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Clinical Evidence of Generalised Mechanical Hypersensitivity in Local Musculoskeletal Pain Syndromes and Headaches

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I. **Fernández-de-las-Peñas C**, Arendt-Nielsen L, Cuadrado ML, Pareja JA. Generalized mechanical pain sensitivity over nerve tissues in patients with strictly unilateral migraine. Clinical Journal of Pain 2009; 25 (6): 401-406.

II. **Fernández-de-las-Peñas C**, Madeleine P, Cuadrado ML, Ge HY, Arendt-Nielsen L, Pareja JA. Pressure pain sensitivity mapping of the temporalis muscle revealed bilateral pressure hyperalgesia in patients with strictly unilateral migraine. Cephalalgia 2009; 29 (6): 670-676.

III. **Fernández-de-las-Peñas C**, Madeleine P, Caminero A, Cuadrado ML, Arendt-Nielsen L, Pareja JA. Generalized neck-shoulder hyperalgesia in chronic tension type headache and unilateral migraine assessed by pressure pain sensitivity topographical maps of the trapezius muscle. Cephalalgia 2010; 301 (1): 77-86.

IV. **Fernández-de-las-Peñas C**, Ge HY, Cuadrado ML, Madeleine P, Pareja JA, Arendt-Nielsen L. Bilateral pressure pain sensitivity mapping of the temporalis muscle in chronic tension type headache. Headache 2008; 48 (8): 1067-1075.

V. **Fernández-de-las-Peñas C**, Galán del Río F, Fernández Carnero J, Pesquera J, Arendt-Nielsen L, Svensson P. Bilateral widespread mechanical pain sensitivity in myofascial temporomandibular disorder: Evidence of impairment in central nociceptive processing. Journal of Pain 2009; 10 (11): 1170-1178.

VI. Ge HY, **Fernández-de-las-Peñas C**, Madeleine P, Arendt-Nielsen L. Topographical mapping and mechanical pain sensitivity of myofascial trigger points in the infraspinatus muscle. European Journal of Pain 2008; 12 (7): 859-865.

VII. Hidalgo Lozano A, **Fernández-de-las-Peñas C**, Alonso Blanco C, Ge HY, Arendt-Nielsen L, Arroyo Morales M. Muscle trigger points and pressure pain hyperalgesia in the shoulder muscles in patients with unilateral shoulder impingement: A blinded, controlled study. Experimental Brain Research 2010; 202 (4): 915-925.

VIII. Fernández Carnero J, **Fernández-de-las-Peñas C**, Sterling M, Souvlis T, Arendt-Nielsen L, Vicenzino B. Exploration of the extent of somato-sensory impairment in patients with unilateral lateral epicondylalgia. Journal of Pain 2009; 10 (11): 1179-1185.

IX. Fernández Carnero J, **Fernández-de-las-Peñas C**, De La Llave Rincón AI, Ge HY, Arendt-Nielsen L. Widespread mechanical pain hyper-sensitivity as sign of central sensitization in unilateral lateral epicondylalgia: A blinded, controlled study. Clinical Journal of Pain 2009; 25 (7): 555-561.

Preface

The present studies were carried out at the Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos (Spain) in collaboration with the Department of Neurology, Fundación Hospital Alcorcón (Spain), and the Center for Sensory-Motor Interaction (SMI), Aalborg University (Denmark) in the period from 2005-2009.

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This work is based on the peer-reviewed papers I-IX. Any publication has previously been submitted for an academic degree.

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Abstract

Introduction: Musculoskeletal pain syndromes in the upper quadrant and headache, especially tension-type headache (TTH) and migraine, are highly prevalent disorders. In the last years, there has been an increasing interest in nociceptive mechanisms in individuals with pain. The presence of both peripheral and central sensitization in widespread chronic pain syndromes, e.g., whiplash associated disorders and fibromyalgia have involved particular attention. There is some evidence demonstrating similar changes in nociceptive gain in local pain syndromes. The current dissertation summarizes a number of clinical studies demonstrating the relationship between peripheral and central sensitization in musculoskeletal local pain syndrome of the upper quadrant and chronic headaches.

Aim: To investigate the relevance of pressure pain hyperalgesia in deep tissues over symptomatic and distant pain-free areas in individuals with musculoskeletal local pain syndromes and headaches, and to compare the presence of peripheral and central sensitization between these pain conditions.

Studies: Pressure pain thresholds (PPT) were assessed over deep tissues, i.e., muscles, joints or nerves, over symptomatic and non-symptomatic pain-free areas in a blinded design in individuals with TTH, migraine, temporomandibular (TMD), shoulder pain and lateral epicondylalgia. Topographical pressure maps over different muscles, i.e., temporalis, trapezius and infraspinatus, were also calculated to assess topographical distribution of pressure pain hyperalgesia. The relationship between PPT and the clinical variables (pain intensity, temporal and spatial profile) was also studied on each condition.

Results: The results of these studies found a generalized and widespread pressure pain hyperalgesia in deep tissues (muscle, nerve and joint) in patients with chronic TTH, migraine, TMD, shoulder pain and lateral epicondylalgia. Pressure pain hyperalgesia was bilateral in patients with unilateral symptoms. Topographical pressure pain sensitivity maps also revealed heterogeneous distribution of mechanical sensitivity over symptomatic muscles. In all pain conditions, pressure pain hyperalgesia was related to ongoing clinical pain and the duration of the pain condition.

Conclusions: These studies suggest that musculoskeletal local pain syndromes of the upper quadrant and headaches exhibit widespread pressure pain hyperalgesia as sign of central sensitization. This pain hyperalgesia seems to be present in different deep tissues: muscles, joints and nerve trunks. In addition, topographical pressure maps revealed generalized pressure hypersensitivity in local syndromes with unilateral symptoms. Finally, pressure hypersensitivity was associated with the intensity and duration of the pain supporting a relationship between peripheral and central sensitization mechanisms.

Dansk sammenfatning

Indledning: Lokale muskuloskeletale smertesyndromer, spændingshovedpine og migræne er meget udbredte lidelser. De seneste år har der været en stigende interesse for perifere og centrale nociceptive mekanismer hos personer med kroniske smerter. Tilstedeværelsen af såvel perifer og central sensibilisering er udbredt i kroniske smertesyndromer som f.eks. piskesmæld og fibromyalgi, men der er også evidens for, at lignende ændringer kan ske hos patienter med lokale smertesyndromer. Denne afhandling sammenfatter en række eksperimentelle kliniske studier, der undersøger forholdet mellem den perifere og centrale sensibilitering hos patienter med kroniske lokale muskuloskeletale smerter og kronisk hovedpine (spændingshovedpine og migræne).

Formål: At undersøge tryksmerte-hyperalgesi fra såvel symptomatiske som smertefrie områder hos patienter med lokale musculoskeletale smertesyndromer og hovedpine, og at sammenligne forekomsten af perifer og central sensibilisering ved disse smertetilstande.

Undersøgelser/studier: Tryksmerte-tærskler blev målt fra symptomatiske og ikke-symptomatiske områder i et blindet design hos personer med spændingshovedpine, migræne, temporomandibulære lidelser, skuldersmerter og lateral epikondylitis. Kortlægning af tryksmerte-reaktionerne fra forskellige muskler blev beregnet til at bestemme fordeling af tryksmerte-hyperalgesi. Forholdet mellem tryksmerte-tærsklerne og de kliniske variabler (smerteintensitet, temporal og spatial profil, varighed) blev undersøgt ved hver tilstand.

Resultater: Resultaterne af disse undersøgelser viste en generel og udbredt tryksmerte-hyperalgesi hos patienter med kronisk spændingshovedpine, migræne, temporomandibulære smerter, skuldersmerter og lateral epikondylitis. Tryksmerte-hyperalgesi var bilateral hos patienter med ensidige symptomer. De topografiske tryksmerte-kort viste heterogen fordeling af den muskulære hyperalgesi. Tryksmerte-hyperalgesi var relateret til intensiteten af de eksisterende kliniske smerter og varigheden af smertetilstanden.

Konklusioner: Studierne viste at lokale muskuloskeletale smertesyndromer samt og hovedpine medfører udbredt tryksmerte-hyperalgesi som et tegn på central sensibilisering.. Endvidere viste de topografiske tryksmerte-kort en ikke homogen tryk-hyperalgesi når blev målt på strukturer over såvel de smertende som de ikke smertende områder. Lokal og generel trykhyperalgesi relaterer til intensiteten og varigheden af de kroniske smerten.

Contents

1. Introduction

In the 21st century, headaches and musculoskeletal local pain syndromes are common and cause substantial pain and disability. In a developed world, musculoskeletal disorders represent the majority of occupational illness, and neck and upper extremity pain is the second cause of work related illness, after low back pain (Palmer, 2006). Pain in the head, neck and upper extremity can arise from a wide range of clinical conditions. In this dissertation we focus on the most prevalent headaches (tension type headache and migraine), and some of the most prevalent musculoskeletal local pain syndromes of the face (temporomandibular pain) and upper extremity (shoulder pain and lateral epicondylalgia).

The second edition of the Classification of Headache Disorders of the International Headache Society has maintained former clinical criteria for the diagnosis of tension type headache (TTH) and migraine (ICHD-II, 2004). According to the ICHD-II (2004), TTH is characterized by attacks lasting from 30 minutes to 7 days, with at least two of the following features: bilateral location, pressing and tightening pain, mild or moderate intensity, and lack of aggravation during routine physical activity. In addition, patients should not report photophobia, phonophobia, vomiting or evident nausea during the headache, although one of these features is sometimes permitted. Depending on the frequency of the headache (ICHD-II, 2004), patients are classified as:

1. *Infrequent episodic TTH*: at least 10 episodes occurring less than 1 day per month on average (less than 12 days per year);
2. *Frequent episodic TTH*: at least 10 episodes occurring more than 1 but less than 15 days per month for at least 3 months (more than 12 but less than 180 days per year);
3. *Chronic TTH*: headaches occurring more than 15 days per month for at least 3 months (more than 180 days per year).

According to the ICHD-II (2004), migraine is characterized by attacks lasting from 4 to 72 hours, with at least two of the following features: unilateral location, pulsating quality, moderate or severe intensity, and aggravation during routine physical activity. In general, patients also report photophobia, phonophobia, vomiting or evident nausea during headache.

Temporomandibular disorder (TMD) is a term including different conditions involving both the temporomandibular joint and the masticatory muscles. Among the different types of TMD, myofascial pain and internal derangements are the two most prevalent (Drangsholt & LeResche, 1999). The most common symptoms of myofascial TMD include pain located over the facial region and tenderness to palpation of the masticatory structures, while internal derangements in the temporomandibular joint are characterized by joint clicking and, in some cases, pain (arthralgia). In fact, there is an overlap between myofascial TMD and TTH (Svensson, 2007), suggesting common nociceptive pathways.

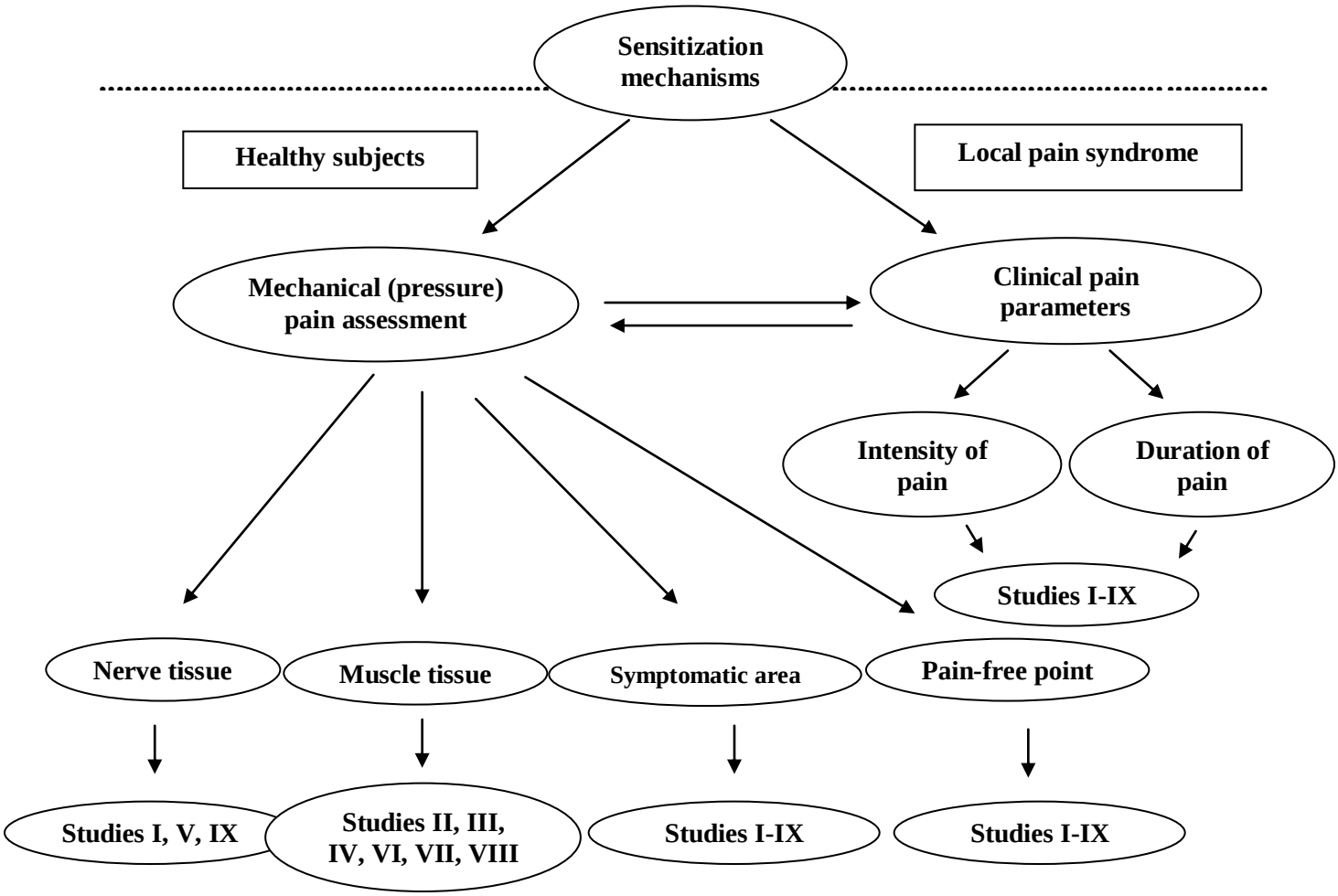
Finally, shoulder pain and lateral epicondylalgia are common health problems that have multi-factorial underlying aetiology and are associated with highly societal costs and patient burden. In fact, they are the most commonly arm pain syndromes experienced by the general population. Due to the convergence between inputs from the shoulder and the elbow within the cervical spine, it is possible that these pain syndromes have also common nociceptive pathways.

2. Aims of the Project

Peripheral and central sensitization mechanisms are common findings in widespread chronic pain syndromes and seem to be also present in local pain conditions. Further, it is suggested a relationship between peripheral and central factors. No studies have systematically investigated this relationship in local pain syndromes such as tension type headache, migraine, temporomandibular pain, shoulder pain and lateral epicondylalgia. In addition, previous studies investigating nociceptive pain mechanisms analysed pressure pain sensitivity over muscles, but not over other deep tissues, e.g., nerve tissues, and also over specific points. Thus, the aims of the present project were:

1) **To investigate the presence of pressure hyperalgesia in muscle tissues and nerve trunks over symptomatic local areas and distant pain-free areas in individuals with headaches and musculoskeletal local pain syndromes such as TMD, shoulder pain and elbow pain.**
2) **To investigate the topographical distribution of pressure hyperalgesia on the symptomatic area in subjects with headaches and musculoskeletal local pain syndromes such as TMD, shoulder pain and elbow pain.**
3) **To investigate the degree of pressure pain hyperalgesia in both the symptomatic and non-symptomatic areas in subjects with headaches and musculoskeletal pain syndromes such as TMD, shoulder pain and elbow pain.**
4) **To assess the relationship between mechanical pain hypersensitivity and clinical variables concerning the intensity and the temporal profile of the symptoms on each condition, that is, to investigate the link between generalised hyperalgesia and pain intensity and duration**
5) **To compare the presence of peripheral and central sensitization between headaches and musculoskeletal local pain syndromes such as TMD, shoulder pain and elbow pain.**

The outline of the project is expressed in the following sketch:



3. Epidemiology

3.1. Epidemiology of Musculoskeletal Pain

Musculoskeletal pain is one of the main causes of disability, health problems and health care utilization in the world (Badley et al., 1994). Further, it implies an enormous cost for the entire society. The epidemiology of musculoskeletal pain has focused on chronic pain (pain with duration of at least 3 month). Different studies reported that chronic musculoskeletal pain is highly prevalent in Sweden (35%) (Bergmanet al., 2001), Spain (24%), (Catalá et al., 2022), Denmark (20%) (Sjøgren et al., 2009), Netherlands (44%) (Picavet & Schouten, 2003), and France (20%) (Euller-Ziegler., 2003) In fact, an old review concluded that the prevalence of musculoskeletal pain seems to increase by the last years of the century (McBeth & Jones, 2007). Nevertheless, this review only included studies conducted before 1998. A recent study conducted in Spain found that the prevalence of invalidating musculoskeletal pain increased from 1993 to 2001, but remained stable from 2001 to 2006 (Jiménez-Sánchez et al., 2010)

It is interesting to note that almost all studies reported that the prevalence of musculoskeletal pain is higher in women than in men (Bassols et al., 1999; Carmona et al., 2001; Bingefors & Isacson, 2004; Wijnhoven et al., 2006; Sjøgren et al., 2009). In addition, more recent studies conducted in Spain have also found that the prevalence of local pain syndromes such as neck or low back pain (Fernández-de-las-Peñas et al., 2011a) or migraine (Fernández-de-las-Peñas et al., 2010a) is almost twice in women than in men. Therefore, musculoskeletal pain should be considered as one of the relevant epidemics of the 21 century.

3.2. Epidemiology of Migraine, Tension-type Headache and TMD pain

Headache is the most prevalent neurological disorder and experienced by almost everyone (Andlin-Sobocki et al., 2005). Migraine and TTH may cause substantial levels of disability to the patient, higher levels of stress to family and higher costs to the society due to very high prevalence in the population (Stovner et al., 2007). TTH is the most common form of headache and what many people consider as their normal headache, in contrast to the more disabling migraine. A recent review of global prevalence and burden of headache reported that the migraine burden was relatively similar for the four continents (Europe, Asia, North-America, South and Central America) and that burden of TTH was greater than that of migraine (Stovner et al., 2007).

Overall, the prevalence of current headache is 47%, current migraine is 10%, current TTH is 38% and current chronic headache is 3% (Stovner et al., 2007). The life-time prevalences are higher, being 66% for headache, 14% for migraine, 46% for TTH, and 3.4% for chronic headache (Stovner et al., 2007). The prevalence of TTH is much higher in Europe (80%) than in Asia and America (20-30%). The life-time prevalence of TTH was 86% in a population-based study in Denmark, but the majority (59%) suffered from episodic infrequent TTH (1 day a month or less) without specific need of medical attention (Lyngberg et al., 2005).

The lifetime prevalence of TMD is under debate, but studies have shown prevalence rates between 3% and 15% in the Western population (LeResche, 1997), with an incidence between 2% and 4% (Drangsholt & LeResche, 1999). A recent survey determined that the overall prevalence of TMD pain was 4.6%, 6.3% for women-2.8% for men (Isong et al., 2008). Further, myofascial TMD is considered as prevalent as TTH since both syndromes seems to be overlapping (Svensson, 2007).

3.3. Epidemiology of Musculoskeletal Pain in the Upper Extremity

In the current dissertation, the most prevalent local pain syndromes from the upper extremity, shoulder pain and lateral epicondylalgia, were included. The results of epidemiological surveys suggest that neck-shoulder pain affects 10-17% of adults at any point in their life, and that pain in the upper extremity exhibit a point prevalence estimate ranging from 7% to 26% (Walker-Bone et al., 2004). In addition, the lifetime prevalence of neck-shoulder pain is 71%.

Shoulder pain lasting > 1 day in the past month was estimated to affect 13% of men and 15% of women aged 53 years old (Bergenudd et al., 1988). A French workforce study reported a 12-month prevalence of upper extremity musculoskeletal symptoms of 35% in women compared to 27% in men (Roquelaure et al., 2006). It is estimated that the incidence of shoulder disorders ranges from 7 to 25 per 1,000 consultations with general physicians (Van der Windt et al., 1995). A more recent survey has found that the prevalence of shoulder pain was 12%, being the most prevalent diagnosis, impingement syndrome (13%) (Pribicevic et al 2009).

Lateral epicondylalgia (LE) is one of the most prevalent arm pain syndromes with an incidence of 1% to 3% in the general population, and 15% in workers (Bot et al., 2005; Rochelarue et al., 2006). Nevertheless, others have reported prevalence rates ranging from 35% to 64% in occupations requiring repetitive manual tasks (Dimberg, 1987; Feuerstein et al., 1998). This pain condition commonly affects individuals between 35-50 years old, and usually affects the dominant arm. In fact, this condition is associated with work-related activities showing a substantially impact on their participation at work and with some specific sports like tennis or golf (Coombes et al., 2009)

4. Assessment of Pain

4.1. Self-reported Scales

Pain exhibits multidimensional aspects depending on personal, cultural, and cognitive aspects. It is generally assumed that pain has 3 components: sensory-discriminative, motivational-affective and cognitive-evaluative. Clinicians should include self-reported scales assessing all these components of the pain from an integrated perspective (Turk & Okifuji, 1999)

Several scales are generally used for addressing the sensory intensity component, that is, the intensity of the pain: numeric pain rate scales, descriptive rating scales, visual analogue scales, and box scales. With these scales, patients can quantify and average their pain retrospectively or at the moment of the assessment. Nevertheless, pain is likely to vary over time and with different daily activities. It is actually recommended that asking about usual or typical pain may not reflect accurately pain severity over time. More valid information is obtained by asking about the current level of pain.

In an 11-point numerical pain rate scale (NPRS), subjects rate their pain intensity from 0 (no pain) to 10 (maximum pain) (Jensen et al, 1999). It is important to note that the minimal detectable change (MDC) and minimal clinically important difference (MCID) for the NPRS have been reported 1.3 and 2.1 points, respectively (Cleland et al., 2008). In the studies included in the current dissertation we used an 11-point NPRS for assessing current level of pain intensity, worst and lowest level of pain experienced in the preceding week depending on the study.

In patients experiencing chronic headaches, a headache diary for 4 weeks is recommended since pain intensity is highly fluctuating (Philip et al., 2007). In studies I-IV of this dissertation, patients completed a headache diary for 4 weeks to record the headache clinical parameters. The headache diary was used to calculate the following variables: 1) headache intensity, calculated from the mean of the

NPRS of the days with headache; 2) mean headache frequency, calculated by dividing the number of days with headache by the number of the analyzed weeks (days per week), and 3) headache duration, calculated by dividing the sum of the total hours of headache by the number of days with headache (hours per day).

A visual analogue scale (VAS) is a 100mm line anchored with a 0 at one end representing no pain and 100 at the other end representing the worst pain imaginable (Bijur et al., 2001). Some studies have determined that the VAS has the ability to detect immediate changes with a MCID ranging from 9 to 11 mms (Todd et al. 1996; Bird & Dickson, 2001; Gallagher et al., 2001). Nevertheless, Bird and Dickson (2001) found that clinically significant changes in pain are not uniform along the entire VAS. For instance, patients with higher pain intensity (VAS score $\geq$ 67) experience a MCID with a greater difference in VAS scores (mean: 28±21) than those patients with lower pain intensities (VAS score 34-66).

Finally, one of the most frequently used instruments to assess the 3 components of pain is the McGill pain questionnaire (Melzack, 1975). This questionnaire consists of three parts which includes a descriptive scale (current pain intensity) with numbers assigned to each of these 5 adjectives: 1 (mild), 2 (discomforting), 3 (distressing), 4 (horrible), and 5 (excruciating). A second part of the questionnaire includes a body diagram with the ventral and dorsal views of a human figure on which patients mark their pain location. The third part is a pain-rating index based on the patient's selection of adjectives from 20 categories reflecting sensory, affective, and cognitive components of pain.

The McGill pain questionnaire provides a great deal of information about pain perception but it takes much longer to complete than numerical scales. Melzack (1987) developed a short-form of the McGill pain questionnaire with 15 adjectives representing both the sensory and affective dimensions of pain, each of which is rated from 1 (none) to 3 (severe).

4.2. Quantitative Sensory Testing (QST)

Quantitative sensory testing is proposed for the assessment of homosynaptic and heterosynaptic mechanisms of sensitization (Hansson et al., 2007) and includes the assessment of vibration, thermal and mechanical stimulus. It is important to note that QST is not suggested to be a diagnostic test for a particular disease; since QST is considered a tool for helping in the mechanism-based diagnosis of pain (Jensen & Baron, 2003). There are different protocols; however, the German Research Network on Neuropathic Pain (DFNS) has developed a standardized QST battery for testing patterns of sensory loss (small and large nerve fiber functions) or gain (hyperalgesia, allodynia, and hyperpathia), and to assess cutaneous and deep pain sensitivity (Rolke et al., 2006a). Briefly, this protocol assessed the conduction of small (thermal thresholds) and large (tactile thresholds) nerve fibres, and increased pain sensitivity (hyperalgesia, allodynia, hyperpathia). The tests can be grouped as follows (Rolke et al., 2006a):

1, Thermal detection thresholds for the perception of cold, warm and paradoxical heat sensations;

2, Thermal pain thresholds for cold and hot stimuli (hot and cold pain thresholds);

3, Mechanical detection thresholds for touch and vibration;

4, Mechanical pain sensitivity (pressure pain thresholds) including thresholds for pinprick and blunt pressure, stimulus/response-functions for pinprick sensitivity and dynamic mechanical allodynia, and pain summation to repetitive pinprick stimuli (wind-up like pain).

Rolke et al (2006b) established reference data for obtaining the full somatosensory phenotype of a patient, including scores for all types of primary afferents, cutaneous and deep pain, peripheral and central sensitization. Nevertheless, these authors concluded that some thresholds (heat hypoalgesia, cold hypoalgesia, or mechanical hyperesthesia) can hardly be diagnosed (Rolke et al., 2006b). More recently, Blankenburg et al (2010) demonstrated that the full QST protocol is also feasible and valid for

children over 5 years of age with their own reference values. Finally, a recent study has concluded that standardized QST performed by trained examiners is a valuable diagnostic instrument with good test-retest (>75%) and inter-observer reliability within 2 days (Geber et al., 2011)

4.2.1. Pressure Pain Threshold Assessment

Among the different QST, pressure algometry is the most commonly used for assessing muscle hyperalgesia (Rolke et al., 2005). Pressure sensitivity is usually assessed by means of a handheld pressure algometer where the probe can be applied to a hard body structure, such as the periost, joints, muscles or tendons (Arendt-Nielsen et al., 2011). In fact, both Aδ- and C- fibers mediate pain induced by pressure stimulation (Adriaensen et al., 1984). To determine a particular threshold the intensity is increased, preferably by a fixed rate (kPa/sec). Different thresholds are usually applied to determine the excitability of the nociceptors: the pressure pain threshold (PPT), that is, the lowest pressure stimulus that is perceived as painful; and the pressure tolerance threshold, that is, the maximal pressure stimulus that is tolerated by the patient (Vanderweeen et al., 1996). This technique is widely used for assessment of treatment and reference values in pain-free subjects have been recently published (Neziri et al., 2011). The most commonly form for assessing PPT is with the use of an electronic algometer (Somedic AB®, Farsta, Sweden). This algometer consists of a 1 cm^2 rubber tipped plunger mounted on a force transducer. The pressure is applied at an approximately rate of 30 kPa/sec. The subjects are instructed to press switch when the sensation first change from pressure to pain. The mean of 3 trials is usually calculated and used for the analysis. A 30-second resting period is allowed between each measure. The reliability of pressure algometry has been found to be high (ICC 0.91, 95%CI 0.82-0.97) (Chesterson et al., 2007). A recent study has confirmed an intra-rater reliability almost perfect (ICC: 0.94-0.97), and

an inter-rater reliability substantial to perfect (ICC: 0.79-0.90) for PPT over the cervical spine (Walton et al., 2011).

In addition, pressure algometry can be also applied consecutively for determining the temporal summation of pain which mimics the initial phase of the wind-up process measured in animal dorsal horn neurons (Arendt-Nielsen & Graven-Nielsen, 2008). To elicit temporal summation of pain, the mechanical stimulus is repeated at constant intervals, for example, five times with a frequency of 1 Hz, at constant intensity. The intensity of 5 consecutive stimuli is gradually increased until the individual feels an increase in pain perception during the repeated stimulation. Nie et al (2005a) demonstrated that temporal summation was more potent for deep tissue stimulation as compared with skin stimulation.

The pain sensitivity of a musculoskeletal structure is dependent on the location of the stimulus application (Andresen et al., 2006). Previous studies investigating pressure pain sensitivity over deep tissues focused on muscle or joint tissues, but not in nerve trunks. In fact, PPT is usually assessed over the cervical spine (articular pillar of the C5-C6 zygapophyseal joint), tibialis anterior muscle (halfway between the most superior attachment to the tibia and its tendon in the upper one third of the belly), the second metacarpal, the painful area (lateral epicondyle, temporomandibular joint, or supraspinatus) according to previous studies (Desmeules et al., 2003; Sterling et al., 2002; Sterling et al., 2003; Scott et al., 2005).

In the current dissertation we present several studies conducted by our research group where we assessed mechanical pain hyperalgesia over different deep tissues including muscles, joints and nerve trunks. For instance, in studies I, V and IX, we assessed PPT over the peripheral nerve trunks of the arm as follows: the median nerve was located in the cubital fossa medial to and immediately adjacent to the tendon of biceps; the ulnar nerve was located in the groove between the medial epicondyle and the olecranon; and the radial nerve was marked where it passes through the lateral inter-muscular

septum between the medial and lateral heads of triceps to enter the mid to lower third of the humerus. These anatomical sites have been used in previous studies on patients with chronic whiplash (Sterling et al., 2002; Sterling et al., 2003; Scott et al., 2005).

In addition, within the study V, we also assessed PPT levels over the trigeminal nerve trunks as follows: the supra-orbital nerve (V1) was located at the supra-orbital foramen (at the junction between the lateral and medial third of the upper part of the margin of the orbit), the infra-orbital nerve (V2) was located over the infra-orbital foramen above the canine fossa, and the mental nerve from the mandibulary nerve (V3) was located over the mental foramen on the anterior surface of the mandible. These points have been also used for assessing pressure pain hyperalgesia in individuals with cluster headache (Fernández-de-las-Peñas et al., 2011b)

4.2.2. Topographical Pressure Pain Sensitivity Maps

It is commonly seen in clinical practice that not all points of the same e.g., muscle exhibit the same hyperalgesia. Therefore, our group has demonstrated the utility of topographical mapping leading to a new imaging modality of mechanical pain sensitivity by assessing PPT within a specific region in a set of predetermined locations (Binderup et al., 2008). This technique has enabled the visualization of non-uniformity deep sensitivity at specific distributed anatomical locations. The technique consists of the assessment of PPT levels in established points around the same muscle or area. The distance among points and the elapsed time between consecutive PPT recordings prevented both spatial and temporal summation (Nie et al., 2009). After PPT assessment, the averaged values over each recorded location are interpolated using an inverse distance weighted interpolation data to determine the topographical distribution of pressure pain hyperalgesia (Shepard, 1968).

In the current dissertation we showed the first topographical mechanical pain sensitivity maps developed by our group for different muscles: temporalis (studies II, IV, **Fig. 1, right**), trapezius (study III, **Fig. 1, left**) and infraspinatus (study VI, **Fig. 1, middle**).

Figure 1, right (study III): The following 11 points were marked (Nie et al., 2005b): 1, occiput: at the suboccipital muscle insertion; 2, cervical muscle: transverse process of C5; 3, cervical myotendinous spot: transverse process of C7; 4, upper trapezius: middle point between the spinous process of C7 and the acromion; 5, levator scapulae: 2cm superior to the superior angle of the scapula bone; 6, superior angle of the scapula; 7, 1cm medial to the acromion-clavicular joint; 8, supraspinatus: 3cm superior to the middle of spina of the scapula; 9, supraspinatus: 2cm distal to the middle of spina of the scapulae; 10, middle trapezius: middle point of spinous process of T4 and medial border of spina scapulae; and, 11, lower trapezius: middle point of spinous process of T6 and medial border of spina scapulae.

Figure 1, middle (study VI): Since the infraspinatus is triangular in shape, the surface area overlying the muscle was divided into 10 circular sub-areas with a diameter of 1.0cm, corresponding to the diameter of the probe of a pressure algometer.

Figure 1, right (study II, IV): Nine points over the temporalis muscle were marked with a wax pencil. The lobe ear was taken as the reference point. The vertical line of the ear defined as the central column was considered as the centre of the muscle belly. In this way, three vertical points separated by 1.5 cm were marked. These 3 points (labelled 2, 5 and 8) were used to define the anterior and posterior columns. The points located in the anterior part of the muscle (labelled 3, 6 and 9) were located 1 cm anterior to each respective vertical point; whereas the points located in the posterior part (labelled 1, 4 and 7) were located 1 cm posterior to each respective vertical point

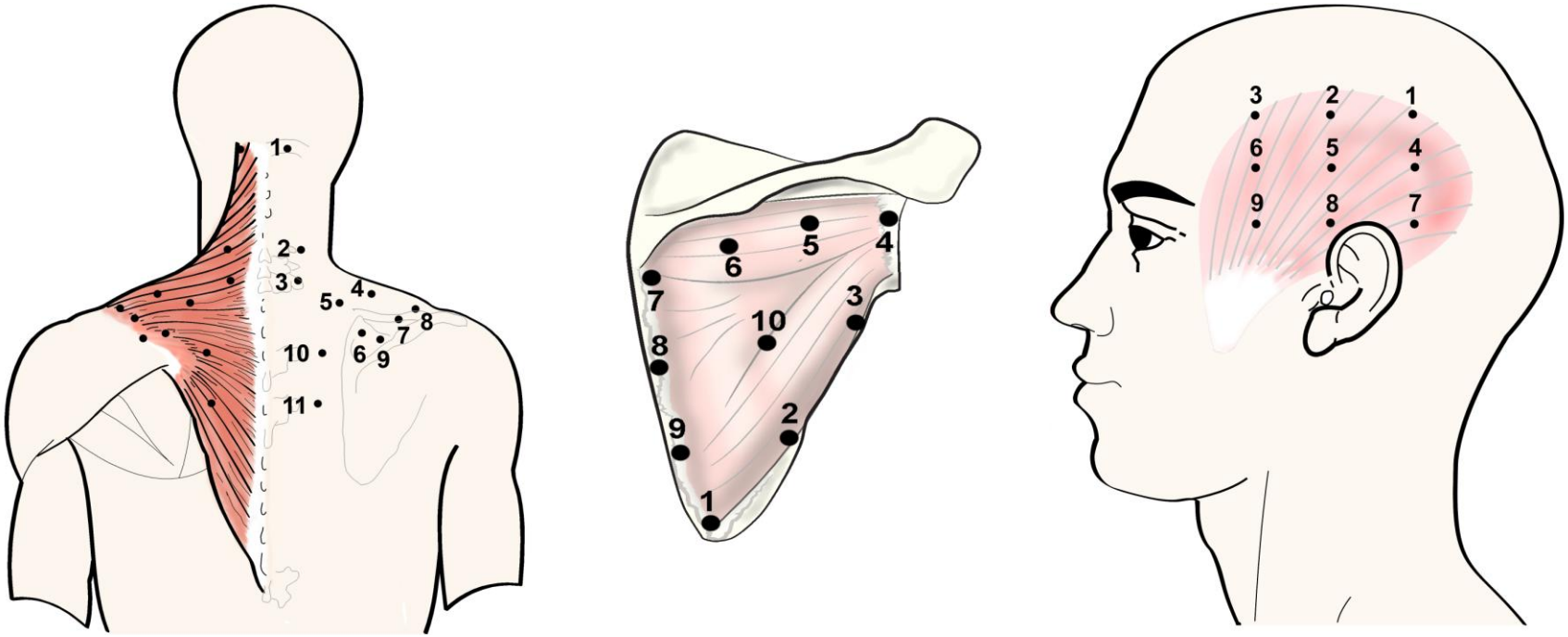


Figure 1: Representation of the points for PPT assessment over the trapezius muscle (right-study III), infraspinatus muscle (middle-study VI) and temporalis muscle (study II and IV, right)

More recently, topographical sensitivity maps of completed anatomical regions have been also developed by our research groups: hand (Fernández-de-las-Peñas et al., 2010a, **Fig. 2**), head (Cuadrado et al., 2010, **Fig. 3**), or low back (Binderup et al., 2010). These maps provide more information of the pressure pain sensitivity of a region of the body involving different muscles or tissues.

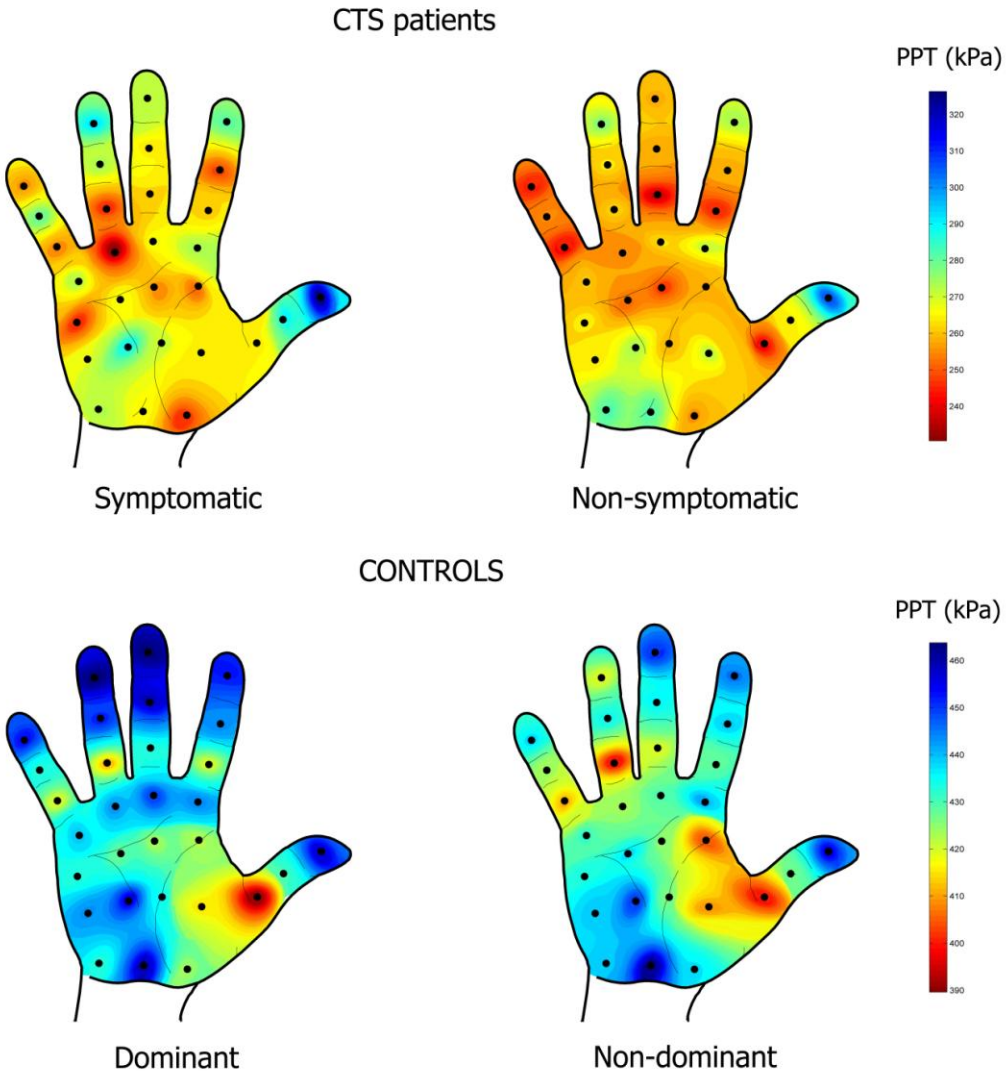


Figure 2: Average PPT maps in the hand of patients with carpal tunnel syndrome (CTS) and healthy controls. Each point represents the location of the points where the PPT was measured (modified from Fernández-de-las-Peñas et al., 2010a).

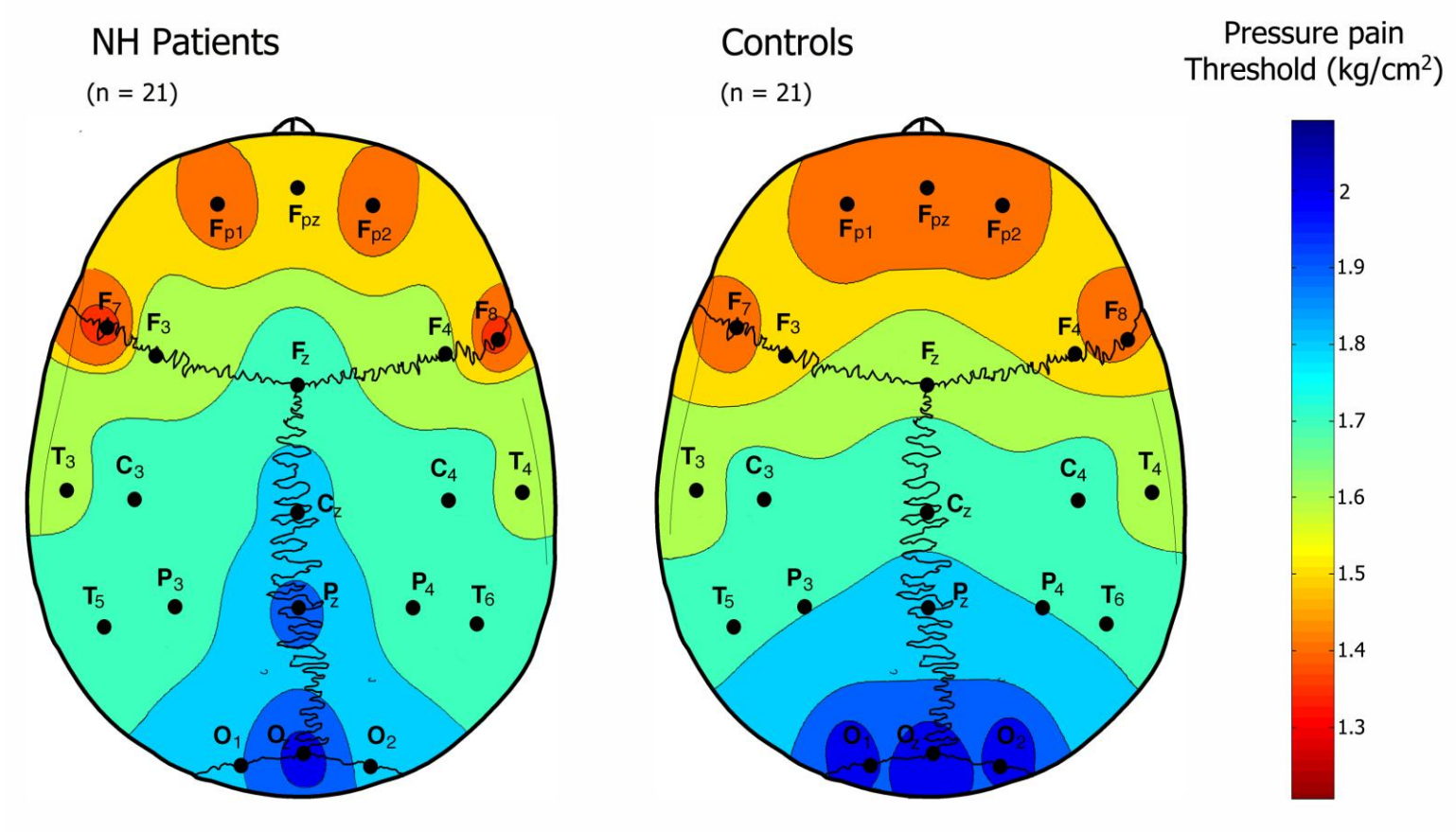


Figure 3: Average PPT maps in the head for patients with nummular headache (NH) and healthy controls. Each point represents the location of the points where the PPT was measured (modified from Cuadrado et al., 2010).

5. Sensitization Mechanisms

5.1. Basic Concepts

5.1.1. Peripheral Mechanisms Involved in Pain Processing

5.1.1.1. Peripheral Nociceptors

The main structure involved in peripheral mechanisms is the nociceptor. Nociceptors are free nerve endings which respond to noxious stimuli, including Aδ (group II, thinly myelinated axon) and C (group IV, un-myelinated axon) fibres. The peripheral terminals of nociceptors, free nerve endings, are found in several tissues including skin, muscles, tendons, joint structures, periosteum, inter-vertebral disks, and peripheral nerves (Willis & Coggeshall, 2004). The nociceptor is a sensory receptor capable of transducing and encoding actually or potentially noxious stimuli. Nociceptors convert mechanical, thermal, and chemical inputs into electrical signals to the central nervous system.

Different nociceptors are involved in musculoskeletal pain syndromes, being the most relevant the *muscle and joint nociceptors*. Primary afferent fibres innervating muscle and joint are classified as groups II, III, and IV (Schaible & Schmidt, 1985; Schaible & Schmidt, 1988; Mense, 1993; Schaible et al., 1993; Hepplemann et al., 1998; Willis & Coggeshall, 2004). Both groups III and IV fibres transmit nociceptive information from free nerve endings in the periphery to the spinal dorsal horn neurons. The adequate stimuli to activate a muscle nociceptor are pressure and ischemia (Diehl et al., 1993; Mense, 1993).

5.1.1.2. Peripheral Sensitization

It is known that the sensitivity of nociceptors to painful stimuli is modifiable by increasing or decreasing in response to peripherally applied mechanical, thermal, or chemical stimuli. *Sensitization* is a term describing the changes in nociceptiye neurons after tissue injury and it is defined as an increased responsiveness of neurons to their normal input or recruitment of a response to normally sub-threshold inputs.

Peripheral sensitization refers to an increased responsiveness and reduced threshold of nociceptors to stimulation of their receptive fields, and it is characterized by an increase in spontaneous activity, a decrease in response threshold to noxious stimuli, an increase in responsiveness to the same noxious stimuli, and/or an increase in receptive field size (Mense & Stahnke, 1983; Schaible & Schmidt, 1985; Schaible & Schmidt, 1988). Different substances can sensitize primary nociceptive fibres. Particularly effective stimulants for muscle nociceptors are endogenous substances such as bradykinin or serotonin (Mense 1993a). Bradykinin is released from plasma after tissue injury and is present in inflammatory exudates, sensitizes nociceptors and produces pain and heat hyperalgesia in humans (Kirchhoff et al., 1990; Manning et al., 1991; Koltzenburg et al., 1992; Cesare, 1996; Petho et al., 2001). Serotonin is released from platelets and activates muscle nociceptors and causes pain (Richardson & Engel 1986).

Several studies have reported that sensitisation of nociceptive nerve endings was greater with the combination of both substances rather than with each substance alone (Babenko et al. 1999; Mork et al, 2003a). Such stimuli causes a neurogenic inflammation, that is an antidromic release of neuropeptides, i.e. calcitonin gene-related peptide, substance P, or neurokinin A, from nerve endings of the C-fibres (O'Brien et al. 1989; Mense et al., 2001). Additionally, there are also changes in the content of fibres labelled for substance P and calcitonin gene-related peptide (Pereira da Silva et al., 1990; Mapp et al., 1994). The release of algogenic substances will lower tissue pH, and then activate the arachidonic acid

cascade which produces a number of unsaturated lipid products. Sensitization of nociceptors explains deep tissue hyperalgesia because this phenomenon decreases the mechanical excitation threshold and increases responses to noxious stimuli (Graven-Nielsen & Mense, 2001).

In such scenario, silent nociceptors begin to respond to innocuous and noxious stimuli (Schaible & Schmidt, 1988). These nociceptors will fire spontaneously inducing an increase in their activity which would increase the input to the central nervous system.

5.1.2. Central Mechanisms Involved in Pain Processing

The processing of nociceptive information and pain in the central nervous system is complex, and involves multiple anatomical pathways and brain sites. These pathways include responses that are coordinated within the spinal cord, ascending nociceptive pathways, descending facilitatory pathways, and descending inhibitory pathways. In addition, pain processing is plastic and modifiable. Central sensitization can occur through multiple mechanisms, including those resulting in increased excitation or decreased inhibition. Short-term sensitization can result from increased release of several excitatory neurotransmitters, e.g., glutamate or substance P that consequently activate their receptor, depolarizing the neuron (peripheral sensitization). Alternatively, decreased release of inhibitory neurotransmitters may also occur resulting in an overall increase in excitability of nociceptive neurons. Although central sensitization occurs within minutes after nociceptive stimulus, and central neurons exhibit an enhanced response to application of noxious stimuli to the injured tissue, this central sensitization most likely reflects the increased activity of the nociceptors. We will briefly summarize the neuro-physiological mechanisms accounting for this process.

5.1.2.1. Sensitisation of Second-order Neurons in the Dorsal Horn

It seems that sensitisation of the central nervous system can be generated by prolonged nociceptive inputs from the periphery (Mendell & Wall, 1965). Inputs from muscle nociceptors are more effective in inducing prolonged changes in the behaviour of dorsal horn neurones than inputs from cutaneous nociceptors (Wall & Woolf, 1984). Muscles and joints send nociceptive information predominantly to lamina I and the deeper dorsal horn, whereas cutaneous tissue has dense projections to lamina II (Craig et al., 1988; Mense & Craig, 1988; Mense, 1993; Schaible & Grubb, 1993).

Neurons in the dorsal horn of the spinal cord are classified as high-threshold mechano-sensitive neurones (require noxious intensities of stimulation for activation), low-threshold mechano-sensitive neurones (activated by innocuous stimuli) and wide-dynamic-range neurones (respond to both noxious and innocuous stimuli). During central sensitisation, these dorsal horn neurones would become hyper-excitable in response to noxious stimulation (Hu et al., 1992; Hoheisel et al. 1993). Noxious stimuli to a specific receptive field generate new receptive fields at a distance from the original within minutes, and referred pain outside the lesion is provoked by sensitisation to adjacent spinal segments (Mense, 1994). Enlargement of the receptive fields occurs after tissue injury and can also include the entire limb (Hoheisel et al., 1993) or even the contra-lateral extremity (Sluka et al., 2003). Thus, the expansion of receptive fields of central neurons is common and widespread, explaining the underlying referred and distant pain associated with deep-tissue injury.

Significant increased excitability of the dorsal horn neurones would alter the pain perception. In this sensitised state, previously ineffective low-threshold Aβ-fibre inputs to nociceptive dorsal horn neurones may become effective (Woolf & Thompson, 1991; Hoheisel et al., 1993). In such scenario, pain could be generated by low-threshold Aβ-fibres, which clinically would manifest as allodynia. It

has been suggested that the major cause of increased pain sensitivity in chronic pain is an abnormal response to inputs from low-threshold Aβ-fibres (Woolf& Doubell, 1994).

Further, in the sensitised state, the afferent Aβ-fibres (that normally inhibit Aδ- and C-fibres by pre-synaptic mechanisms in the dorsal horn) will on the contrary stimulate the nociceptive second order neurones. Therefore, the effect of Aδ- and C-fibre stimulation of the nociceptive dorsal horn neurones will be promoted and the receptive fields of the dorsal horn neurones will be expanded (Coderre et al., 1993). The nociceptive input to supra-spinal structures is increased resulting in increased excitability of supra-spinal neurones (Lamour et al., 1983), decreased pain inhibition, or also increased facilitation of nociceptive transmission in the spinal dorsal horn (Wall & Devor, 1981) which clinically will manifest as generalized hypersensitivity. Although, sensitization of the dorsal horn neurons can be maintained by sensitized nociceptive inputs; sensitization of the central nervous system can also persist in absence of nociceptive peripheral input.

5.1.2.2. Structural Changes in the Thalamus

In the last decades, central pain processing has been assessed with imaging techniques, such as magnetic resonance imaging (MRI) and positron emission tomography (PET) looking at cerebral blood flow changes following nociceptive stimuli (May, 2008). Plasticity refers to changes that occur in the established nervous system. Recent studies have demonstrated that neuroplasticity at several levels of the central nervous system is related to the presence of chronic pain. Neuroplastic changes relating to function, chemical profile, or structure during the process of chronic pain have been described for both, peripheral (receptor and ion-channel reorganization, neurotransmitter changes) and central (functional changes of representational fields) nervous systems, including the spinal cord (sensitization and dis-

inhibition) (May, 2008). Different studies found that cortical regions most reliably activated by painful stimuli are SI and S2 and also the anterior cingulate cortex (Coghill et al., 1994; Rainville et al., 1997; Hofbauer et al., 2001).

Different studies have demonstrated the presence of altered brain morphology in areas related to pain in individuals with chronic back pain (Apkarian et al., 2004; Schmidt-Wilcke et al., 2006), fibromyalgia (Kuchinad et al., 2007; Schmidt-Wilcke et al., 2007; Hsu et al., 2009), complex regional pain syndrome (Geha et al., 2008), tension-type headache (Schmidt-Wilcke et al., 2005), and migraine (Kim et al., 2008; Valfre et al., 2008). Some authors discuss these data as atrophy, reinforcing the idea of damage or loss of brain gray matter (Apkarian et al., 2004; Rocca et al., 2006; Kuchinad et al., 2007; Kim et al., 2008); nevertheless, a decrease in the brain gray matter does not necessarily mean neuronal destruction. Independent of the exact nature of these changes, it is accepted that chronic pain patients have a decrease in gray matter as a common feature, and while the exact loci differ between groups, there seems to be overlap in some areas: the cingulate cortex, insula, and dorso-lateral prefrontal cortex (Apkarian et al., 2004; Schmidt-Wilcke et al., 2005, 2006; Draganski et al., 2006; Kuchinad et al., 2007). Additionally, most of these studies have reported a more or less significant correlation between brain gray matter changes and duration of pain, suggesting that these changes may be the consequence of pain (Apkarian et al., 2009). This hypothesis was confirmed in an interesting study as gray matter decrease is, at least, partly reversible when the pain is successfully treated (Rodriguez-Raecke et al., 2009). These authors suggested that the gray matter abnormalities found in chronic pain do not reflect brain damage but rather are a reversible consequence of chronic nociceptive pain transmission, which normalizes when the pain and the peripheral nociceptive input is properly treated (Rodriguez-Raecke et al., 2009).

5.1.2.3. Dynamic balance between Descending Facilitation and Inhibition

Descending modulation of nociceptive information occurs through several nuclei including the periacueductal gray substance (PAG), the rostral ventro-medial medulla (RVM), and the lateral pontine tegmentum. Anatomically, the PAG sends projections to the RVM and the lateral pontine tegmentum, but not directly to spinal cord neurons. The RVM and lateral pontine tegmentum project to the spinal cord and modulate dorsal horn neuron activity and nociceptive information. Other nuclei involve in this process are the anterior pretectal nucleus, hypothalamus, somato-sensory cortex, thalamus, red nucleus, parabrachial region, hypothalamus, prefrontal cortex, amygdala, reticulo-spinal tract, and rubro-spinal tract (Heinricher, 1997; Sluka & Rees, 1997; Neugebauer & Li, 2003).

It is thought that there is a balance between facilitation and inhibition from these descending modulatory pathways (Porreca et al., 2002). In fact, some experimental studies have found mechanical hypoalgesia in the referred pain area after unilateral or bilateral injection of hypertonic saline in the upper trapezius muscle in healthy subjects suggesting the activation of descending inhibitory pain pathways as a physiological response after peripheral nociceptive muscle input (Ge et al. 2003; 2006a). If the nociceptive input decreases or ceases, the referred pain gradually disappears, and mechanical hypoalgesia or no changes on mechanical pain sensitivity are found in the referred pain areas (Ge et al. 2003, 2004b, 2006a). On the other hand, if the nociceptive input does not decrease, both peripheral and central sensitisation mechanisms appear and descending pain inhibition maybe decreased and can be dysfunctional (Ge et al. 2004c).

Diffuse noxious inhibitory control (DNIC) is a term used to describe an innate pain modulatory system where application of noxious stimuli induces generalized analgesia. DNIC can be demonstrated experimentally by the application of painful stimuli to a distant site (arm) which produces analgesia at the test site (leg) in healthy people (Villanueva & Le, 1995). Activation of DNIC pathways reduces

hyperalgesia and pain in humans and also reduces dorsal horn neuron activity (Villanueva & Le, 1995). The analgesia produced by DNIC is non-opioid and involves pathways outside the PAG-RVM pathway (Villanueva & Le, 1995). Several studies have reported less efficient DNIC, i.e., decreased inhibition to a noxious stimulus, in chronic pain conditions such as temporomandibular pain (Bragdon et al., 2002), low back pain (Peters et al., 1992), fibromyalgia syndrome (Kosek & Hansson, 1997; Lautenbacher & Rollman, 1997), osteoarthritis (Kosek & Ordeberg, 2000), chronic tension-type headache (Pielstickera et al., 2005), and migraine (Sandrini et al., 2006).

5.2. Clinical Concepts

5.2.1. Local Chronic Pain Syndromes

In this dissertation we have included temporomandibular, lateral epicondylalgia, shoulder pain, tension-type and migraine headaches as musculoskeletal local pain syndromes of the upper quadrant. All the studies presented revealed that these local pain syndromes exhibited widespread pressure pain hyperalgesia as sign of central sensitization mechanisms (studies V-IX).

5.2.1.1. Myofascial Temporomandibular Disorder (TMD)

In the first study (V), we found bilateral and widespread pressure pain hypersensitivity over different deep tissues such as nerve, joint and muscle tissues in patients with strictly myofascial TMD according to the Research Diagnostic Criteria for TMD (RDC/TMD) (Dworkin & LeResche, 1992). PPT was significantly decreased bilaterally over the supra-orbital, infra-orbital, mental, median, ulnar, and radial nerve in women with strictly myofascial TMD suggesting trigeminal and extra-trigeminal sensitization of afferent inputs from neural tissues in myofascial TMD. In fact, the magnitude of PPT

changes within the TMD group was similar between trigeminal and extra-trigeminal areas suggesting that pressure pain hyperalgesia was uniform. These results agree with previous studies conducted in other chronic pain conditions: whiplash (Sterling et al., 2003; Scott et al., 2005), lateral epicondylalgia (study IX), unilateral migraine (study I), unilateral carpal tunnel syndrome (Fernández-de-las-Peñas et al., 2009a), and cluster headache (Fernández-de-las-Peñas et al., 2011b) which have also reported a generalized decreases in PPTs over nerve tissues as sign of hyper-excitability of the central nervous system (Zusman, 1992).

Consistent with a significant decrease in PPT over nerve trunks, a significant bilateral decrease in PPT over the lateral pole of the TMJ, the C5-C6 zygapophyseal joint and the tibialis anterior muscle was also present in women with TMD, suggesting extra-trigeminal and multi-segmental sensitization in women with strictly myofascial TMD. In agreement with our findings, previous studies have reported lower PPT levels in the index finger and the tibialis anterior muscle in patients with myofascial TMD, supporting a generalized sensitization (Maixner et al., 1995; Svensson et al., 2001). In addition, clinical evidence consistent with the principle that myofascial TMD is associated with a hyper-excitability of central nervous system is that these patients often report persistent pain in multiple body areas (Türp et al., 1998) and TMD is highly co-morbid with fibromyalgia syndrome (Wright et al., 1997).

An interesting result of the current study was that the magnitude of PPT changes within the TMD group was similar in the lateral pole of the TMJ (49.5%), the C5-C6 zygapophyseal joint (49.8%) the tibialis anterior muscle (49%), trigeminal nerves (49-52%) and extra-trigeminal nerve trunks (47-52%), suggesting a widespread increased responsiveness to pressure pain in women with TMD. These results differ from the data previously reported by Svensson et al (2001) who found that the magnitude of sensitization was higher in the symptomatic area (masseter: 24%-32%) than the non-symptomatic (tibialis anterior: 18%). Therefore, current and previous (Maixner et al., 1995; Wright et al., 1997; Türp

et al., 1998; Svensson et al., 2001; Sarlani et al, 2004) findings suggest that sensitization is not only restricted to the trigeminal second order neurons, but also to extra-trigeminal nociceptive pain neurons, supporting the concept of a central amplification of nociceptive pain in TMD patients.

Other QST, particularly thermal pain thresholds, have been also used for assessing nociceptive processing in patients with TMD pain; however, the results are conflicting. Maixner et al (1995, 1998) reported lower heat pain thresholds over the masseter region and forearm in patients with myofascial TMD pain and combined of myofascial TMD and TMJ pain. On the contrary, Svensson et al (2001) and Raphael (2009) did not find significant differences for heat pain thresholds between patients with myofascial TMD and healthy controls in both trigeminal and extra-trigeminal regions. Fernández-de-las-Peñas et al (2010c) found bilateral heat and cold hyperalgesia (lower heat pain and increased cold pain thresholds) but normal warm and cold detection thresholds in both trigeminal and extra-trigeminal regions in women with myofascial TMD. These results further support the hypothesis that myofascial TMD is characterized by sensitization processes not only in the trigeminal second order neurons, but also in extra-trigeminal nociceptive pain neurons, as previously suggested (Maixner et al., 1995; 1998; Svensson et al., 2001; Sarlani & Greenspan, 2003; Sarlani et al., 2004; Mohn et al., 2008). Nevertheless, due to that sensory disturbances are heterogeneous in individuals with myofascial TMD, patients could be classified into subgroups. In fact, Pfau et al (2009) described two subgroups of TMD patients (sensitive and insensitive) based on fibromyalgia tender point count. The sensitive subgroup was more sensitive to pressure and thermal stimuli as compared to the non-sensitive TMD group and to the control group (Pfau et al., 2009). These authors also suggested that their results indicate TMD as precursor of fibromyalgia syndrome in a continuous spectrum sharing the same underlying pathology, supporting common nociceptive pain pathways.

The existence of sensitization of central nervous system does not exclude the role of peripheral nociception in myofascial TMD, since both processes are clearly implicated in the patho-physiology of TMD pain (Sarlani & Greenspan, 2003; Svensson et al., 2004). We also found that widespread pressure pain hypersensitivity was associated with the intensity and duration of symptoms supporting a role of the peripheral nociceptive input in sensitization mechanisms. Since central sensitization is a dynamic condition influenced by multiple factors including the activity of peripheral nociceptive inputs (Herren-Gerber et al., 2004), it is possible that the peripheral nociceptive barrage from the masticatory muscles may contribute to this mechanism of sensitization. Some studies have reported lower PPT levels in the masticatory muscles as reflects of sensitization of primary nociceptive afferents in muscle tissues in individuals with myofascial TMD (Maixner et al., 1998; Kashima et al., 1999; Farella et al., 2000). In fact, experimental studies have reproduced clinical features of myofascial TMD by injecting different algogenic substances into the masseter muscle, e.g. glutamate (Svensson et al., 2003), bradykinin (Babenko et al., 1999) or hypertonic saline (Schmidt-Hansen et al., 2006). These findings support the notion that masticatory muscles can be the nociceptive source and may be involved in the genesis of myofascial TMD (Svensson & Graven-Nielsen, 2001). In our study (study V), PPTs over the tibialis anterior muscle, the mental nerve, C5-C6 zygapophyseal joint and the lateral pole of the TMJ were negatively associated with the intensity of the pain and the duration of symptoms suggesting a potential role of peripheral nociception in this pressure pain hyperalgesia. In this clinical scenario, the initial painful condition, i.e., muscle pain, possibly induced by tissue trauma, overload, inflammation, or trigger points (Fernández-de-las-Peñas et al., 2010b) may act as a trigger for chronification of pain and sensitization of nociceptive pathways in myofascial TMD. In agreement with this hypothesis, Younger et al (2010) found that patients with myofascial TMD exhibited decreased or increased gray matter volume in areas of the trigemino-thalamo-cortical pathway, including the brainstem trigeminal sensory

nuclei, the thalamus, and primary somatosensory cortex, and increased gray matter volume in limbic regions, e.g., the posterior putamen, globus pallidus, and anterior insula, compared to controls. In this study, self-reported pain intensity was associated with increased gray matter within the rostral anterior cingulate cortex and posterior cingulate (Younger et al., 2010), supporting a role of the peripheral input in these changes. Similarly, since previous studies investigating gray matter changes have also reported some correlation between these brain gray matter changes and duration of pain, it seems that changes within the brain gray substance is the consequence of the pain (Apkarian et al., 2009). More important, Rodriguez-Raecke et al (2009) confirmed that gray matter decrease is, at least, partly reversible when the pain is successfully treated suggesting that the gray matter abnormalities found in chronic pain do not reflect brain damage but rather are a reversible consequence of chronic nociceptive transmission, which normalizes when the peripheral nociceptive input is properly identified and treated

5.2.1.2. Shoulder Pain

Recent evidence supports that individuals with shoulder pain also exhibit central sensitization processes. We found a generalized decrease in PPT over the infraspinatus muscle within the painful side compared with the non-painful side in individuals with strictly unilateral shoulder pain (study VI). In addition, we also found that PPTs were significantly different throughout the infraspinatus muscle, although pressure pain sensitivity distribution was similar between the painful and non-painful sides, supporting that intrinsic features of the muscle are not relevant for pressure pain hyperalgesia. In this study, PPT at measurement sites over the mid-fibre region of the muscle belly (numbers 2, 3, 10) was lower than at the remaining points (**Fig. 4**). Therefore, topographical mapping of PPT revealed that mechanical pain sensitivity is heterogeneously distributed in the infraspinatus muscle in patients with unilateral shoulder pain. Further, bilateral sensitization pain mechanisms were also present in unilateral

shoulder pain since pain mapping exhibited similar distributional characteristics of PPT on both sides. In fact, there is substantial evidence suggesting that deep tissues injury results in a robust and long-lasting contralateral hyperalgesia, including mechanical hyperalgesia or allodynia (Sluka et al., 2001; Radhakrishnan et al., 2003; Clark et al., 2007), hypothesis supported by our results (study VI). In addition, clinical data showed that in patients with neck-shoulder pain, pain is initially unilateral but spreads bilaterally over time (Waling et al. 2000) showing pain drawings with a symmetrical left-right distribution (Madeleine et al., 1999; Toomingas 1999). An interesting finding of this study was that the location of the trigger points (TrPs) identified correspond well to the results by topographical mapping since PPT was much lower at active TrPs than on latent TrPs and lower than the non- TrPs.

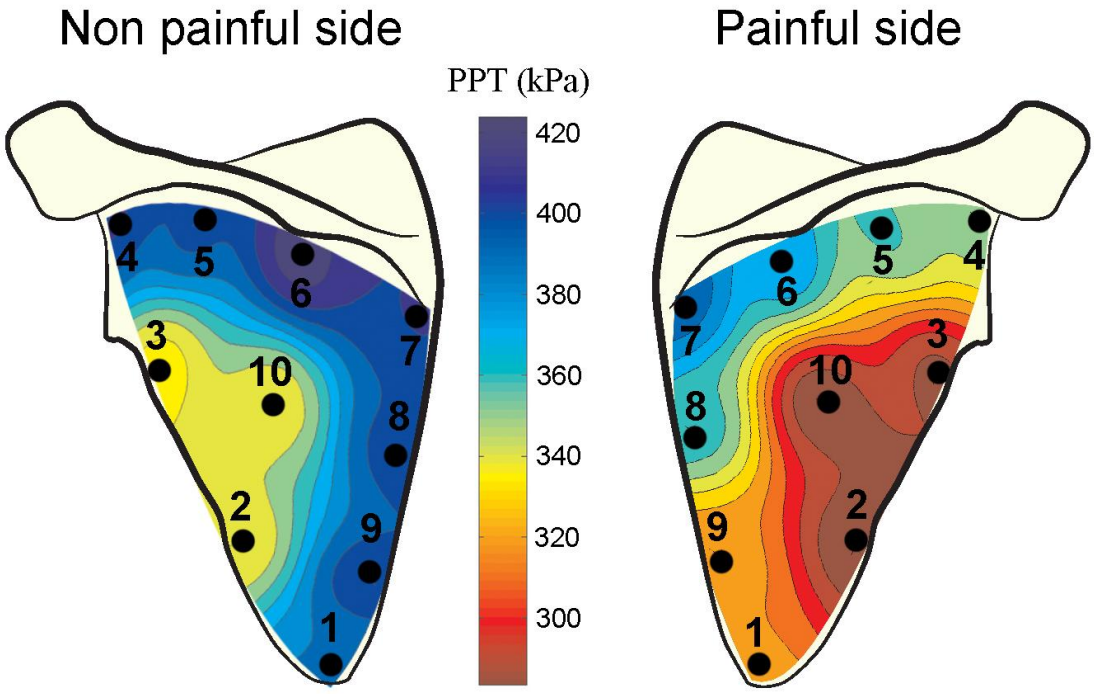


Figure 4: Topographical mapping of PPT on the painful side and non-painful side. Each point indicates the centre of each PPT measurement sites (point No. 1-10) in the infraspinatus muscle. The colour bar in the middle indicates the PPT (modified from study VI).

Current results of bilateral pressure pain hyperalgesia disagree with those recently reported by Coronado et al (2011) who found higher experimental pressure pain sensitivity in the involved side of patients with unilateral shoulder pain, but not on the contra-lateral unaffected side. These authors have suggested that side-to-side discrepancies between studies are related to the fact that it is possible that varying stages of the same disease process may yield different results in experimental pain sensitivity; since peripheral sensitization may be more relevant and easier to detect in acute and sub-acute stages, while central sensitization is more prevalent and easier to detect in chronic stages. Additionally, it is possible that gender differences in pain sensitivity also explain discrepancies between studies. Kindler et al (2011) reported that women with shoulder pain experienced greater clinical pain and enhanced sensitivity to pressure pain than men and the relationship between clinical and experimental pressure pain was stronger in women as compared to men, supporting this hypothesis. Other factor influencing pressure pain sensitivity is pain-related fear. In fact, George & Hirsh (2009) showed that pain-related fear contributed to variance in experimental pain sensitivity, suggesting that pain-related fear and pain catastrophizing may influence different components of the pain experience in shoulder pain (George & Hirsh, 2009).

In the study VII, we found that individuals with unilateral shoulder impingement also exhibited unilateral widespread decreases in PPT over the symptomatic area (i.e., levator scapulae, supraspinatus, infraspinatus, pectoralis major and biceps brachii muscles) and over distant pain-free areas (i.e., tibialis anterior muscle) when compared to controls. The fact that patients with shoulder impingement exhibit decreased PPT levels over the levator scapulae, the supraspinatus, the infraspinatus, the biceps brachii, and pectoralis major muscles suggests a sensitization mechanism of the symptomatic area in this pain population which is expected since these muscles are involved in arm motion. It is also important to note that these muscles receive innervation from the same cervical spine segments (C4-C6) suggesting

a segmental sensitization process of dorsal horn neurons. This sensitization can explain why several patients with unilateral pain develop bilateral pain symptoms. In addition, consistent with significant decreases in PPT levels over the shoulder muscles, we also found lower PPT over the tibialis anterior muscle suggesting sensitization of the central nervous system in unilateral shoulder impingement; although this assumption should be consider with caution at this stage as we only assessed one side of the body. This finding has been also recently reported in elite swimmers with shoulder pain showed significant lower PPT in all muscles compared with healthy controls (Hidalgo-Lozano et al., 2011b). More interestingly, a recent study reported that patients with shoulder pain exhibiting higher levels of central sensitisation pre-operatively experienced worse post-operative outcomes (Gwilym et al., 2011). Therefore, central sensitization seems to be a poor prognosis factor for post-surgery outcomes in this condition. Nevertheless, the magnitude of PPT changes in the shoulder impingement group was similar between the symptomatic muscles, but less over the tibialis anterior muscle. It is possible that central sensitization found in patients with shoulder pain is lower than in other chronic pain conditions, e.g., TMD or fibromyalgia syndrome.

In addition, we also found significant negative correlations between spontaneous pain intensity and PPT over the neck-shoulder musculature (i.e., levator scapulae, supraspinatus and biceps brachii muscles) in shoulder impingement: the greater the pain intensity, the lower the PPT levels. Similarly, Coronado et al (2011) also reported an association between local PPT and clinical pain intensity in individuals with unilateral shoulder impingement. These findings support a role of the peripheral input as an important factor driving the development of spreading sensitization, at least in this population. This hypothesis is further supported by the role of active TrPs in mechanical hypersensitivity observed in patients with shoulder pain (study VI) or shoulder impingement (study VII). In fact, a recent case series has demonstrated that manual treatment of active TrPs help to reduce shoulder pain and pressure

sensitivity in individuals with shoulder impingement (Hidalgo-Lozano et al., 2011a), supporting that active TrPs in the shoulder muscles may contribute directly to shoulder complaints and sensitization in shoulder impingement syndrome, although future randomized controlled trials are required.

Finally, two studies have investigated thermal pain thresholds in individuals with shoulder pain. Coronado et al (2011) reported bilateral lower heat pain thresholds in patients with unilateral shoulder impingement indicating the presence of central sensitization. Valencia et al (2011) found that supra-threshold heat pain responses were a stronger predictor of pain intensity compared with measures of pain threshold and tolerance in patients with shoulder pain. Future studies combining different QST in patients with unilateral or bilateral shoulder pain are urgently needed to further confirm the presence of central sensitization mechanisms.

5.2.1.3. Lateral Epicondylalgia

There are few data related to central sensitization mechanisms and pressure pain hyperalgesia in lateral epicondylalgia (LE). Previous studies have reported that LE is characterised by mechanical, but not thermal hyperalgesia proposing that LE resembles a secondary hyperalgesia area (Wright et al., 1994; Sran et al., 2002). Recent studies have demonstrated that patients with LE also exhibit central sensitization mechanisms. In the study VIII, we reported bilateral lower PPT levels over the elbow and the dorsal aspect of the wrist in patients with unilateral lateral epicondylalgia. In addition, the affected elbow of the patients exhibited higher pressure pain hypersensitivity (lower PPT) than the non-affected side; however, this finding was not replicated for the dorsal aspect of the wrist. These results suggest that mechanical hyperalgesia seems to be a clear somato-sensory characteristic of LE; although other sensory disturbances were also found. Additionally, the fact that patients exhibited bilateral pressure pain hyperalgesia in the symptomatic area and in a distant area (wrist) also suggests, at least, a contra-

lateral segmental sensitization of the dorsal horn neurons. The presence of sensitization of dorsal horn neurons is also supported by the fact that patients with strictly unilateral LE exhibited latent TrPs in the unaffected arm (Fernández-Carnero et al., 2008)

In the last study included in the current dissertation (study IX) we showed widespread and bilateral pressure pain hyperalgesia in patients with strictly unilateral LE as lower PPT levels were bilaterally found over nerve trunks of the upper extremity (median, ulnar, and radial nerves), lateral epicondyle, C5-C6 zygapophyseal joint and tibialis anterior muscle. These results further support the presence of central sensitization mechanisms in patients with LE since patients with strictly unilateral symptoms exhibited bilateral pressure pain hyperalgesia. In fact, current results were similar to those previously found in patients with TMD pain (study V), whiplash associated disorders (Sterling et al., 2003), carpal tunnel syndrome (Fernández-de-las-Peñas et al., 2009a), cluster headache (Fernández-de-las-Peñas et al., 2011b), TTH (Ashina et al., 2006), low back pain (O'Neill et al., 2007), knee osteoarthritis (Bajaj et al., 2011; Arendt-Nielsen et al., 2010), or fibromyalgia syndrome (Desmeules et al., 2003).

Ruiz-Ruiz et al (2011) have recently investigated topographical distribution of pressure sensitivity in individuals with unilateral LE and reported that patients with LE heterogeneous pressure pain maps with the most sensitive localizations being the muscle belly of the extensor carpi radialis brevis muscle (**Fig. 5**). These findings further support the concept that pressure pain hypersensitivity is a clear feature of patients with LE. Additionally, this study also support a potential role of the extensor carpi radialis brevis muscle in LE as previously suggested (Coombes et al., 2009).

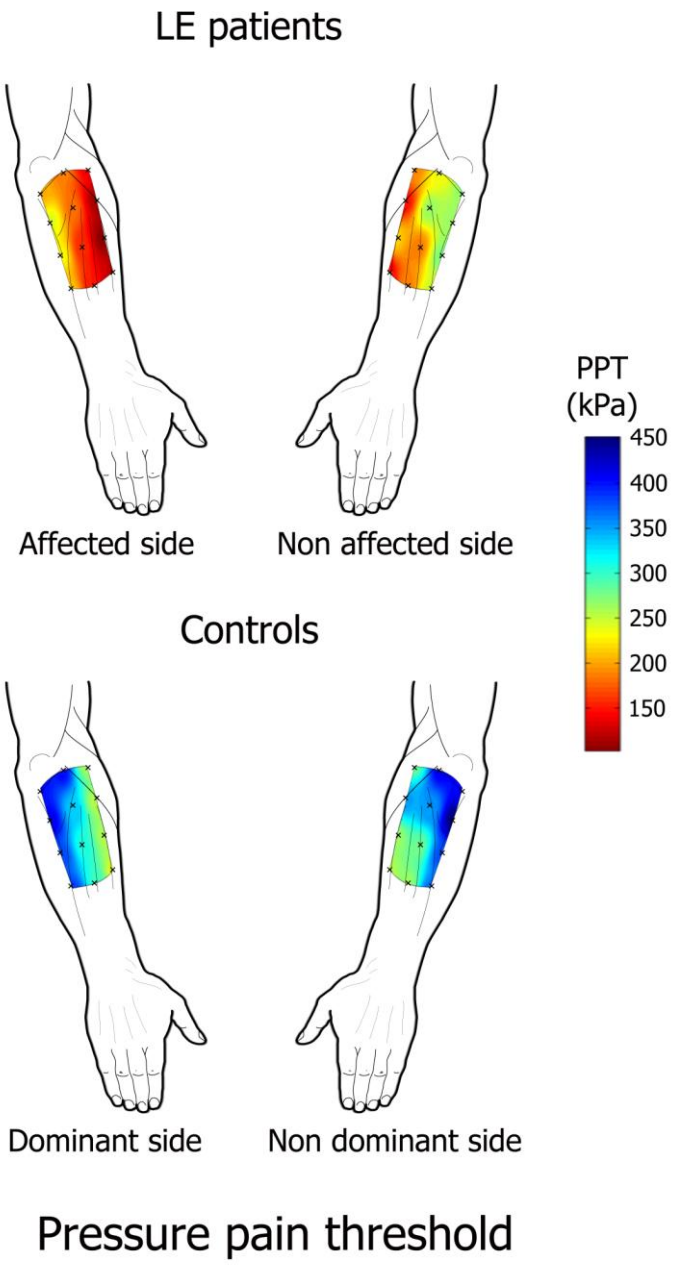


Figure 5: Topographical pressure pain maps in patients with unilateral lateral epicondylalgia (LE) and healthy controls. Representation of the 12 points forming a 3×4 matrix (modified from Ruiz-Ruiz et al., 2011)

We also found that individuals with LE exhibited generalized pressure pain hyperalgesia over nerve trunks (study IX), similar to patients with whiplash (Sterling et al., 2003; Scott et al., 2005), TMD pain (study V), cluster headache (Fernández-de-las-Peñas et al., 2011b), carpal tunnel syndrome (Fernández-de-las-Peñas et al., 2009) and unilateral migraine (study I). These results also support that nerve tissues can be involved in the clinical feature of LE. This hypothesis is supported by the fact that patients with LE exhibited positive upper limb tension test 2 (radial nerve bias) (Yaxley & Jull, 1993; Wright et al., 1994). In fact, Fernández-de-las-Peñas et al (2010d) found that bilateral mechanical nerve pain hypersensitivity in patients with unilateral LE is related to specific and particular nerve trunks, in this case the radial nerve. This study revealed mechanical pain hyperalgesia over the radial nerve in women with LE and over the median nerve in CTS. Furthermore, pain symptoms were also related to pressure pain sensitivity over these specific nerves, radial nerve for LE but median nerve for CTS. Our results suggest the presence of central and also peripheral sensitization mechanisms in individuals with LE (Fernández-de-las-Peñas et al., 2010d). This hypothesis is supported by our study IX, where several significant negative correlations between PPT and clinical pain features were found: the greater the pain intensity, the lower was the PPT, in this case on the affected side. Similar results are reported by Ruiz-Ruiz et al (2011) where the degree of pressure, but not thermal, pain hyperalgesia correlated with pain intensity. Again, these results support a relationship between peripheral sensitization nociception (pain) and central sensitization in patients in LE.

The presence of cold and heat hyperalgesia in individuals with LE is still a matter of debate as some studies have not found thermal pain hyperalgesia over the lateral epicondyle in patients with LE (Wright et al., 1994; Sran et al., 2002) whereas our study VIII challenged this finding. Leffler et al (2000) found lower perception of thermal threshold stimulus in the forearm, i.e. referred pain area, in patients with LE. Ruiz-Ruiz et al (2011) demonstrated bilateral cold and heat pain hypersensitivity over

the elbow region in patients with LE as compared to controls. Heat pain hyperalgesia is considered a sign of peripheral nociceptor sensitization (Raja et al., 1984) whereas cold hyperalgesia is considered a feature of neuropathic pain as result of peripheral nerve injury (De Medinaceli et al., 1997). Current results would suggest that the elbow area may constitute a primary source of nociception in individuals with LE, supporting the hypothesis of peripheral sensitization mechanisms. Nevertheless, cold and heat hyperalgesia may be also representing changes in the central pain processing (Berglund et al., 2002). In fact, bilateral heat and cold hyperalgesia further reflect impairment in central nociceptive processing or dysfunctional state of endogenous pain modulatory systems. This is supported as bilateral heat and cold hypersensitivity was found in individuals with strictly unilateral symptoms (Ruiz-Ruiz et al., 2011).

5.2.2. Chronic Tension Type Headache (CTTH)

There has been an increasing interest in the pathogenesis of chronic tension type headache (CTTH) over the last decades; however, despite several advances in aetiology, the pathogenesis is not completely understood (Fernández-de-las-Peñas & Schoenen, 2009). It is clear that the most prominent finding in patients with CTTH is an increased tenderness to palpation of peri-cranial tissues and lower PPT in both cephalic and extra-cephalic locations (Schoenen et al., 1991; Jensen et al., 1992; Bovim, 1992; Bendtsen et al., 1996; Bove & Nilsson, 1999; Ashina et al., 2005; Ashina et al., 2006; Fernández-de-las-Peñas et al., 2007a; Schmidt-Hansen et al., 2007). These hyperalgesic and allodynic responses support the role of both peripheral and central mechanisms in the development of the clinical picture of CTTH (Fernández-de-las-Peñas & Schoenen, 2009). For instance, Buchgreitz et al (2007) showed that the increase in the prevalence of headache was associated with an increase in sensitivity to peri-cranial pain, confirming that pain sensitivity is enhanced in CTTH.

Previous studies showing differences in PPT levels between CTTH and healthy subjects have used a standardized point in the anterior part of the temporalis muscle (Schoenen et al., 1991; Jensen et al., 1992; Bovim, 1992; Bendtsen et al., 1996; Bove & Nilsson, 1999; Ashina et al., 2005; Fernández-de-las-Peñas et al., 2007a). Furthermore, it has been recently demonstrated that children with CTTH also exhibit widespread pressure hyperalgesia (Fernández-de-las-Peñas et al., 2010e). Nevertheless, it is commonly seen in clinical practice that hypersensitivity of deep tissues is not uniformly distributed over an area, which can explain why some authors have not found differences in PPT between patients with CTTH and healthy people (Peddireddy et al., 2009). Therefore, to explore anatomical distribution of pain sensitivity, we developed topographical pressure pain sensitivity maps as described above.

In studies III-IV we assessed topographical pressure pain maps of the temporalis and trapezius muscles in patients with CTTH. In fact, the study IV was the first one to apply topographical pressure sensitivity maps to evaluate muscle sensitivity distribution in patients with headache (Fernández-de-las-Peñas & Schoenen, 2009) In this study, we found that patients with CTTH exhibited bilateral lower PPT as compared to controls in agreement with precious studies (Schoenen et al., 1991; Jensen et al., 1992; Bovim, 1992; Bendtsen et al., 1996; Bove & Nilsson, 1999; Ashina et al., 2005; Fernández-de-las-Peñas et al., 2007a). The most important data from this study was that topographical pressure pain sensitivity maps showed a posterior to anterior PPT decreased distribution in both dominant and non-dominant sides in patients with CTTH; whereas in controls, maps were more heterogeneous **(Fig. 6**).

These results suggest that the anterior and middle parts of the temporalis muscles are the most sensitive since lower PPT were found in CTTH patients; however, these results were not replicated in healthy people. In healthy controls, the most sensitive point was the centre of the muscle belly (study IV). It is most likely that sensitisation of central pathways could lead to a more uniform distribution of hypersensitivity in patients with CTTH, but not in people without pain. In addition, the distribution of

nociceptors in the temporalis muscle could be also responsible for spatial distribution of pressure pain sensitivity maps. In fact, Nie et al (2005) found that PPT levels in muscle belly locations of the upper trapezius muscle were more sensitive to pressure pain than musculo-tendinous junction sites (Nie et al., 2005).

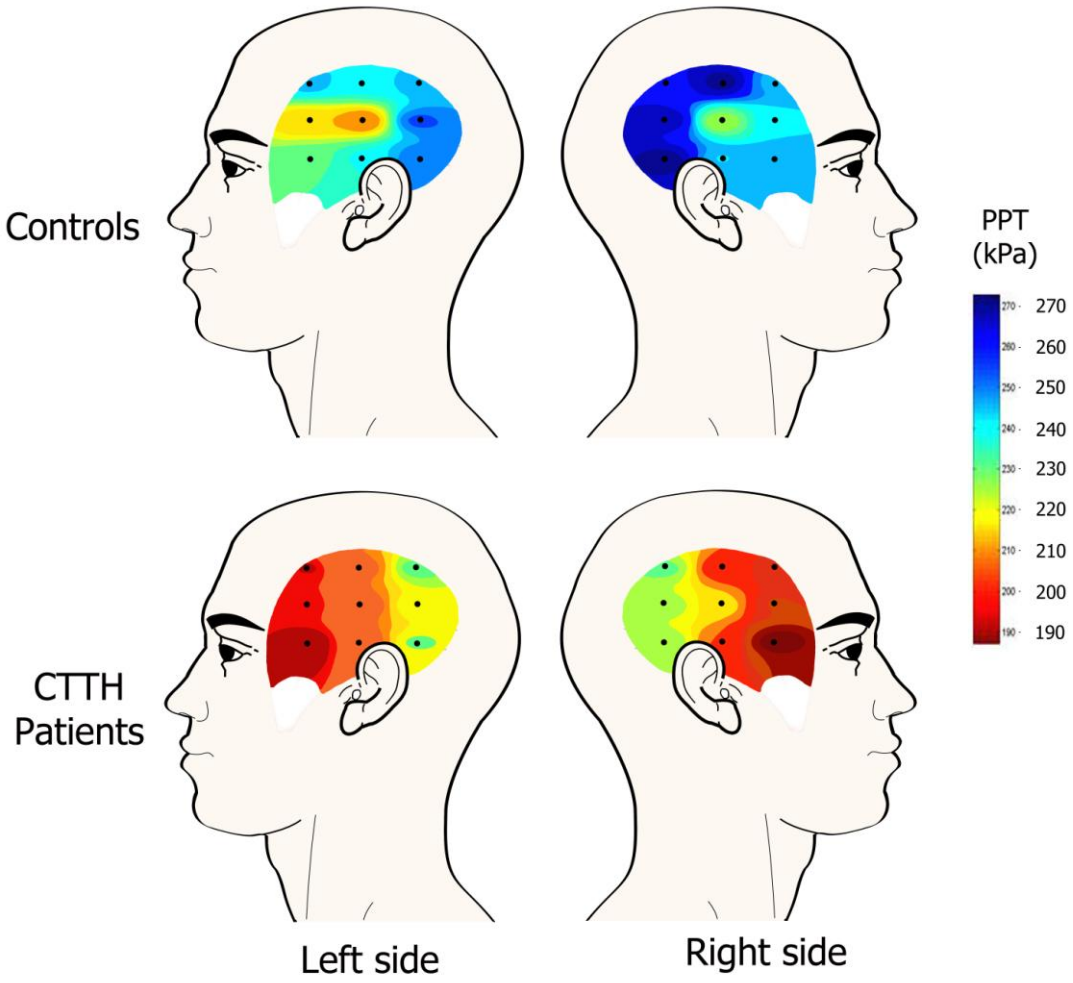


Figure 6: Average pressure pain threshold maps for chronic tension type headache (CTTH) patients (bottom) and healthy controls (top) in both temporalis muscles (modified from study IV)

It is also possible that the presence of TrPs also influence the topographical pain sensitivity, since PPT levels are lower over TrPs. In fact, Fernández-de-las-Peñas et al (2009b) found that active TrPs in the temporalis muscle were found mostly in the anterior column and in the middle of the muscle belly and that the location of active TrPs in this muscle corresponded to areas with lower PPT, supporting the relationship between active TrPs and topographical pressure pain maps in the temporalis muscle in CTTH. These results are similar to those previously reported in patients with shoulder pain (study VI).

Additionally, we also found that pressure pain sensitivity of the muscle belly (point 5), but not the remaining 8 points of the temporalis muscle was related to a greater headache pain intensity and longer headache duration. This finding is in line with that previously reported by Langemark et al (1989) who found a negative correlation between headache severity and PPT in the anterior part of the temporal muscle, but contrary to other studies where no correlation between PPT and headache parameters were found (Tüzün et al., 2005; Fernández-de-las-Peñas et al, 2007a). These discrepancies between previous studies can be explained by current results: pressure pain sensitivity is different depending on the point of assessment in the temporalis muscle and also between patients with central sensitization and healthy controls.

In addition, within the study III, we also found generalized and bilateral lower PPT over the whole trapezius muscle in CTTH patients as compared to both patients with strictly unilateral migraine and healthy controls (**Fig. 7**), suggesting a more generalized sensitization in this headache population. Similarly than in patients with migraine, the upper part of the trapezius muscle was the most sensitive part of the muscle in CTTH. This can be due to a different distribution of muscle nociceptors between the different sub-divisions of the trapezius muscle. Further, the neuro-physiological and morphological evidence of convergence from cervical sensory and muscle afferent inputs onto trigeminal sub-nucleus caudalis nociceptive and non-nociceptive neurons explain the phenomenon of cervical-to-trigeminal

and trigeminal-to-cervical referred pain. This study confirms the presence of pressure hyperalgesia in cervical muscles in patients with headache. In addition, an interesting finding was that topographical pressure pain sensitivity maps in individuals with CTTH were uniformly and symmetrical distributed between dominant and non-dominant sides. In line with these results, Bovim (1992) and Fernández-de-las-Peñas et al (2007a) also reported no side-to-side differences in PPT levels in patients with CTTH. Therefore, current evidence support bilateral pressure sensitisation of head (temporalis) and cervical (trapezius) muscles in CTTH. Our results are very similar to those previously reported for individuals with strictly unilateral migraine for the temporalis muscle (study II), but contrary to those data reported for the trapezius muscle (study III). It is possible that central sensitization mechanisms account for bilateral hyperalgesia in the trigeminal-related region (temporalis muscle) in headache, but the pressure pain hyperalgesia of the cervical-related region (upper trapezius) is related to the presence of symptoms (unilateral or bilateral).

Nevertheless, whether this mechanical pain hypersensitivity is a primary (cause) or a secondary (consequence) phenomenon to CTTH has been under debate. A 12-year follow-up longitudinal study demonstrated that subjects who later will develop CTTH showed normal tenderness scores and PPT levels before the beginning of the symptoms, which suggests that the mechanical pain hypersensitivity is rather a consequence than a risk factor for the development of CTTH (Buchgreitz et al., 2008). The results of topographical pressure pain maps support that central sensitization can account for changes in the distribution of mechanical pain sensitivity in chronic headache supporting this hypothesis, although this conclusion needs further studies.

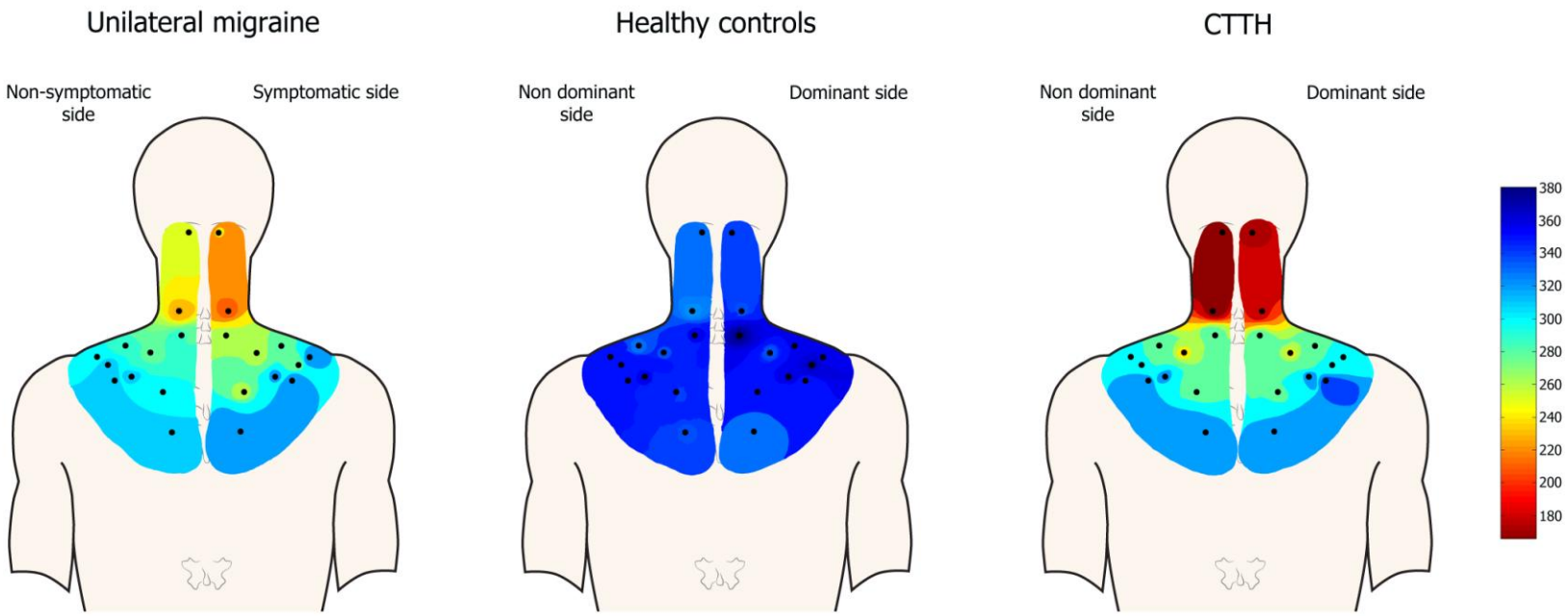


Figure 7: Average pressure pain threshold maps for the trapezius muscle in unilateral migraine (left), healthy controls (middle) and chronic tension type headache (CTTH-right) patients (modified from study III).

5.2.3. Migraine

Again, despite major advances in the understanding of pathophysiology of migraine a number of unresolved issues persist. It seems clear that migraine is also characterized by a hyper-excitability of the nociceptive pathways within the central nervous system (Burstein, 2001) which induces increased tenderness (Jensen et al., 1988) and cutaneous allodynia (Ashkenazi et al., 2007; Cuadrado et al., 2010). The results of pressure pain hyperalgesia in migraine are contradictory since some studies have reported lower PPT levels in adults (Weissman-Fogel et al., 2003; Grossi et al., 2011) and children (Zohsel et al., 2006) with migraine, whereas others have not found such differences in adults (Bowim, 1992) and children (Metsahonkala et al., 2006). These studies used a standardized point in the anterior part of the temporalis muscle for PPT assessment. According to the results of our study IV, the anterior column of the temporalis muscle seems to be the most sensitive part in patients with CTTH, but not in healthy controls. It is possible that discrepancies between these studies may be related to heterogeneous anatomical distributions of pressure pain hypersensitivity in the temporalis muscle in individuals with migraine and healthy people. Additionally, migraine attacks are usually unilateral, but several patients exhibit changes of the side of the pain. Therefore, it is also possible that mechanical hypersensitivity in patients with migraine is related to the side of the pain.

In studies II-III, we applied topographical pressure sensitivity maps to evaluate the distribution of pressure pain hypersensitivity in the head (temporalis) and neck (trapezius) muscles in individuals with strictly unilateral migraine attacks. We found that individuals with unilateral migraine exhibited bilateral lower PPT than controls in all points assessed over the temporalis muscle. Similarly than in CTTH, topographical pain sensitivity maps of the migraine patients were characterized by an anterior-posterior PPT gradient on both symptomatic and non-symptomatic sides being the anterior part more

sensitive than the posterior part. Again, in healthy people, pain sensitivity maps did not follow any particular spatial distribution being the mid-muscle belly the most sensitive point to pressure (**Fig. 8**).

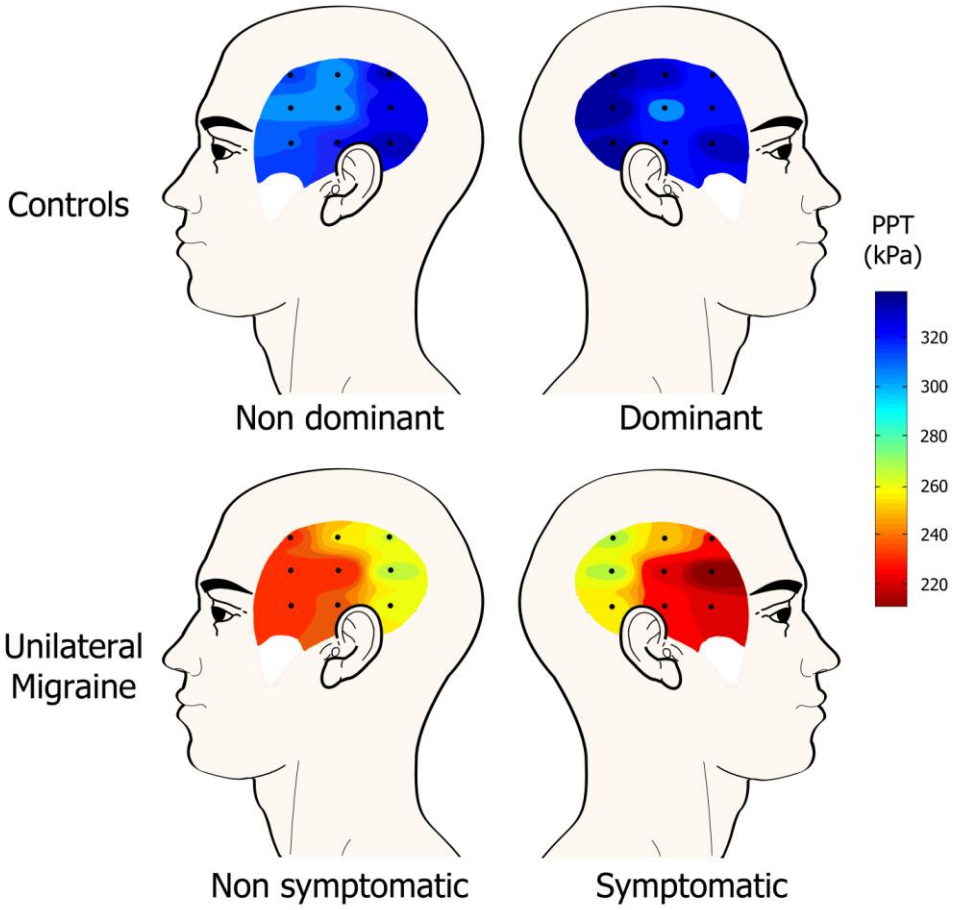


Figure 8: Topographical pressure pain sensitivity maps of the temporalis muscle for migraine patients and controls (modified from study II)

The presence of bilateral and symmetrical topographical pressure pain maps in individuals with strictly unilateral migraine symptoms was unexpected since our patients had a unilateral distribution of their symptoms. In fact, bilateral pressure pain sensitivity maps in unilateral migraine were similar to those maps reported in CTTH (study IV), and are consistent with bilateral pressure pain hyperalgesia in the cephalic region in both headache disorder. A different distribution of nociceptors between headache patients and healthy controls in the temporalis muscles could be responsible for these findings, but this is unlikely. It is more plausible that central sensitization probably account for the bilateral hyperalgesia seen in unilateral pain syndromes (Arendt-Nielsen et al., 2011). The presence of lower PPT on the non-symptomatic side further supports the hypothesis that central sensitization is responsible of mechanical hyperalgesia in migraine (Burstein, 2000). It can be that central sensitization accounts for bilateral pain hyperalgesia in the trigeminal-related region (temporalis muscle) in patients with unilateral migraine; although sensitization mechanisms in the neck exhibits side-to-side differences (study III). We showed that the upper part of the trapezius muscle is the most pain sensitive part of this muscle in headache patients and controls (study III). Topographical pain distribution could be due to a different distribution of muscle nociceptors between the different sub-divisions of the trapezius muscle; although this has not been yet confirmed.

Individuals with strictly unilateral migraine exhibited lower PPT in the trapezius muscle (upper, middle and lower parts) than controls. Further, side-to-side differences in PPT levels were also found in patients with strictly unilateral migraine, but not in controls or CTTH (**Fig. 7**). These results support the relevance of assessing pressure sensitivity at multiple sites also in the trapezius muscle in patients with headaches (study III). Our data would support the relevance of cervical afferences in patients with migraine and CTTH and pointed towards a generalized pressure hyperalgesia of neck-shoulder muscles in these headache conditions.

An interesting finding was that we observed unilateral differences in topographical pressure pain maps of the trapezius muscle in patients with unilateral migraine, suggesting a lateralization of pressure pain hyperalgesia over the neck-shoulder region. These findings are in contrast with our previous study where bilateral pressure pain hyperalgesia in the temporalis muscle was found in a similar population (study II). In agreement with these findings, side-to-side differences in tenderness over the upper trapezius, but not the temporalis, muscle was also found in another cohort of 25 patients with unilateral migraine (Fernández-de-las-Peñas et al., 2008b). It may be possible that central sensitization (Burstein, 2001) accounts for bilateral pain hyperalgesia in the trigeminal region (i.e., temporalis muscle) but not in the cervical-related region (upper trapezius) in unilateral migraine headache.

Burstein (2000) proposed that hyperalgesic and allodynic responses found in migraine patients are due to central sensitization involving second-order neurons in the trigeminal nucleus and at least third-order neurons in the thalamus. It has been also proposed that central sensitization in migraine may be induced by afferent inputs from the dura mater travelling on the trigemino-vascular pain pathways (Cady, 2007). Repeated noxious stimuli may lead low-threshold neurons with large receptive fields to depolarize with innocuous mechanical stimuli, and injured neural tissue may actually alter its chemical make-up and reorganize synaptic contacts in the central nervous system. This assumption is supported by some authors who have pointed out that neurogenic inflammation during migraine pain attacks may activate trigeminal afferents projecting to brain areas involved in nociceptive processing (Parsons & Strijbos, 2003; Silberstein, 2004). The fact that trigeminal neurons release the calcitonin gene-related peptide mimicking neurogenic inflammation supports its role during migraine attacks (Durham, 2005). These assumptions have contributed to the development of the neural hypothesis in migraine (Parsons & Strijbos, 2003). Although these findings suggest a role of the nerve tissues in migraine, there are few studies investigating pressure pain hyperalgesia over nerve trunks in migraine.

We found generalized pain hypersensitivity to nerve pressure in patients with strictly unilateral migraine (study I). In fact, patients with unilateral migraine showed lower PPT levels bilaterally over nerve trunks of the trigeminal nerve (supra-orbital nerve) and of the upper extremity (median, radial and ulnar nerves). In addition, the supra-orbital nerve exhibited higher pressure hypersensitivity on the symptomatic side as compared to the non-symptomatic side in patients. Current results are similar to those previously found in both adults (Fernández-de-las-Peñas et al., 2008a) and children (Fernández-Mayoralas et al., 2010) with CTTH. These studies showed that subjects with CTTH exhibited bilateral lower PPT over different nerve tissues, such as the supra-orbital nerve, median, radial and ulnar nerves, suggesting pressure pain hyper-sensitivity over nerve tissues in CTTH. Further, widespread pressure pain hypersensitivity over nerve tissues has been also reported in e.g., whiplash (Sterling et al., 2003; Scott et al., 2005), carpal tunnel syndrome (Fernández-de-las-Peñas et al., 2009a), TMD (study V), LE (study IX), or cluster headache (Fernández-de-las-Peñas et al., 2011b). Current evidence suggests that widespread pressure pain hyperalgesia over nerve tissue seems to be a common finding in chronic pain syndromes as reflect of central sensitization (Zusman, 1992).

Generalized pain hypersensitivity over peripheral nerve trunks of the arm found in patients with strictly unilateral migraine may be a manifestation of the sensitization of third order neurons (Burstein, 2000). In such a way, a neurogenic inflammation triggered by antidromic discharges originating from the central nervous system could sensitize peripheral nerve trunks, which would lower the threshold of the nociceptive fibres of the *nervi nervorum* (Daemen et al., 1998). Alternatively, low-threshold Aβ-fibre input in states of central sensitization can depolarize nociceptive second order neurones, and this may enhance pain (Woolf et al., 1991; Hoheisel et al., 1993). This hypothesis is supported by the fact that, the evaluation in patients with migraine was held when all patients were headache-free, and when

at least 1 week had elapsed since the last migraine attack to avoid migraine related allodynia (Mathew et al., 2004). Alternatively, another explanation maybe that once central sensitization is established, sensitivity of peripheral nerves may become a perpetuating factor for hyper-excitability of the central nervous system in patients with headache. It seems that nerve endings of the *nervi nervorum* may become sensitized by different chemical mediators (Bove & Light, 1997; Watkins & Maier, 2004). The sensitization of nerve nociceptors may result in spontaneous neural discharges Bove & Light, 1997; Quintner, 1998; Watkins & Maier, 2004) which can contribute to the irritation of the trigeminal nerve nucleus caudalis resulting in the activation of the trigemino-vascular system (Malick & Burstein 2000). Our studies are the first reporting the presence of nerve trunk pain sensitivity in patients with headache.

5.2.4. Fibromyalgia and Whiplash as Widespread Chronic Pain Syndromes

Peripheral and central sensitization are important mechanisms for musculoskeletal pain conditions accounting for widespread sensory pain symptoms, e.g., fibromyalgia syndrome (FMS) or whiplash associated disorders (WAD) (Arendt-Nielsen & Graven-Nielsen, 2003).

FMS is a musculoskeletal pain condition characterized by widespread pain, allodynia and/or hyperalgesia and associated with sleep disturbances and pronounced fatigue. Although the aetiology of FMS is not completely understood, it is well accepted that central mechanisms are relevant for this pain condition. In fact, several studies had demonstrated that subjects with FMS show a hyper-excitability and hyper-responsiveness of the central nervous system (Desmeules et al., 2003; Petzke et al., 2003; Montoya et al., 2005). This central sensitization usually plays an important role in the development and maintenance of spontaneous pain and centrally mediated allodynia seen in FMS (Staud & Rodriguez, 2006; DeSantana & Sluka, 2008). A hallmark of FMS is the presence of widespread mechanical pain

hyperalgesia, since PPT levels have been found to be lower in both FMS and non-FMS tender points (Desmeules et al., 2003; Petzke et al., 2003; Montoya et al., 2005; Alonso-Blanco et al., 2011; Blumenstiel et al., 2011). Amris et al (2010) has demonstrated that pressure pain hyperalgesia is related to the presence of neuropathic pain symptoms in FMS.

There is also no question that individuals with WAD suffer from central sensitization which can cause seemingly exaggerated pain responses, even with low-intensity nociceptive input (Curatolo et al, 2004). Several studies have reported pressure pain hypersensitivity both locally over the symptomatic area as well as at more distal, usually pain-free, areas where there is no tissue damage (Sterling et al., 2002; Sterling et al., 2003; Scott et al., 2005; Sterling et al., 2010). In addition, an important finding is that widespread pressure pain hypersensitivity is present in individuals with acute WAD, particularly in those with higher levels of pain and disability (Sterling et al., 2004).

These results found in patients with widespread musculoskeletal pain, i.e., FMS and WAD, are similar to those found in migraine and CTTH (studies I-IV; Schoenen et al., 1991; Jensen et al., 1992; Bovim, 1992; Bendtsen et al., 1996; Ashina et al., 2006; Fernández-de-las-Peñas et al., 2007a), TMD (study V; Maixner et al., 1995; Wright et al., 1997; Türp et al., 1998; Svensson et al., 2001; Sarlani et al, 2004), shoulder pain (study VII; Coronado et al., 2011; Gwilym et al., 2011), LE (study IX), carpal tunnel syndrome (Fernández-de-las-Peñas et al., 2009a), low back pain (O'Neill et al., 2007), and knee osteoarthritis (Bajaj et al., 2011; Arendt-Nielsen et al., 2010). These results correspond well to studies showing that regional and widespread chronic pain conditions can be considered as part of a continuum rather than distinct entities with distinct aetiologies (Macfarlane, 1999), since most pain syndromes exhibit similar pressure pain hyperalgesia. Obviously, since nociceptive mechanisms involved different pain pathways, some differences in nociceptive gain will exist between these syndromes.

6. Referred Pain: Sign of Central Sensitization in Local Pain Syndromes

Musculoskeletal pain conditions are often accompanied by local and referred pain. Pain located in a determined area around the source of pain is termed local or primary pain (peripheral mechanism), whereas pain perceived in a different region away from the source of pain is denominated referred pain (central mechanism). It is known that central sensitisation is involved in the genesis of muscle referred pain (Arendt-Nielsen & Svensson, 2001; Graven-Nielsen, 2006). Animal studies show expansion and development of new receptive fields by muscle nociceptive stimuli (Hoheisel et al., 1993). In the context of referred pain, the unmasking of new receptive fields due to central sensitization can mediate this phenomenon (Graven-Nielsen, 2006). Furthermore, the frequency of referred pain from prolonged mechanical stimulation on the tibialis anterior muscle is significantly higher than for brief stimulation, indicating the time-dependency of referred pain (Gibson et al, 2006). Additionally, central sensitization may be reflected by the size and location of referred pain (Graven-Nielsen & Arendt-Nielsen, 2010). Different studies have found that the referred pain area correlated with the intensity of the muscle pain (Graven-Nielsen et al. 1997a; 1997b). Gazerani et al (2005) suggested that referred pain represents deep somatic secondary hyperalgesia resembling what is found in secondary hyperalgesic skin areas following e.g. capsaicin application. Arendt-Nielsen & Ge (2009) determined that muscle referred pain is a process of central sensitization which is mediated by a peripheral activity and can be facilitated by sympathetic activity and dysfunctional descending inhibition.

Another manifestation of central sensitization is enlarger referred pain areas (Arendt-Nielsen et al, 2000). Larger referred pain areas have been obtained after intramuscular injections of hypertonic saline in widespread pain conditions, e.g. FMS (Sörensen et al. 1998), or WAD (Johansen et al. 1999), and in local pain conditions, e.g., myofascial TMD (Svensson et al. 2001), or knee osteoarthritis (Bajaj

et al., 2001). These studies demonstrated that patients with sensitisation of central pathways exhibited larger referred pain areas in both symptomatic and distant non-symptomatic areas after injections of hypertonic saline. These findings suggest that nociceptive inputs to the central nervous system facilitate referred pain mechanisms, possibly resulting from the central sensitisation (Arendt-Nielsen & Graven-Nielsen 2003).

There is some evidence demonstrating that most of the local pain syndromes investigated in the current dissertation exhibit larger muscle referred pain areas after hypertonic saline injection. Schmidt-Hansen et al (2007) reported that patients with CTTH exhibited enlarger referred pain areas after the injection of hypertonic saline into head and neck muscles as compared to healthy subjects. Svensson et al (2001) demonstrated that individuals with myofascial TMD also exhibit larger referred pain areas with intramuscular injection of hypertonic saline into the masseter muscle. Slater et al (2005) found that individuals with LE reported more widespread pain and extended referred pain areas in the wrist extensor muscles compared with controls. These studies support that central sensitization mechanisms are involved in muscle referred pain in these conditions.

In the clinical context, experimentally-induced referred pain is represented by muscle trigger points (TrPs). TrPs are defined as hyperirritable spots located within a taut band of a skeletal muscle that are painful on compression, stretching, palpation or needle of the affected tissue and respond with a referred pain pattern (Simons et al., 1999). TrP diagnosis is based on a proper clinical examination by an experienced assessor (Gerwin et al., 1997) which has derived in a debate about the existence of the TrPs. It has been demonstrated that TrPs can be visualized using magnetic resonance elastography and sonographic elastography (Chen et al., 2007; 2008; Sikdar et al., 2009). Chen et al (2007) demonstrated that the stiffness of the taut bands in patients with TrPs is higher than that of the surrounding tissue in the same subject and in people without TrPs. Sikdar et al (2009) showed that vibration amplitudes were

27% lower on average in the TrP compared to the surrounding tissue. The findings from these methods suggest that TrP taut bands are detectable and quantifiable, providing useful tools for TrP diagnosis and future research. From a clinical viewpoint, TrPs are classified as active and latent TrPs. Active TrPs are those which local and referred pain reproduce the symptoms reported by the patient, and the pain is recognized by the patient as a usual symptom. Latent TrPs are those which local and referred pain did not reproduce any symptom experienced by a subject (Simons et al., 1999). Active and latent TrPs have similar physical findings but the difference is that latent TrPs do not reproduce any spontaneous symptom. Clinical distinction between active and latent TrPs has been substantiated by the study of Shah et al (2005) where higher levels of chemical mediators, e.g., bradykinin, substance P or serotonin, were found in active TrPs as compared to latent TrPs and non-TrPs. The activation of a TrP may result from different factors, e.g. repetitive muscle overuse, acute or sustained overload, psychological stress, or other key TrPs. Particular attention has been recently paid to injured or overloaded muscle fibres in the patho- genesis of muscle TrPs (Gerwin et al., 2004). In fact, the aetiology of TrPs is not completely understood, and readers are referred to other publications (Gerwin et al., 2004; Dommerholt et al., 2006; McPartland & Simons, 2006; Dommerholt & Shah, 2010).

In addition to generalized and widespread mechanical pain hypersensitivity in migraine, CTTH, myofascial TMD pain, shoulder pain and LE, there is evidence demonstrating the relevance of referred pain from active TrPs in these conditions. Our group has demonstrated that the referred pain elicited by active TrPs in head, neck, and shoulder muscles reproduces the pain during migraine pain attacks (Fernández-de-las-Peñas et al., 2006a; 2006b). In these studies, active TrPs were mostly located ipsi-lateral to the migraine headaches in patients with strictly unilateral symptoms. Others have reported the same findings in patients with bilateral migraine (Calandre et al., 2006). In addition, active TrPs from the suboccipital, upper trapezius and temporalis muscles also reproduce the headache pain pattern in

individuals with CTTH (Fernández-de-las-Peñas et al., 2006c; 2006d; 2007b; 2007c). Patients with CTTH and migraine exhibited enlarger referred pain areas from active TrPs in the evaluated muscles than controls. In addition, the presence of active TrPs was related to higher pressure hypersensitivity in patients with CTTH, supporting a relevance of muscle referred pain in central sensitization (Fernández-de-las-Peñas et al., 2007b; 2007c). These findings have been recently replicated in children with CTTH (Fernández-de-las-Peñas et al., 2011c).

Fernández-de-las-Peñas et al (2010b) also confirmed that the referred pain from active TrPs in the masticatory muscles also reproduces the pain symptoms in patients with myofascial TMD. Further, women with pure myofascial TMD exhibited enlarger TrP referred pain areas than healthy controls. In the study VII of the current dissertation, we also found that TrPs from the shoulder muscles reproduced the pain symptoms in individuals with shoulder impingement. Additionally, the presence of active TrPs in the shoulder muscles was related to higher pressure pain hyperalgesia in the affected side, supporting that active TrPs were associated with the degree of sensitization. Further, the relevance of active TrPs in shoulder pain has been recently confirmed by Bron et al (2011) who found that the number of active TrPs was moderately correlated with the DASH score (disability).

Fernández-Carnero et al (2007) showed pressure pain hyperalgesia and enlarger referred pain areas elicited by active TrPs in the extensor carpi radialis brevis and longus muscles in patients with LE as compared to controls. This study also revealed a relationship between pressure hypersensitivity and the presence of active TrPs, suggesting a potential relevance of active TrPs in sensitization mechanisms in this condition. Fernández-Carnero et al (2008) also reported that patients with strictly unilateral symptoms also exhibited TrPs, in this case latent TrPs, in the unaffected side, supporting a contra-lateral sensitization process of muscle referred pain in this musculoskeletal pain condition.

Current evidence suggests that referred pain elicited by TrPs can be related to the presence of pressure pain hyperalgesia in local pain syndromes. Fernández-de-las-Peñas et al (2007d) formulated the following updated pain model for CTTH involving peripheral sensitization by active muscle TrPs and central sensitization: active TrP located in those muscles innervated by the C1-C3 segments (upper trapezius, sternocleidomastoid, suboccipital) and by the trigeminal nerve (temporalis, masseter, extra-ocular) are responsible for peripheral nociceptive inputs and may produce a continuous afferent barrage into the trigeminal nerve nucleus caudalis, sensitizing the central nervous system. In this pain model, pressure pain hyperalgesia, referred pain and central sensitization mechanisms are interconnected. It is possible that a similar pain model can be applied for the musculoskeletal pain syndromes discussed in this dissertation, that is, myofascial TMD, shoulder pain and LE. Nevertheless, there is no evidence to claim a major role for peripheral or central sensitisation, since both sensitization mechanisms would be probably interconnected at the same time.

7. Sensitization Mechanisms in Local Pain Syndromes: from Localized to Widespread Pain

Today there is no definitive model explaining the transition from localized to widespread pain conditions. A progressive sensitization of the central nervous system is a potential mechanism involved in the transition from acute to chronic pain. This assumption partially supports the hypothesis that both regional and widespread chronic pain conditions should be considered as part of a continuum rather than distinct entities (Macfarlane, 1999). The increased mechanical pain sensitivity may result from a dysregulation in peripheral afferents and central nervous system pathways inducing dynamic and time-dependent changes in excitability and response characteristics of neuronal and glial cells. This

dysregulation contributes to altered mood, motor, autonomic and neuro-endocrine responses as well as pain perception (Maixner et al. 1995; Watkins et al. 2003). This hypothesis is supported by the fact that the overall spontaneous FMS pain is not only diffuse pain but is located to certain body areas (Staud et al., 2006) and related to TrP activity (Alonso-Blanco et al., 2011; Ge et al., 2011).

In fact, it is commonly seen in clinical practice that if a patient with an initial musculoskeletal local pain problem is followed over years and if the problem is not properly treated or resolved the pain starts to spread outside the origin of pain due to development of sensitization mechanisms and referred pain (Arendt-Nielsen et al., 2010a). **Figure 9** graphically shows a sketch of what is seen when pain develops from a localized pain condition into a widespread condition.

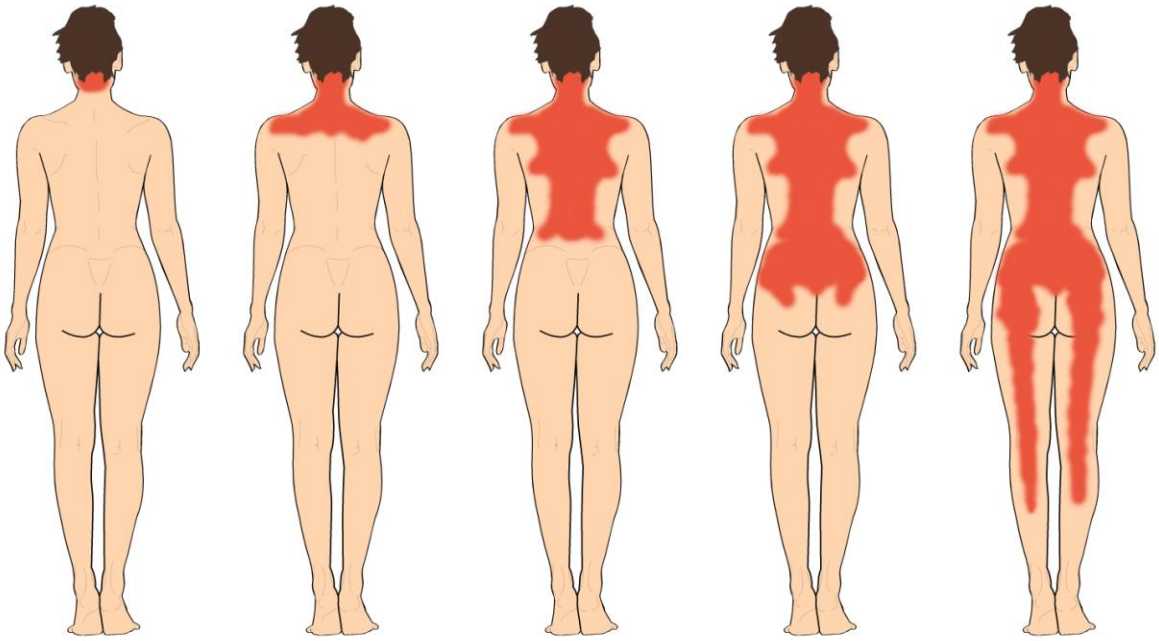


Figure 9: Spreading pain in a patient with localized pain with time

It is likely that that initial excitation and sensitization of nociceptors (peripheral sensitization) will cause continued nociceptive barrage to the central nervous system causing the central sensitization of dorsal horn neurons and higher centres (Mendell & Wall, 1965; McMahon et al., 1993). In addition to central sensitization, an imbalance between descending inhibition and facilitation is also involved in this process. The relationship between peripheral and central sensitization in local pain syndromes has been demonstrated in the current dissertation as the intensity and/or duration of the pain was associated to higher pressure pain hypersensitivity, supporting that the nociceptive input is important for driving the process of generalized muscle hyperalgesia (**Figs. 10-11**).

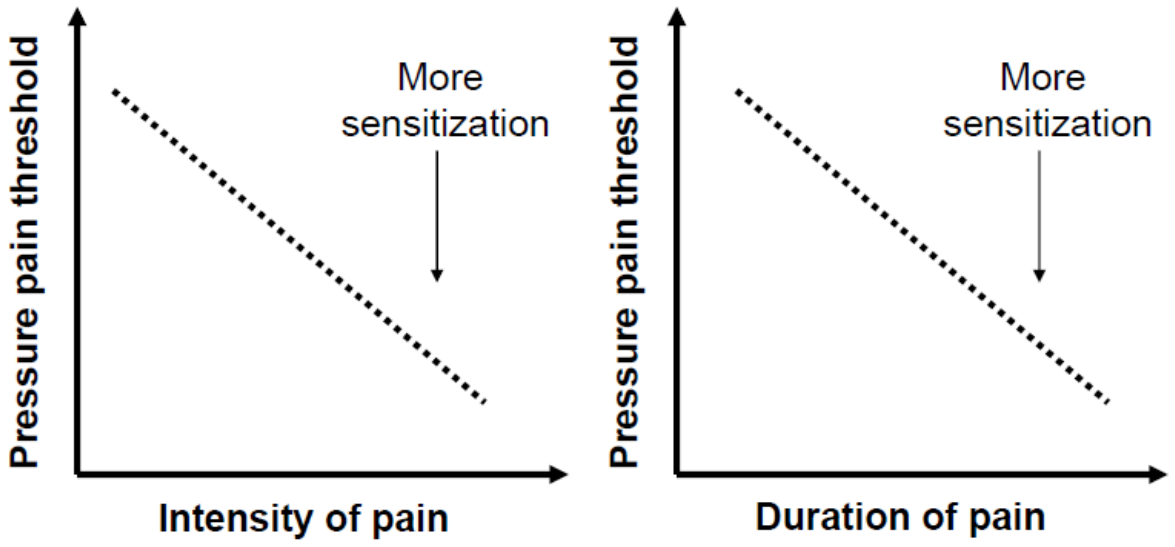


Figure 10: The sketch summarizes the findings on how increased intensity, ongoing clinical pain, and increased duration of the pain condition result in increased muscle hyperalgesia as assessed by PPT (modified from Arendt-Nielsen et al., 2010a)

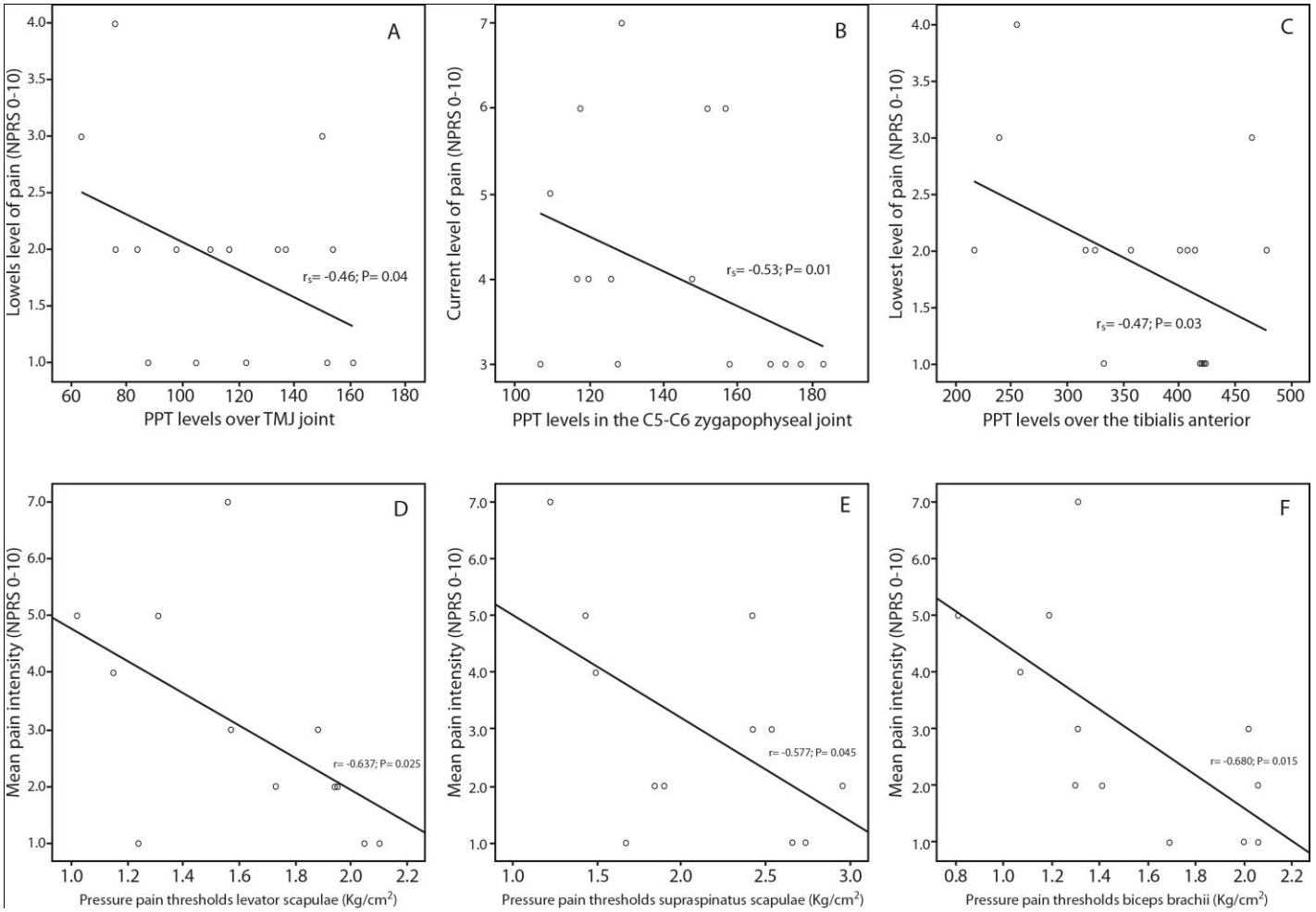


Figure 11: Scatter plots of relationships between intensity of pain and PPT levels. TMD pain and PPT over (A) TMJ; (B) C5-C6 joint (C), tibialis anterior (n = 20, from study V). Shoulder pain and PPT over (D) levator scapulae; (E) supraspinatus; (F) biceps brachii (n = 12, from study VII). Note that some points are overlapping. A negative linear regression line is fitted to the data

In such a scenario, it would be clinically important to identify, if possible, the source of pain (peripheral sensitization) as soon as possible to decrease these sensitization mechanisms. In fact, time and frequency of pain is another relevant factor, since negative associations between pain duration and frequency are also related to lower PPT levels (**Fig. 12**).

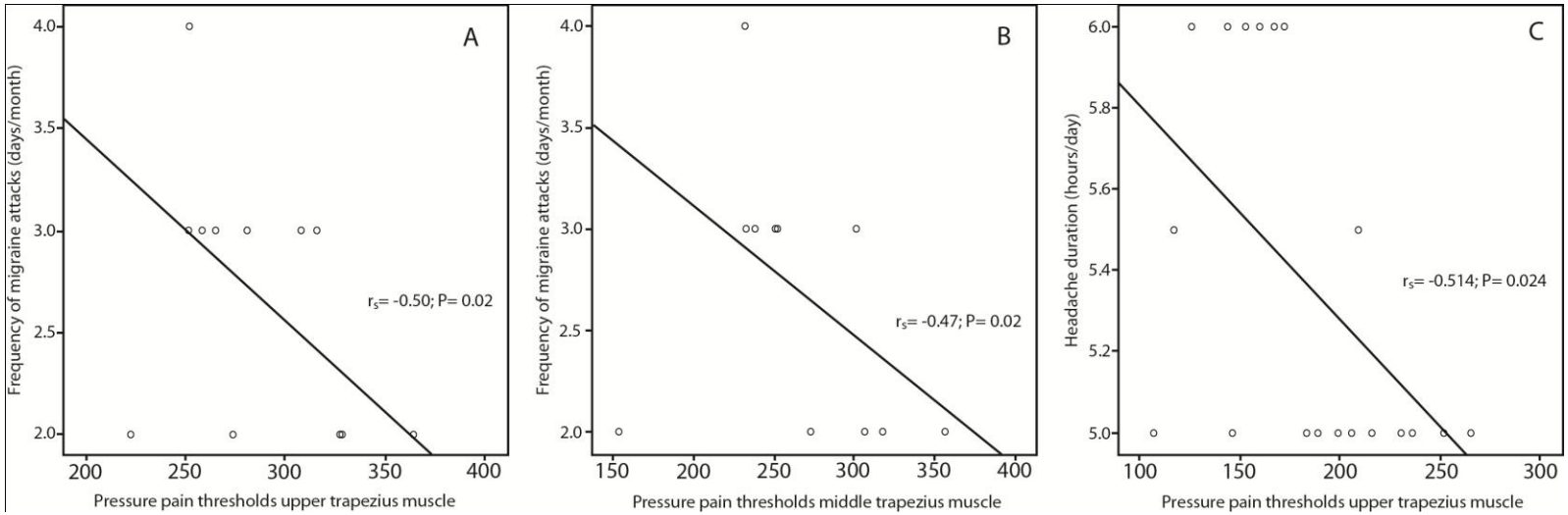


Figure 12: Scatter plots of relationships between the frequency of migraine attacks and PPT levels over the (A) upper and (B) middle trapezius muscle in patients with strictly unilateral migraine (n = 20, from study III), and between the headache duration and PPT levels over the (C) upper trapezius muscle in patients with CTTH (n = 20, from study III). Note that some points are overlapping. A negative linear regression line is fitted to the data

In the current dissertation, we discussed the role of active TrPs in sensitization processes in local pain syndromes. In fact, there is evidence supporting that TrPs are a clear source of peripheral sensitization and pain. Two microdialysis studies have demonstrated that the concentrations of chemical mediators are higher in the vicinity of active TrPs (Shah et al. 2005) and in remote pain-free distant areas (Shah et al., 2008). The concentration of protons, bradykinin, substance P, calcitonin gen-related peptide, TNF-α, IL-6, IL-8, IL-1β, serotonin, and nor-epinephrine was higher in active TrPs than in latent TrPs or non-TrPs (Shah et al., 2005). In addition, concentrations of these biochemical substances in distant pain-free areas, e.g., gastrocnemius muscle, were also higher in subjects with active TrPs in the upper trapezius muscle as compared to those with latent TrPs or non-TrPs (Shah et al., 2008). Kuan et al (2007) reported that spinal cord connections of TrPs were more effective in inducing neuroplastic changes within the dorsal horn neurons than non-TrPs and that TrPs are connected to a greater number of small sensory neurons (mainly nociceptive neurons) than non-TrP tissues. Further, imaging data suggest that TrP hyperalgesia is also processed in the brain areas as enhanced somato-sensory (primary and secondary somatosensory cortex, inferior parietal, and mid-insula) and limbic (anterior insula) activity was present in individuals with TrPs in the upper trapezius muscle compared with controls (Niddam et al., 2008; Niddam, 2009). Finally, Xu et al (2010) have reported that mechanical stimulation of latent TrPs induced central sensitization in healthy subjects, suggesting that stimulation of latent TrPs can increase pressure pain hypersensitivity in extra-segmental tissues. These data support that TrPs represent an ongoing source of pain and peripheral sensitization and that TrPs can contribution to development and/or maintenance of central sensitization processes. More importantly, it has been also reported that experimentally-induced muscle pain is able to impair

diffuse noxious inhibitory control mechanisms, further confirming an important role of muscle tissues in chronic pain (Arendt-Nielsen et al, 2008).

Based on current data, a link between the referred pain from TrPs and spreading pain symptoms in musculoskeletal pain syndromes can be hypothesized, where TrPs can be the origin (in some cases) of central sensitization. This assumption has been previously proposed in CTTH (Fernández-de-las-Peñas et al., 2007d) since it seems that the presence of prolonged peripheral inputs is a mechanism of major importance for the conversion of episodic into CTTH (Bendtsen & Schoenen, 2006). As it has been previously suggested in this dissertation, this pain model could be also suggested to some patients with myofascial TMD, shoulder pain and LE as all these conditions exhibit similar sensitization mechanisms than CTTH and active TrPs are related to central sensitization in a similar way.

8. Clinical Applications and Future research directions

Current data claim for a common patho-physiological mechanism in musculoskeletal local pain syndromes, e.g. CTTH, shoulder pain, myofascial TMD or LE, since these conditions exhibited similar peripheral and central sensitization mechanisms. An important topic to discuss for future research is that central sensitization seems to be a reversible process in individuals with myofascial pain; although some authors suggested that central sensitization is an irreversible process (Sluka et al., 2001). On the contrary, some clinical studies have demonstrated that sensitization mechanisms related to TrPs may be reversible with proper management. For instance, TrP injection into neck muscles produced rapid relief of mechanical pain hyperalgesia and allodynia associated with migraine (Mellick & Mellick, 2003; Giamberardino et al., 2007), FMS (Affaitati et al., 2011) and chronic WAD (Freeman et al., 2009). The cause of the rapid decrease in local and referred pains observed in clinical practice is not completely

understood, although there is speculation that it is the result of local stretch of the muscle fibre. Loss of referred pain is related to the decrease in nociceptive input to the dorsal horn of the spinal cord and interruption of spreading of pain through convergence and central sensitization. Nevertheless, the reversal in referred pain is amazingly rapid suggesting that central sensitization can be reversed quickly if the treatment is proper. This effect may be related to the release of endocannabinoids that soft tissue therapies can exert (McPartland, 2008).

These results indicate that referred pain is a reversible process of the central nervous system neuro-plasticity (Arendt-Nielsen et al., 2000) maintained by increased peripheral nociceptive inputs from active TrPs. Probably the degree of central sensitization in myofascial pain is not as high as that in FMS or neuropathic pain. Multiple factors can also influence the degree of sensitization including descending inhibitory pain mechanisms, sympathetic activity, or neuropathic activation. In clinical practice it is commonly seen that patients with lower degree of central sensitization need less number of treatment for being the patient pain-free. The results of the current dissertation open several research questions related to modulation of central sensitization after active TrP treatment or other therapeutic approaches in these syndromes.

An important question that still needs to be determined is whether there are individuals with a higher inherited propensity (genetic contributors) for developing central sensitization than others, and whether this conveys an increased risk in developing widespread musculoskeletal chronic pain (Wolff, 2011). Proper diagnostic criteria to determine the presence of central sensitization in individuals with pain will greatly assist the phenotyping of patients for choosing the proper treatments for normalizing hyper-excitable central neural activity. In line with this, Nijs et al (2009) introduced a guideline for clinicians for identifying altered central processing in patients with musculoskeletal pain disorders. One of the primary recommendations in the examination is the use of multiple modalities for pain

sensitivity in locations local and distal to the area of the initial injury (or primary pain complaint). In this scenario, the presence of widespread pressure pain hyperalgesia seems to play a critical role, since mechanical pain sensitivity can be easily assess in clinical practice (Nijs et al., 2009).

Finally, a recent study has introduced topographical pressure pain maps of the knee region onto a Magnetic Resonance Imaging extracted 3D surface to get a tri-dimensional impression of the regions of the joint which are sensitized the most (Arendt-Nielsen et al, 2010b). In addition, topographical pain maps of the head of patients with nummular headache (Cuadrado et al., 2010) have been converted into 3D maps giving a more comprehension of pressure hypersensitivity of the head (**Fig. 13**, Fernández-de-las-Peñas, unpublished data). Future studies are needed to elucidate 3D topographical distribution of generalized and widespread pressure pain hypersensitivity in local pain syndromes.

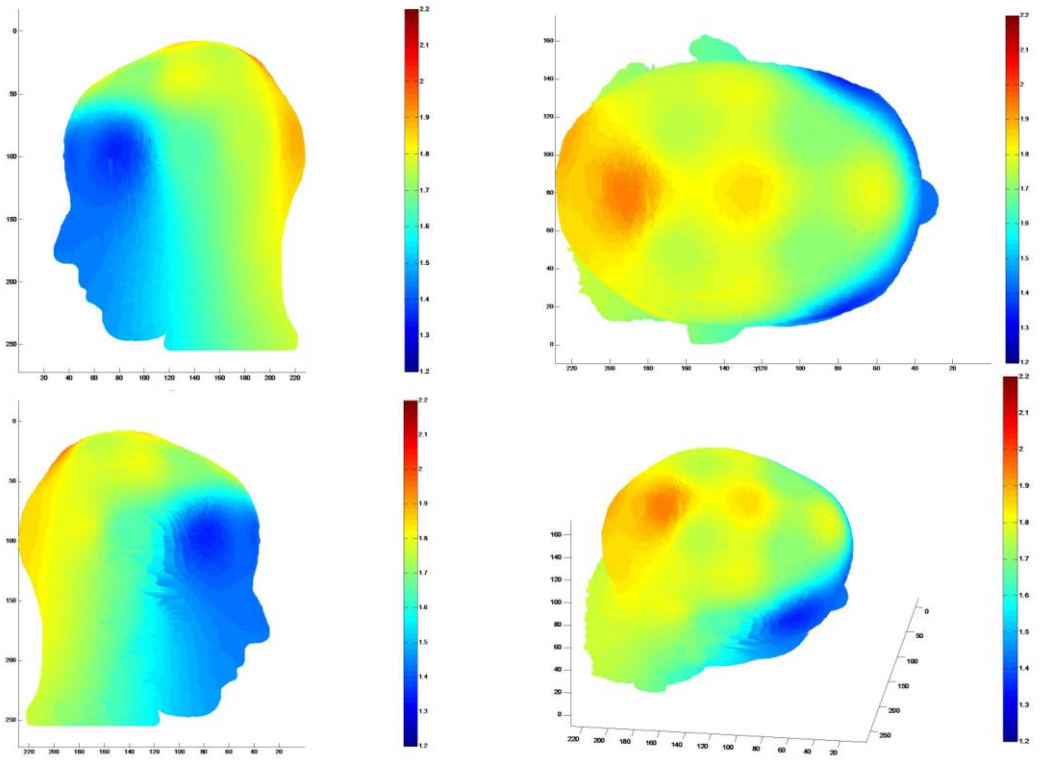


Figure 13: 3D topographical map assessing PPT over several sites around the head in patients with nummular headache (Fernández-de-las-Peñas, unpublished data).

9. Conclusions

The current dissertation have demonstrated that individuals with migraine, CTTH, myofascial TMD pain, shoulder pain and LE exhibit widespread pressure pain hypersensitivity as sign of central sensitization. Pressure pain hyperalgesia seems to be present in different deep tissues such as muscles, joints and nerves in all pain conditions suggesting that the sensitization process is not tissue-dependent. These results are similar to those previously found in widespread chronic pain syndromes.

The use of topographical pressure pain maps also revealed generalized pressure hypersensitivity in local syndromes with unilateral symptoms, indicating contra-lateral sensitization mechanisms. In addition, these maps evidenced that pressure pain hypersensitivity is heterogeneous distributed around e.g. infraspinatus, temporalis or trapezius muscles. Differences in the density of muscle nociceptors or changes in pain modulation can be involved in these findings.

Pressure hypersensitivity was associated with the intensity and duration of the pain supporting a relationship between peripheral and central sensitization mechanisms. In fact, we found that increased intensity, ongoing clinical pain, and increased duration of the pain condition result in increased muscle hyperalgesia in migraine, CTTH, TMD, shoulder pain and LE.

Therefore, the results of the current dissertation support the hypothesis that local/regional and widespread pain conditions should be considered as part of a continuum rather than distinct entities with distinct aetiologies. This hypothesis is further supported by the fact that these conditions showed similar sensitization mechanisms, exhibit enlarger referred pain areas elicited by active muscle TrPs, and central sensitization is related to the presence of active TrPs. Future studies are now needed to clarify these relationships and potential implications for modulation of these sensitization processes.

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