. However, if these other components significantly affect the treatment outcome, the sham design is inappropriate since it delivers them to both groups. As a consequence, the difference in treatment outcome might be greatly underestimated and lead to false-negative results. Therefore, the sham acupuncture design can only be used to compare two acupuncture interventions; that is, comparing two different needling techniques.

The reduction in pain and improvement in function were larger in the group treated with acupuncture 12 months after inclusion. McConnell (1986) reports that a treatment-induced improvement in symptoms from PFPS is only temporary in many cases, since many investigators have found that only 30% of patients remained symptom-free at 12-month

follow-ups. If non-specific or psychological factors significantly affect the effectiveness of acupuncture, the initial effect might be expected to wear off. However, we observed a gradually increasing improvement in the treatment group over the 12-month follow-up, indicating a real treatment effect. A similar effect of acupuncture stimulation on PFPS subjects was subsequently confirmed by Naslund et al. (2002). The mean treatment efficacy in favour of the acupuncture group measured 12 months after inclusion, as expressed by the NNT, was 3.2 (95%CI = 2.1–6.9) for “no pain” or “occasional pain with strenuous sports”. This is a favourable result compared to other studies. It has not been confirmed that exercise reduces pain in PFPS (Heintjes et al. 2003). The effect of NSAIDs on PFPS is uncertain (Heintjes et al. 2004), and the NNT for tricyclic antidepressants – which is the recommended treatment across various neuropathic pain conditions – to achieve a 50% reduction in pain has ranged from 2.1 (95%CI = 1.8–2.6) to 3.1 (95%CI = 2.2–5.5) (Finnerup et al. 2007). Clinical trials regarding the use of acupuncture for chronic knee pain have produced conflicting results. Positive trials have been criticized for inadequate blinding or placebo control, and negative trials have been criticized because the interventions were not administered by a properly trained practitioner or because control interventions might have had an effect on the outcome measures. Still, recent systematic reviews of high-quality RCTs suggest that acupuncture can reduce pain and disability in patients with chronic knee pain of various origins (White et al. 2007;Selfe and Taylor 2008;Jubb et al. 2008). Recent RCTs have confirmed the beneficial effects of acupuncture on knee pain from osteoarthritis (Berman et al. 2004;Kukuk et al. 2005;Jubb et al. 2008). The effects of NSAIDs on arthritic knee pain might be no better than those of acupuncture (Bjordal et al. 2007a;Bjordal et al. 2007b). When considering cost-effectiveness and potential negative side effects of NSAIDs, the use of physical modalities such as acupuncture should be recommended in the treatment of musculoskeletal pain (Wonderling et al. 2004). Acupuncture is a highly demanded treatment option for patients with chronic musculoskeletal pain conditions, and the treatment results generally indicate that acupuncture is both safe and beneficial (White et al. 2001b;Yamashita et al. 2006;Staud 2007;Weidenhammer et al. 2007;Bucker et al. 2008).

The knowledge of being treated can be a powerful placebo. Therefore, was the effect observed in this study mainly a placebo effect? Both acupuncture and sham acupuncture stimulate the patient’s expectation and belief regarding a potentially beneficial treatment and modulate activity in the reward system of the central nervous system (CNS) (Lundeberg

et al. 2007). The observed variations in the responses to acupuncture stimulation might also be genetically based (Chae et al. 2006), or due to diverse treatment doses (Vas and White 2007;White et al. 2008). Acupuncture stimulation appears to reduce pain by influencing opioidergic and/or monoaminergic neurotransmission involving the brainstem, thalamus and pituitary (Carlsson 2002). There is also strong evidence of a therapeutic effect mediated through the limbic-paralimbic network (Napadow et al. 2007;Fang et al. 2008). In particular, the amygdala, thalamus and brainstem are key regions that moderate the conscious affective experience of pain (Casey et al. 1994;Craig et al. 1996;Becerra et al. 1999;Borsook et al. 2007). In strong needle stimulation, stress-induced analgesia and DNIC can produce short-term analgesic effects (Murase and Kawakita 2000;Carlsson 2002;Dhond et al. 2007). These mechanisms might influence the well-known clinically observed analgesic effects of acupuncture (Lundeberg 2006).

Knee pain itself might influence the results, since it has been shown to influence the normal function of the quadriceps (Stokes and Young 1984a;Arvidsson et al. 1986). Leroux et al. (1995) found that pain thresholds and nociceptive flexion response thresholds were significantly lower in patients with PFPS. Thomee et al. (1995) found significantly reduced extensor strength in the most painful knee and that the strength of the quadriceps were significantly lower in patients with PFPS than in normal controls. The reduction in pain due to acupuncture treatment might modulate a nociceptive flexion reflex, and normalize a disturbed recruitment pattern of the quadriceps, hence improving knee biomechanics. We found that acupuncture improved the overall activity level 12 months after inclusion, with a NNT of 3.7 (95%CI = 2.2–12.7) for “no functional limitations” or “some limitations to heavy labour”. Pain reduction by acupuncture stimulation might also inspire patients to increase their general level of physical activity, and hence the initial treatment effect might be enhanced by increased physical activity, which would improve the long-term results. We found only minor side effects of acupuncture, with minor bleeding at the needling sites and slight tiredness. There is substantial evidence from several large surveys that acupuncture is a relatively safe treatment (Yamashita et al. 2000;White et al. 2001b;Melchart et al. 2004).

7.2 Paper II

The results of this Study suggest that PFPS patients can suffer from mental distress and reduced self-perceived health status, in addition to knee pain. Our sample of PFPS patients exhibited poor scores on the COOP-Wonca charts for physical fitness and daily activities, and according to the scores of the HSCL-25, as many as one –third of them might need psychological counselling (Derogatis et al. 1974). According to the results from Norway’s Health Statistics Database less than 10% of those aged 25—44 years scored above the cut-off of 1.75 on the HSCL-25 (Norhealth 2005). Further, there appears to be an association between mental status and the intensity of knee pain and degree of knee function, since more pain and disability were found in subjects who expressed mental distress. Previous observations confirm that individuals with PFPS suffer more than healthy subjects from depression, anxiety and somatization (Carlsson et al. 1993; Witonski 1999; Witvrouw et al. 2000; Thomee et al. 2002). These psychological issues are not always evident to the patients themselves or to the therapist, and they can vary. We found no other studies that have addressed the relationship of knee function and pain to mental distress and self-perceived health in PFPS patients. However, similar results were produced by a study on rheumatoid arthritis patients, where the correlation coefficient was 0.46 both between the pain index and anxiety, and the pain index and depression (Smedstad et al. 1995). That study supported the hypothesis that mental distress is secondary to pain rather than vice versa. On the other hand, it is widely appreciated that the psychological state of a patient can modify the perception of pain, and possibly even exacerbate it (Witvrouw et al. 2000). Assessing mental factors is therefore warranted in addition to physical tests when treating PFPS patients. We recommend using the COOP-Wonca charts in both clinical practice and research.

There is increasing evidence that chronic pain affects not only the sensory perception of nociception but also the cognitive and affective dimensions of pain. Improved pain tolerability in gonarthrosis patients after acupuncture stimulation has been explained by an improved ability to cope with cognitive and emotional aspects of pain (Kukuk et al. 2005). Acupuncture stimulation is known to modulates brain activity (Dhond et al. 2008), with the limbic system being an important structure in processing pain and emotional responses (Hamann and Canli 2004). By moderating the activity of the limbic system, acupuncture stimulation could influence the emotional state (Campbell 1999; Wang et al. 2007; Lundeberg

et al. 2007; Napadow et al. 2007; Dhond et al. 2008; Fang et al. 2008). Several clinical trials have concluded that acupuncture is an effective therapy for depressive disorders (Luo et al. 1998; Han et al. 2002; Han et al. 2004). This is supported by an animal model indicating a clear antidepressant effect of acupuncture (Dos, Jr. et al. 2008). However, a recent review of RCTs concluded that the available evidence is insufficient to claim that acupuncture is an effective treatment for depression (Mukaino et al. 2005).

We hypothesize that dysfunctions of the neuromusculoskeletal system and long-term pain, as in PFPS patients, can influence brain functions so as to promote mental distress, which in turn reduces the pain tolerance level. The therapeutic effect of acupuncture stimulation in PFPS patients might be achieved, at least partially, by modulating the activity of the limbic-paralimbic-neocortical network.

7.3 Paper III

QST of both the thermal and tactile thresholds is regarded as a sensitive but not specific method of testing afferent sensory pathways. Both QST and the clinical neurological examinations used in Study 3 indicate that the thresholds of C and A δ sensory channels were significantly higher in both the painful and contralateral pain-free knees of the PFPS patients than in the healthy controls. This indicates that dysfunction of the CNS might cause pathophysiological pain in PFPS subjects (Voerman et al. 2000). A gradually developing contralateral pain and signs of spinal sensory modulations following unilateral peripheral nerve injury and after repeated injections of acid saline has been demonstrated in animal models (Sluka et al. 2001; Arguis et al. 2008). Injury to the L5 nerve in rats has been shown to increase contralateral sensitivity (mechanical allodynia) and also induce immunohistochemical changes in the dorsal root ganglion and structural changes in the contralateral dorsal horn associated with neuropathic pain conditions (Hatashita et al. 2008). Increased levels of glutamate in the dorsal horn has been found, and activation of acid-sensing ion channels type 3 (ASIC3) in DRG innervating muscles has been proposed for initiating bilateral mechanical hyperalgesia after local muscle injury. (Skyba et al. 2002; Sluka et al. 2003; Skyba et al. 2005). Referred contralateral pain in animals and humans has been described as “mirror pain” (Aloisi et al. 1993; Maleki et al. 2000). We believe that initial unilateral knee pain can lead to the development of bilateral PFPS via central modulation of

the nervous system. Bilateral complaints have been reported in at least two-thirds of PFPS patients (Goldberg 1991;Vahasarja 1995;Naslund et al. 2002;Naslund et al. 2005). It is noteworthy that the results of thermotesting at a pain-free area (hands) differed little, if at all, between our PFPS and control groups. The paradoxical combination of sensory loss within the painful area and the pain evoked by non-noxious stimuli from mechanoreceptors in tissue close to or in the painful area is a characteristic feature of neuropathic pain (Rowbotham and Fields 1996). This can be seen in trigeminal neuralgia and post-herpetic neuralgia following acute herpes zoster. In PFPS patients, non-noxious tension or stress on tissue of the anterior knee area can induce pain with qualities similar to neuropathic pain. Galanty et al. (1994) reported 94% sensitivity to pain in PFPS subjects from activities such as squatting, prolonged sitting, and ascending or descending stairs. The present study endorses the value of QST in assessing somatosensory function in patients with PFPS, with the results indicating that patients suffering from PFPS can suffer from pathophysiological pain expressed as possible neuropathic pain from the knee area. Since initial unilateral knee pain can progress to bilateral knee pain (i.e. “mirror pain”), we recommend not using the contralateral knee as the only control in experimental studies.

7.4 Paper IV

By following recommendations of neuropathic pain assessments, Study 4 attempted to identify a subgroup of PFPS subjects with neuropathic pain (Crucchi et al. 2004;Hansson and Haanpaa 2007;Treede et al. 2007). Although we found ample signs of sensory dysfunctions related to the painful area, no clear subgroup of patients with neuropathic pain was identified. This lack of association between data from bedside examinations and QST was also shown in a group of patients with painful partial nerve injury (Leffler and Hansson 2008). Possible explanations for the heterogeneity of the findings include patients being assessed at different stages in a pathological process and the same aetiology initiating different mechanisms. Because there is no consensus on the definition, classification, assessment or management of PFPS (Arroll et al. 1997;Wilk et al. 1998;Blond and Hansen 1998;Bizzini et al. 2003;Naslund et al. 2006;MacIntyre et al. 2006), it is reasonable to suspect that different aetiologies underlie differences in the pain and disability experienced by PFPS patients, rather than this being due to different stages of the pathological development. This

heterogeneity of pathology makes a mechanism-based classification of PFPS patients difficult both clinically and in research.

We hypothesize that the pain experienced by PFPS patients with a clearly dysfunctional sensory system is partly explained by a central anatomical and/ or functional reorganization. This might be a consequence of peripheral nerve fibre degeneration or deafferentation. There is evidence from animal models that neurons in lamina II (substantia gelatinosa) of the spinal cord dorsal horn normally receive direct input from small-diameter (C and A δ) fibres and respond best to noxious stimulation (Wall et al. 1979;Hylden et al. 1986). Peripheral nerve damage can result in substantial degeneration of C-fibre primary afferent terminals in lamina II (Janig and McLachlan 1984;Lisney 1989). The loss of synaptic contacts that are normally present between C-fibre afferents and pain-signalling neurons in lamina II (Castro-Lopes et al. 1990) results in the central terminals of A β mechanoreceptive afferents that normally terminate in deeper laminae (III and IV) growing into lamina II and directly contacting the synaptic cells (Woolf et al. 1992;Shortland and Woolf 1993). This sprouting of A β terminals depends critically on the extent of C-fibre degeneration (Woolf et al. 1992). After such reorganization, large-diameter primary A β afferents – including those that respond best to innocuous mechanical stimuli – provide a major direct input to spinal neurons that normally receive input exclusively from unmyelinated primary afferents. Thus, such reorganization has been suggested as a neural mechanism for the pathophysiological pain observed in some patients who have loss of C-fibre function, rather than C-fibre sensitization (Attal and Bouhassira 1999). Sprouting of thick myelinated afferents (A fibres) from laminae III and IV of the spinal cord is a well-established hypothesis for the structural basis of neuropathic pain. However, much of the evidence for the sprouting of myelinated fibres stems from the bulk transport of the β -cholera-toxin–horseradish-peroxidase conjugate, a technique that has recently been shown to be unreliable (Santha and Jancso 2003;Shehab et al. 2003). In fact, Bao et al. (2002) showed that sprouting from deeper to superficial layers is much less pronounced than previously assumed. Although they claimed that such sprouting is only marginal, it cannot be ruled out that this still represents a functional circuit involved in generating pathophysiological pain. A recent study found that mechanical and polymodal myelinated nociceptive afferents – rather than low-threshold mechanoreceptive cutaneous afferents – give rise to recurving collaterals in the dorsal horn

(Woodbury et al. 2008). These collaterals project into the superficial pain-specific laminae (I and II) after peripheral nerve injury. This newly identified group of myelinated nociceptive fibres might well account for the described sprouting of mechanoreceptive afferents. It is suggested that these myelinated nociceptors cause pain by establishing a spinal pain network after nerve injury (Woodbury et al. 2008).

We found increased thresholds of A β pathways in many of PFPS subjects. Also, a loss of input from mechanoreceptive fibres might diminish the inhibition of the projecting neurons and thus give rise to a “low-input” pain (Loeser 1983). Consistent with the disinhibition theory, thermal sensory deficits in the painful area are almost always found in patients suffering from centrally caused pathophysiological pain (Vestergaard et al. 1995; Bowsher 1996; Bowsher et al. 1998). Further, it is suggested that sensory dysfunctions can induce pain due to imbalance of afferent activity in the dorsal column versus spinothalamic pathways (Beric et al. 1988; Beric 1993).

Our findings indicate that PFPS subjects experienced deafferentation of sensory pathways from the region of the painful knee and also, to a smaller degree, from that of the contralateral non-painful knee. In addition to histological changes with anatomical and/or functional reorganization in the dorsal horn, other functional changes in the CNS might occur to induce pathophysiological pain. Such pain caused by altered function of the nervous system was previously defined as neuropathic pain by the IASP. According to the revised definition proposed by Treede et al. (2007), a history suggestive of a relevant injury affecting the peripheral and/ or CNS must always be present to diagnose neuropathic pain (see Section 1.8, criteria 2). Biomechanical dysfunctions in the lower extremity are still considered by most experts to be the aetiology of PFPS. Hence, PFPS patients will not comply with the new diagnostic criteria to diagnose neuropathic pain until solid evidence that show neural damage is produced. We believe that PFPS subjects might suffer from secondary neuroplastic changes in the sensory system that were caused by an original nerve lesion or dysfunction that affected the peripheral nerve endings (Sanchis-Alfonso 2008). Both histological and biochemical changes found in the painful area suggest an involvement of the peripheral nervous system in subjects with long-term anterior knee pain (Fulkerson et al. 1985; Fulkerson 1989; Mori et al. 1991; Sanchis-Alfonso et al. 1998; Sanchis-Alfonso et al. 1999; Witonski and Wagrowska-Danielewicz 1999; Sanchis-Alfonso and Rosello-Sastre

2000;Sanchis-Alfonso et al. 2001;Sanchis-Alfonso and Rosello-Sastre 2003;Sanchis-Alfonso et al. 2005). Our results indicate the presence of an additional dysfunction in the CNS.

7.5 Methodological limitations

The sampling process used in the studies might have introduced bias. Since most participants were recruited to the studies by reacting to advertisements in the local newspaper we might have selected samples of subjects which differ economically, socially, intellectually from the target population.

The participants in the control group of the experimental study were not given sham acupuncture but they were allowed to receive other non-acupuncture treatments. This decision was made due to ethical considerations and methodological difficulties in implementing a true placebo treatment procedure. It has been suggested that sham acupuncture involving the needling of incorrect and sites that are theoretically irrelevant to the aim of the treatment represents a placebo treatment. However, any needling of the body could induce a physiological response that imitates the real treatment effect. Hence, such a design does not control for a placebo effect. Since most of the subjects had received conventional treatment and experienced negative results, it is likely that participants in the control group experienced a nocebo effect, meaning that the expectations to a treatment effect differed between the groups. To minimize the nocebo effect, we informed participants before randomization that if they were assigned to the control group they would be offered acupuncture treatment after the completion of the study. Acupuncture was a novel intervention for most of the participants, which is known to be associated with a placebo response (Paterson and Dieppe 2005). People are more motivated to participate in research studies at a time when they are experiencing increased discomfort, and hence a “reduction to the mean” phenomenon might have influenced the effect of treatment (Hrobjartsson and Gotzsche 2001). The study employed a semi-standardized acupuncture strategy. The intervention was based on a fixed number of treatment sessions (eight) and a small number of acupuncture points were used. The treatment strategies and numbers of treatment sessions can vary considerably between acupuncture trials (Ezzo et al. 2001; Berman et al. 2004; Brinkhaus et al. 2007). From a scientific point of view, standardized interventions are required to ensure the reproducibility of the results of a trial. Our semi-pragmatic methodology was chosen since most practitioners individualize the treatment, believing this to produce the best results (Lao et al. 2000). We cannot rule out that the outcome might have been different if we had applied a different acupuncture intervention

strategy. Further research should include trials using different numbers of acupuncture points and different amounts and types of needle stimulation, and it might also be beneficial to use consensus-reaching by experts when defining treatment strategies. To improve internal validity, retesting was carried out by an independent, blinded tester, and the participants were blinded to the outcome measurements. The outcome measurements were from tests validated for knee injuries, but none of the tests had been validated specifically for research involving PFPS subjects, which might reduce the validity of the obtained results. The apparent heterogeneity regarding aetiology in PFPS patients calls for stricter criteria for including PFPS subjects to clinical trials, in terms of gender, age, length of discomfort, activity level, medical history and mental profile.

An inherent possible weakness of most small observational studies is that the sample is too small to be representative of the studied population. No symptoms and signs unequivocally diagnose the presence of PFPS. We decided to use typical inclusion criteria that are commonly used by other researchers (Arroll et al. 1997;Bizzini et al. 2003). Further, all subjects included in our four studies had been diagnosed with PFPS prior to their inclusion. Most had been referred to receive physiotherapy, or to an orthopaedic department because of their knee complaint. Therefore, the PFPS patients were probably representative of the total population. The criteria used to include and exclude healthy controls might have produced a sample healthier than the normal population and a clustering phenomenon (with reduced variability between the subjects). This might have resulted in differences in the measurements between the groups being overestimated.

QST is a psychophysical method widely accepted for evaluating the function of small nerve fibres (Gruener and Dyck 1994;Yarnitsky 1997;Dyck and O'Brien 1999;Meier et al. 2001). The subjective character of the data gathered through psychophysical methods reduces their acceptance, since the subject's attention, concentration, motivation, reaction time and ability to reverse the switch quickly can influence the results. People in our climate are used to having cold hands and feet, which would have influenced reaching the painful cold thresholds. Thus, the thresholds for painful cold are the least-valid thermal thresholds (Leffler and Hansson 2008). A lack of reproducibility and the ability to separate pretenders and patients with real pathology have been questioned (Verdugo and Ochoa 1992;Shy et al. 2003). Yarnitsky et al. (1994) reported a large variability in pretenders compared to patients with real pathology, whereas another study found no such difference (Freeman et al. 2003).

The method has been regarded to be more useful for population studies than individual cases (Shy et al. 2003; Hansson et al. 2007; Leffler and Hansson 2008). Based on extensive clinical experience, Leffler and Hansson (2008) advise not to use normative data but $\geq 1^{\circ}\text{C}$ side-difference for thermal detection thresholds as pathological cut-off value. Left-right comparisons are normally used in neurological testing, but can only be used where the contralateral side is 100% normal. Rolke et al. (2006) advise to use normative data adjusted for gender, age and body sites. We compared QST thresholds to data from the same body area in healthy subjects and calculated the normal-range to be wider than recommended. In the studies constituting this project, the same operator (the candidate) performed all the QST in the same manner every time. Moreover, none of the tested subjects was able to derive an explicit benefit economically or socially from the outcome, making it less likely that the results were influenced by feigning.

Bedside clinical tests are qualitative and lack an adequate control and standardized stimulus intensity (Hansson and Haanpaa 2007). The inherent inaccuracies in such clinical testing might reduce the validity of the obtained results.

Methodological weaknesses can produce errors and reduce both the internal and the external validity. However, the methodologies used in the studies were generally appropriate to their objectives.

7.6 Conclusion and implications

Various causes of pathologies underlying the signs and symptoms of PFPS have been proposed previously. Anatomical and biomechanical abnormalities are often considered principal causes of the underlying pathogenesis. However, such causes are weakly correlated with the reported signs and symptoms. For example, often a contralateral healthy pain-free knee coexists with the same type of anatomical or biomechanical abnormality in the same individual. There is currently no evidence supporting a specific modality of treatment for PFPS patients.

No previous study has assessed the somatosensory system in PFPS patients. The results from our studies indicate that substantial numbers of PFPS patients have a dysfunctional sensory system. The dysfunctions are related to sensory pathways from the painful region, and appear to affect central modulatory mechanisms. Further, our results indicate sensory changes in the spinal dorsal horn or DRG which might cause contralateral knee-pain. It is outside the scope of this thesis to identify or speculate in which specific changes in the nervous system that can cause the observed dysfunctions. However, alterations in the CNS due to central sensitization, anatomical reorganisation, reduced inhibition or microglial activation are known causes for pathophysiological and neuropathic pain. We believe that the observed sensory aberrations related to the knee area promote pain from non-noxious mechanical stimuli in subjects with PFPS, but this remains to be confirmed. We found no clear relationship of the degree or quality of pain with the degree or type of sensory dysfunctions. Still, we suggest that a local peripheral nerve injury induced by inflammation or trauma can in some subjects initially lead to alterations in the afferent processing. The resulting secondary maladaptive neuroplastic changes might influence the inhibitory and disinhibitory nociceptive mechanisms. These changes cause motor dysfunction of the quadriceps in addition to pathophysiological pain.

It is well documented that acupuncture stimulation can improve pain and function in patients suffering from knee pain. We found that sensory stimulation by acupuncture normalized pain in one-third and function in one-fourth of patients with PFPS. As the optimal treatment dose for acupuncture stimulation is still not known, further research is needed. Widespread effects on the nervous system have been used as explanation for the observed clinical effects of acupuncture stimulation. Impulses from acupuncture stimulation ascend

via the same sensory pathways as pain and temperature sensations. We hypothesize that sensory stimulation by acupuncture improves sensory dysfunction along these pathways and the pain-coping ability in PFPS patients. This should be further tested in future studies.

The following conclusions can be drawn from the work described in this thesis:

- Somatosensory stimulation by acupuncture should be recommended as a treatment modality for patients with PFPS.
- QST is a method that can detect altered somatosensory function in PFPS subjects. In future research it should only be used in subjects with pathological outcome from clinical neurological tests.
- Since sensory dysfunctions from the contralateral non-painful knee might also be present, we recommend that results from research be compared to those in healthy controls.
- We were unable to identify a subgroup of PFPS subjects with neuropathic pain according to present recommendations for diagnosing neuropathic pain. The second diagnostic criterion in this recommendation excludes all painful disorders with underlying unknown neurological lesion or disease to be diagnosed as neuropathic pain. Hence, we propose that the definition is too narrow.
- A mechanism-based understanding of the signs and symptoms in PFPS is essential to providing adequate treatment. Clinical neurological testing should be applied in addition to orthopaedic clinical test, when assessing PFPS patients.
- Future treatment trials should be designed to: assess somatosensory processing from the painful area, record changes in functions of the nervous system and correlate such changes with changes in clinical signs and symptoms.
- Mental distress seems to be frequently found in PFPS patients. We recommend using COOP-Wonca charts in assessing this dimension in PFPS subjects.

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