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THE ROLE OF CENTRAL SENSITIZATION IN CHRONIC SHOULDER PAIN.
-A SYSTEMATIC LITERATURE REVIEW-

Degree Programme in Physiotherapy
2014

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Degree Programme in Physiotherapy
February 2014
Supervisor: Kangasperko, Maija
Number of pages: 48
Appendices: 2

Keywords: shoulder and central nervous system sensitization, sensitization, chronic shoulder pain, subacromial impingement syndrome., central sensitization.

The purpose of this thesis was to gather information to confirm or reject the presence of central sensitization in subjects with chronic subacromial impingement syndrome, and, if present, analyze the prevalence of this phenomenon in that population. The thesis data collection was conducted in the form of a systematic literature review. Moreover the thesis includes background information about of peripheral and central mechanisms of pain, shoulder anatomy-, shoulder impingement syndrome and central sensitization for a better understanding of the topic before going in depth on the review. In addition, this thesis aims to be published as part of a future article in a physiotherapy peer-reviewed journal.

The searching process was carried out in Ebsco, Web of Science and PubMed databases. As a result, eleven studies were selected and, after the methodological quality assessment using Pedro scale, only eight of them received 6/10 or more points, the minimum required to be included in the review.

This review confirmed the presence of central sensitization in subjects with chronic subacromial impingement syndrome. In addition high prevalence of this phenomenon was detected in the population. However, has to be noted that only eight papers were used in this review to make conclusions. Therefore further research is needed in order to obtain stronger evidence of the possible role of central sensitization plays in chronic subacromial impingement syndrome.

CONTENTS

1 INTRODUCTION

Shoulder is one of the most sophisticated and complicated joints of the body, showing the greatest range of motion of any joint in the body. Shoulder pain has turn into a common musculoskeletal disorder in the general population that may be primarily caused by intrinsic disorders of the shoulder or be secondary to damage to distant structures (i.e: referred pain). Shoulder impingement syndrome, in particular can arise after acute injuries such chronic inflammation of the shoulder joint, tendons, surrounding ligaments, or periarticular structures. (Andersson, 19-20.)

Traditionally, the shoulder impingement syndrome has been considered a clinical condition of mechanic origin. However, is well known that, in some cases there is no direct correlation between the pain experienced by the patients and the extent of the injury at subacromial space.(Gwylim, Oag, Tracey & Carr 2011,498-502.) After an acute injury there is an ongoing barrage of nociceptive inputs from the affected tissue to the brain, which if sustained, may lead to a reversible state of hyperexcitability of the central nervous system neurons. This state is characterized by spontaneous or persistent pain, expansion of painful areas and qualitative sensory disturbances (including allodynia and hyperalgesia). Sometimes this state of hyperexcitability can becomes irreversible and symptoms can persist even when the tissue has completely healed. This state of hypersensitivity of the central nervous systems is known as central sensitization (CS). (Azkue, Torre, Aguilera & Ortiz 2007,136-140.)

Current evidence has shown that some patients with hemiplegic shoulder pain and shoulder impingement syndrome present extended and remote areas of hyperalgesia, increases in nociceptive transmission at dorsal horn neurons and loss of descending pain inhibitory mechanisms. All these changes are recognized indicators of CS. (Paul, Soo Hoo, Chae & Wilson 2012, 2206-2209.)

The topic of this thesis was given by Quique Lluch, assistant professor at University of Valencia, who is interested in the role of CS in subjects with chronic osteoarthritis. Since the first moment I got interested in this topic. This thesis is the

result of the cooperation of SAMK with Quique Lluch. Although preliminary evidence seems to support the role of CS plays in subjects with chronic shoulder pain, there are not studies that systematically reviewed the literature regarding CS in populations with chronic impingement syndrome and hemiplegic shoulder pain.

2 PAIN

2.1 Definition

Pain has become in a huge problem in the modern society with over 1'5 billion of people worldwide suffering from chronic pain. Only in England 10 million of English suffer pain almost daily, women affected by pain lose approximately 55 days of work per year in England. The NHS (National Health Service of England) expends over 4 billion of pounds per year between teenagers due to pain. In U.S.A. the costs of unrelieved pain are around $560-$635 billion annually, and approximately 100 million of Americans suffer chronic pain. (Website of the British Pain Society, 2008, Website of the American Academy of Pain Medicine, 2011.)

The IASP (International Association for the Study of Pain), describe pain as " an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Therefore, pain is always subjective and can be considered a response to what the brain interprets as a dangerous situation. In fact, many people report pain in the lack of tissue damage. They link their experience as pain, and as they account in the same way as pain caused by tissue damage, it should be considered as pain. (Website of International Association for the Study of Pain, 2012, Butler & Moseley 2003, 8-9.)

2.2 Types of pain

From the point of view of the duration of the symptoms there are two main types of pain , acute and chronic. The acute pain is temporarily related to injury that resolves

along the appropriate healing time, normally responds to analgesic drugs and to the treatment of the main cause of injury. Moreover, this type of pain does not last more than three months, the intensity of the pain is higher at the beginning and gradually decrease as healing take place, the central nervous system is rarely affected, and normally it disappears when the tissue has healed.(Website of Pain Community Centre, 2007, Nicholson 2006,256-262.) The second type of pain is known as chronic pain. It is defined as any pain that last more than 3 months, may arise from an initial injury, such as rotator cuff tear, or there may be an ongoing cause, for instance a disease. However, there is not always a clear cause behind it. Chronic pain, is linked very often with sleeplessness, tiredness and lack of motivation. As a consequence of the pain the movements of the affected person become limited, and flexibility and strength are lost. All these changes may lead to disability and despair. (Webpage of National Institutes of Health and National Library of Health, 2011, Website of International Association for the Study of Pain, 2012.) Some studies have suggested some of the causes behind chronic pain and have investigated the several alterations that are widely spread across the nervous system contributing to the complicated pain phenotypes. Moreover they have explored how the age, gender, stress and fears can influence the risk of developing persistent pain. (Costigan, Scholz & Woolf 2009,1-32.)

From the point of view of the physiopathology mechanisms behind the pain, we can differentiate three types: nociceptive, neuropathic and the one caused by central sensitization pain. Nociceptive pain is described as pain that arises from a present or threatened damage, activating the nociceptors and not affecting the neural tissue, is classified regarding the noxious stimulus where arise from: thermal (heat and cold), mechanical (tearing) and chemical (iodine in a wound). Also depending of the depth of the stimulation can be divided in visceral which is initiated after stimulation of receptors in muscles, ligaments or bones.(Website of Pain Community Centre, 2007, Website of International Association for the Study of Pain, 2012 .) The second type is the neuropathic pain, is caused by a damage or disease that affects the somatosensory nervous system, and therefore this pain is divided depending it has an effect on peripheral or on central nervous system. This pain does not occur in all patients and the mechanisms which cause neuropathic pain are unclear. The nerve fibers may be damaged, injured or not functioning well. In fact, the injuries affects

the function of the nerve at the site of injury and around it. Consequently, incorrect signals are send it to the brain. The brain interprets that this signals are coming from the pain receptors in the skin or organs where in fact is not. Some features of this pain are allodynia, hyperalgesia and hyperpathia. The last one is central sensitization, nociceptive neurons in the CNS (central nervous system) increases their sensitivity to their normal or subthreshold afferent input. (Website of Pain Community Centre, 2007, Website of International Association for the Study of Pain, 2012, Finnerup, Sindrup & Jensen 2007, 129-136.)

The latest findings of brain neuroimaging, have shown that there is not only one centre of pain, but many. These brain parts, that work as a pain centre are called ingnition nodes , and include clusters of nodes used for sensation, movement, emotions and memory, in chronic pain the pain experience involve them. Motor cortex, cingulated cortex, prefrontal cortex, amygdale, sensory cortex, hypothalamus, cerebellum, hippocampus and spinal cord are the brain parts that usually are active during the pain experience, in addition, within them, there are electrical and chemical links, these system made up by cortical mechanisms are known as a pain neuromatrix, and the activation of this system will create the pain perception, that is called pain neurotag (Figure 1). However the brain imaging techniques have demonstrated that some cortical areas are involved more frequently than others: frontal cortex, premotor cortex, thalamus, and anterior cingulated cortex, insular and sensorimotor cortex. Recently, some studies have shown through magnetic spectroscopy data that there are important neurochemical changes in the anterior cingulated cortex, thalamus and prefrontal cortex subjects with chronic low back pain in comparison to healthy controls. (Moseley 2003,130-140; Wand, Parkitny, O'Connell, Luomajoki, Mc Auley, Thacker & Moseley 2010,1-6; Butler & Moseley 2003, 38-39).

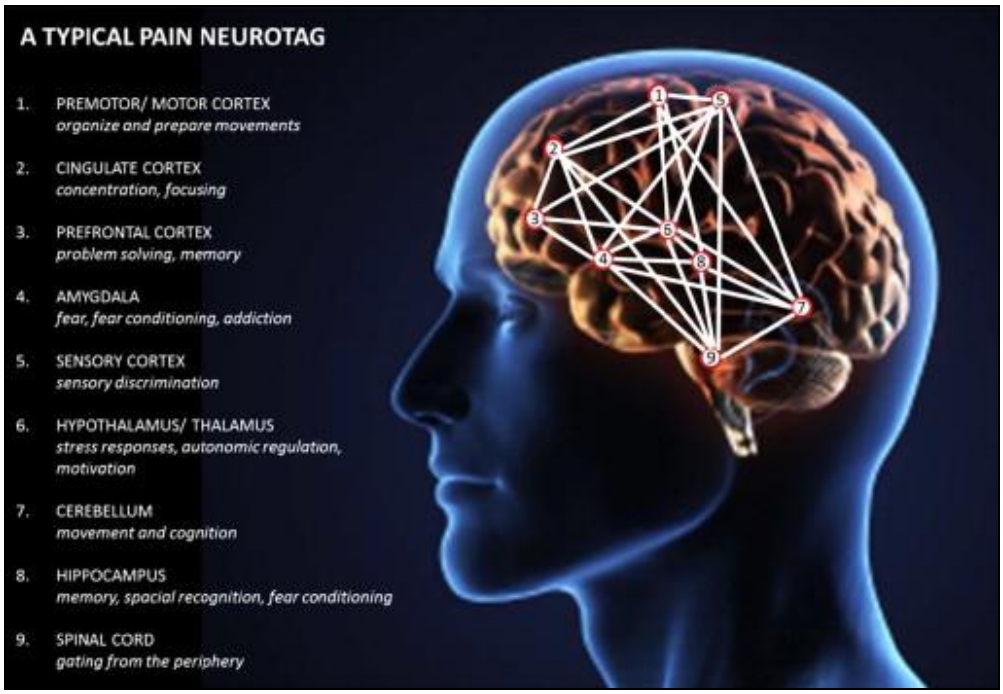

Figure 1: Pain Neurotag.
(Website of Neuro Orthopaedic Group 2012)

2.3 Pain pathways

Is defined as the bundle of myelinated nerves fibers that connect the sensory neurons from the periphery to the brain, through the spinal cord. This path is used to send the pain messages from the injured tissue towards the brain, previous been analyzed at the spinal cord. (Brooks & Tracey 2005, 19-33)

2.3.1 Peripheral mechanisms

When a tissue is injured, the sensors from the peripheral nerves (made up by sensory neurons) are stimulated. when they reach certain level of excitability, they generate dangerous messages, and send them to the nucleus of the neuron that is in dorsal root ganglion(DRG)(Figure 2). The DRG works as a "minibrain" where the message can experience some modulation and evaluation. In the DRG, is also located the DNA of the neurone, that is ready to create new sensors. The DRG is very sensitive, particularly to the substances that are in the blood, to adrenaline and to chemicals that are segregated during stress reactions. Therefore one of the ways that the

nervous system has to increase the sensibility and thus protect you, is through production of more adrenaline and consequently increasing the pain. (Butler & Moseley 2003, 39,62-63.) When impulses from the inflamed tissue continue arriving at the synapse in the dorsal horn, or when neurons from the brain release excitatory chemicals, the neurone in the spinal cord experience some changes aiming to improve the capacity to send danger messages towards the brain. However only 10% of the stimuli that arrive to the dorsal horn are strong enough to stimulate the activation of WDR(wide dynamic range) neuron, which will sent the danger message to the brain. It can be differentiate three important neurons. The first, neurone goes from the peripheral receptor till the DRG, the second neurone is in the dorsal horn (Figure 3), is the danger messenger neurone, which increase sensitivity to excitatory chemicals, and takes the danger/pain messages to the brain (ascending pathways) to the thalamus. Finally, the third neuron projects to the poscentral gyrus. When these neurones deliver the pain messages to the brain, the brain reacts increasing the sensitivity, things that were painful, are now more painful(hyperalgesia) and things that did not hurt before, now will do (allodynia). Moreover, neurons that did not carry danger messages, but sprout close to the danger message neurons are activated. As a result, brain is working with imperfect information about the tissues ,touching the skin, may at this point provoke danger messages. (Butler & Moseley 2003, 72-73; Guan, Borzan, Meyer & Raya 2006,298-307.)

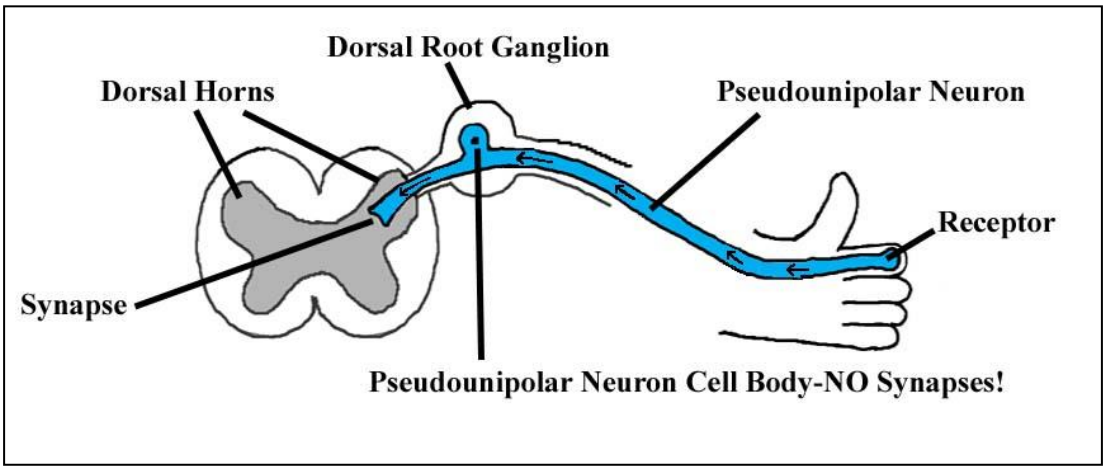

Figure 2: Peripheral mechanisms, dorsal root ganglion and dorsal horns.
(Website of Michigan University Health System 2013)

2.3.2 Central mechanisms

Currently, different studies have been investigating the structural changes affecting the brain when there is chronic pain. (Wand, Parkitny, O'Connell, Luomajoki, Mc Auley, Thacker & Moseley 2010,1-6.) Using the newest technologies in the brain scan, called voxel-based morphometry (which analyze the anatomy of the brain) they have found a reduction of the grey matter in the dorsolateral prefrontal cortex, the right anterior thalamus, the brainstem, the posterior parietal cortex and the somatosensory cortex in people with chronic low back pain. In addition the sensory and affective dimensions of pain shown strong connection between the level of density changes and pain intensity and unpleasantness. Therefore ,appear to be less brain cells or at least less neuron brain cell in patients with chronic low back pain than in healthy subjects. (Wand, Parkitny, O'Connell, Luomajoki, Mc Auley, Thacker & Moseley 2010,1-6; Apkarian, Sosa, Sonty, Levi, Harde, Parrish & Gitelman 2004,410-415; Schmidt-Wilcke, Leinisch, Ganssbauer, Draganski, Bogdhan, Altmeppen & Mays 2006, 89-97.)

In this sensitized state, the brain is being informed wrongly about the level of danger in the peripheral tissues. This persistent pain may lead to changes in the spinal cord, and consequently changes in the brain. The brain starts to increase the production of sensors in the ignition nodes and of more chemicals in the body, to activate the sensors. Meanwhile in the cortex, areas that have been dedicated to different body parts or functions, start to overlap. In the sensory cortex, is present the homunculus, which is a representation of all skin and body parts in the brain. The areas more used and best sensation have a wider representation there. The more chronic pain becomes, the more important the changes in the brain develop. (Flor, Braun, Elbert & Birbaumer 1997, 5-8, Butler & Moseley 2003,76.)

Butler and Moseley explain the brain changes occurring when the pain becomes chronic, through the orchestra model. The brain has been playing the pain song, over and over, losing creativity and curiosity to play new songs. The best musicians quit because they get tired, and the others get sick because they play all the time the same. Some of the musicians overlap the function of others(i.e: a violinist playing the flute), tours get cancelled and orchestra stays at home. In the real life, the pain

starts to dominate every aspect of patients life, hobbies, emotions or beliefs. (Butler and Moseley 2003,40.) Therefore, when the brain gets sensitized, is not only the experience of pain that is constantly produced, but it also leads to persistent changes in the sympathetic , parasympathetic, endocrine , immune and motor systems. They combined can perpetuate the pain song (neurotag: a network of neurons which stimulates pain activation), due to a persistent activation of pain ignition nodes. (Butler & Moseley 2003, 78.) Furthermore, humans are able to learn from the experience and use the logic to predict , we can recognize dangerous situations even before there is an input in the tissue level. However, when the nervous system is very sensitive, innocuous inputs, can be codified as a noxious inputs , leading to pain. Different studies have shown that thoughts and fears are strong enough to maintain a pain state.(Butler & Moseley 2003,80, Moseley 2004, 1644.)

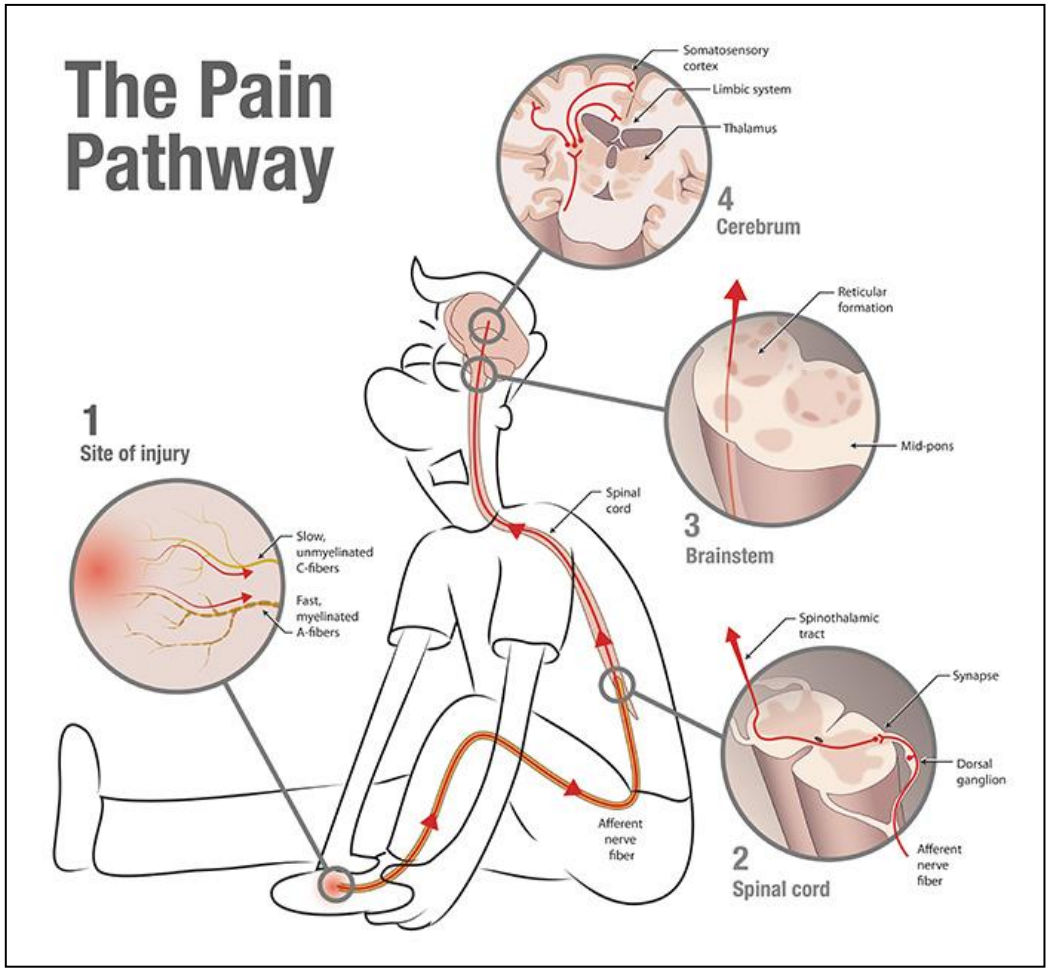

Figure 3: The pain pathway: peripheral and central mechanisms

(Website of Physiotherapy Prescription 2012)

2.3.3 Sympathetic and parasympathetic nervous system

The sympathetic nervous system is a highly advanced networks of neurons widely distributed throughout the body, acting more as a gland than as an electrical system. This system allows us to cope and protect us from a potential danger. As the adrenaline gland, segregates adrenaline when is necessary into all the tissues, which regulates the breathing, digestive system or the blood pressure for example. The stimulation of sympathetic nervous system combined with the action of cortisol, deliver energy to the brain, muscles and heart, and suppress the immune activity.(Butler & Moseley 2003, 84.)

The sympathetic nervous system, is designed to be activated in a rapid manner returning to a normal situation once the stressful situation has finished. Increased level of adrenaline is related to stress situations and chronic pain, the adrenaline amplify the danger message and together with other brain changes may lead to pain. (Butler & Moseley 2003, 85.)

Conversely, the parasympathetic nervous system acts slowing and conserving energy, storing energy, and favouring cellular replenishment and reproduction. This system is more active during rest. However, sleeplessness is common in chronic pain, leading to illness and increased sensitivity of the tissues. Moreover, insufficient rest may cause a lack of ongoing repair of the injured tissue. (Website of Chronic Pain Australia 2013, Butler & Moseley 2003, 85.)

2.3.4 Endocrine response and immune system

The sympathetic and the immune system work together with the endocrine in the stress response. The effects of the last one may last, weeks or months. The main areas for control of stress in the brain are the hypothalamus, the pituitary gland and the adrenalin gland, which is close to the kidneys. Inputs recognized as noxious or fear by the brain, make the hypothalamus liberate hormones which secondarily stimulate the pituitary gland to release ACTH (adrenocorticotropic hormone) into the blood. In a few minutes this hormone is caught up by the chemical sensors of the

outer layer of the adrenalin gland. This gland segregates an important hormone called cortisol. Cortisol and adrenaline work together in protection tasks. Cortisol , slows down the systems that are carrying out other tasks and stimulates the once that are involved in protection tasks. If the danger engages a physical or mental challenge, the emergency augments the cortisol production. Maintained altered levels of this hormone may lead into slow tissue healing, loss of memory or depression and a decrease in physical activity. Along the day the production of corstisol is highest in early morning, and is the lowest in early evening. That is the reason why people with maintained inflammation frequently have more pain in the evening. (Butler & Moseley 2003,86-87.)

The immune organ (bone marrow, T-cells), synthesize two kinds of specific molecules called cytokines, once are pro-inflammatory and the others anti-inflammatory. Current studies have shown the strong links between the immune system, cortisol and adrenaline. (Watkins & Maier 2000, 29-57.) In addition, it is well-known that there is a good connection between the brain and the immunes system. Endocrine, sympathetic, parasympathetic and immune system are continuously giving feedback to each other . For instance, when there is an input recognized as noxious, the hypothalamus is stimulated liberating ACTH, this in turn excites the adrenal gland liberating cortisol ,which finally activates the immune system (the immune system can be also activated by the sympathetic nervous system). This latter system produces cytokines that are send it to the tissues and stimulates the hypothalamus and so on. Furthermore, the immune system is more engaged in chronic pain or in serious infections. Some studies have demonstrated that long-term stress and pain, may alter the activity of the immune system, increasing the production of pro-inflammatory cytokines. This increased of production of pro-inflammatory cytokines is having an straight effect on the peripheral nerves damage which rises their sensibility. (Butler and Moseley 2003,88-89; Watkins & Maier 2000, 29-57; Watkins, Mayer & Goehler 1995,289-302.)

2.3.5 Motor alterations and fears

Alterations in back muscles function might be important in some kinds of spinal pain. Changes on trunk muscles activation, in particular in deep muscles with a stabilizing function (i.e: transverses abdominis) have been demonstrated following an acute episode of low back pain .In addition muscle function does not return spontaneously to normal levels even though the pain has gone. As a consequence, the structures of the spine may be more vulnerable to mechanical stress due to this lack of motor control by stabilizing muscles. These changes in muscle function can happen in different parts of the body, putting tissues at risk of injury and, avoiding tissues from healing. These alterations of motor activity, may change the way we move. It has been shown that fear of movement may prevent these motor control changes returning to normal.(Butler & Moseley 2003,91; Hodges, Moseley, Gabrielsson & Gandevia 2003,262-271.)

The last research done about catastrophising and chronic pain have found different alterations that could be underlying this relationship. (Johansson, Gunnarsson, Linton, Bergkvist, Stridsberg, Nilsson & Cornefjord 2008,633-640). Some studies suggest that pain catastrophising is related to an alteration in hypothalamic-pituitary-adrenal axis. It has been shown how the catastrophising was associated with a greater interruption of the morning cortisol decline, in response to a sequence of experimental pain stimulus in samples with pain free patients and subjects with persistent orofacial pain.(Johansson, Gunnarsson, Linton, Bergkvist, Stridsberg, Nilsson & Cornefjord 2008,633-640; Edwards, Kronfli, Haythornthwaite, Smith, McGuire & Page 2008,135-144; Quartana, Campbell & Edwards 2009,745-758.)

However, these are not the only relevant findings. Along, the last years some studies have investigated the neural link of danger in pain catastrophising using pain neuroimaging during application of hurting stimulus. As pain catastophising is related to exaggerated negative affective responses to pain, the investigators have concentrated on the brain areas mostly involved in processing and regulating of the unpleasantness dimension of pain and emotions more roughly such as anterior cingulated cortex(ACC) and dorsolateral and ventromedial prefrontal cortex. One investigation found out that during mild pain, pain catastrophising was related to

exaggerated activity in the prefrontal cortex and caudal ACC, showing exaggerated processing of the affective dimension of pain. (Seminowicz & Davis 2006,297-306.) Furthermore, in one study with fibromyalgia patients, the pain catastrophising was related to activation of the ACC and medial prefrontal cortex. In addition a recent study, using thermal stimuli, found that fear of pain was linked to activation in the ventral lateral prefrontal cortex and in the ACC (involved in monitoring and analyzing of affective states in the context of stress and pain). Therefore it is suggested that fear of pain and pain catastrophising are probably overlapping the neural circuits. In persistent or chronic pain where the alarm system and the brain are sensitized, pain catastrophising and fear of pain can help to preserve the pain by triggering the ignition nodes. (Seminowicz & Davis 2006,297-306; Wager, Davidson, Hughes, Lindquist & Ochsner 2008,1037-50; Ochsner, Ludlow, Knierim, Hanelin, Ramachandran, Glover & Mackey 2006,69-77; Quartana, Campbell & Edwards 2009,745-758; Butler & Moseley 2003, 100.)

3 CENTRAL SENSITIZATION

3.1 History of central sensitization.

Previous to the origin of central sensitization (CS), there were two major models of pain. The first one was, Labelled-line system in which specific pain pathways were turn on, only by particular peripheral pain stimuli, and the amplitude and length of pain was determined exclusively by the intensity and timing of these inputs. The second one was, Gate Control in the central nervous systems (CNS) by Melzack and Wall, which suggest that the spinal cord contains a neurological ”gate ” that either blocks pain signals or allows them to continue to the brain facilitating or preventing pain. (Latremoliere & Woolf 2009, 895-926.)

Clifford J Woolf, in 1983, using electrical stimulation or natural activation generated a brief (10-20 second) and low frequency (1-10Hz) burst of action potentials into the nociceptors of the CNS. As a result of these stimuli, synaptic efficacy at nociceptive neurons in the dorsal horn of the spinal cord increased, and lasted for minutes after

the end of the conditioning stimulus. Woolf's experiment demonstrated that after their activation , the synaptic efficacy of nociceptive neurons remained autonomous for some time, with the only requisite of a very low level of nociceptive input. Moreover, this phenomenon of central sensitization showed a chain effect, whereby input in one set of nociceptor sensory fibres amplified subsequent responses to other non stimulated non-nociceptor or nociceptor fibres. Recently, it has been discovered that changes in microglia, astrocytes, gap junctions, membrane excitability and gene transcription can contribute to the persistence of CS. (Woolf 2011, 3-15.)

3.2 The last findings about central sensitization.

During the last 20 years, there have been important advances in the study of signs and nature of the phenomenon. Nowadays, it is well known that the previous models of pain were right in part, there are specific nociceptive pathways which are subjected to complex facilitating and inhibitory control mechanisms. But noxious stimulus while sufficient it does not necessarily generate pain. However, if there is a considerable gain of neurons in the pain pathway, they can start to be activated by low threshold, innocuous inputs.(Woolf 2011, 3-15.) Central sensitization is defined as an "amplification of neural signalling within the CNS that elicits pain hypersensitivity". It is present in some inflammatory, neuropathic and dysfunctional disorders such arthritis. (Michaud , Bombardier & Emery 2007,35-45). (Costigan, Scholz & Woolf 2009, 1-32.)

When neurons in the dorsal horn of the spinal cord are affected by CS, they may develop spontaneous activity, a decrease of the activation threshold by peripheral stimuli, augmented responses to suprathreshold stimulation and an enlargement of their receptive fields (spatial summation). Some characteristics are specific for CS like; conversion of nociceptive-specific neurons to wide- dynamic range neurons (WDR) that now react to both innocuous and noxious stimuli , gradual increases in the responses caused by a standard series of successive innocuous stimuli and extension of the spatial extent of their input, and adjusts that outlast an initiating trigger. These electrophysiological changes are the origin of clinical signs related to CS. The pain can increases suddenly, can be triggered by normally innocuous

stimuli(allodynia), is exaggerated and prolonged in response to noxious stimuli(hyeperalgesia) and spreads beyond the location of injury(widespread hyperalgesia).(Latremoliere & Woolf 2009, 895-926.)

3.3 Presence of central sensitization across different pathologies.

Clinically central sensitization can be determined by the presence of hypersensitivity to peripheral stimuli and referred pain sensations (widespread hyperalgesia) at the affected and at the unaffected side. (Albuquerque Sendín , Camargo , Vieira & Salvini 2011, 478-486.) Along the last years, several studies have demonstrated that CS plays a key role the in different pathologies. Such as whiplash associated disorders (Sterling, Jull, Vicenzino & Kenardy 2003,509-517), fibromyalgia and low back pain (Desmeules ,Cedraschi ,Rapiti ,Baumgartner ,Finckh ,Cohen , Dayer & Vischer 2003, 1420-1429, Neill , Manniche , Graven-Nielsen & Arendt-Nielsen 2007,415-420.)

Recently, some studies have shown that the CS should be considered in patients with chronic shoulder pain. For instance, in relation to so called shoulder impingement syndrome (SIS), CS has been identified by means of the presence of widespread hyperalgesia at the affected and unaffected side, the amount of pain experienced by the patient with SIS does not necessarily correlate with the degree of joint pathology.(Hidalgo Lozano, Fernàndez de las Peñas, Alonso Blanco, Hong-You , Arendt-Nielsen & Arroyo Morales 2010, 915-925; Gwylim, Oag, Tracey & Carr 2011,498-502.)

4 THE SHOULDER

4.1 Anatomy of the shoulder

The shoulder is made up by four joints (glenohumeral, acromioclavicular, sternoclavicular and scapulothoracic joint) and three linked bone groups(humerus,

scapula and clavicula) (Figure 4). It should be “unstable” compared to other joints of the body to allow a great quantity of movement. The shoulder can perform motion in three different planes: flexion/extension, external/internal rotation, and abduction/adduction. (Tortora & Derrickson, 2006, 261-262.)

Although an instable joint, the shoulder is surrounded with a big variety of structures that provide passive and dynamic stability, to remain in a stable position. The passive stability is provided by the joint capsule (a watertight sac that surrounds the joint) and the main ligaments of the shoulder; the gleno-humeral ligaments (superior, middle and inferior), coraco-acromial ligament, coraco-clavicular ligaments (trapezoid and conoid) and transverse humeral ligament.(Tortora & Derrickson, 2006, 277.) In addition, the dynamic stability of the shoulder is supplied by the muscles such as: the scapula stabilizers which offers dynamic support for the head of the humerus during arm movements (rhomboid major and minor, serratus anterior and lower portion of trapezius) and by the rotator cuff muscles tendons (infraspinatus, subscapularis, teres minor and supraspinatus, Figure 5) which work stabilizing the head of the humerus on the glenoid cavity and providing a wide range of motion to this joint. In addition, there are other muscles tendons which are related to the shoulder stability, it can be distinguished, superficial muscles (pectoralis major, trapezius, scalene, biceps brachii, triceps brachii, latisimus dorsi and deltoid) and deep muscles(pectoralis minor, coracobrachialis, brachialis anticus, subclavius, levator scapulaes, teres major and minor, supraspinatus, infraspinatus and subscapularis). (Lewis ,Green & Dekel 2001,458-469, Website of National Institute of Arthritis and Musculoskeletal and Skin Diseases USA 2010, website of National Library of Medicine and National Institutes of Health USA 2011.)

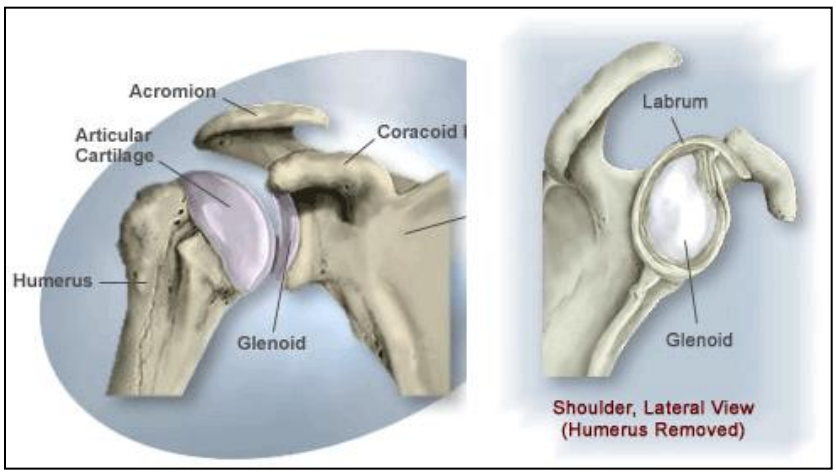

Figure 4: Shoulder joint: anterior and lateral view 2008.
(Website of Go orthopedics, Arthroscopic, Sports & Medicine).

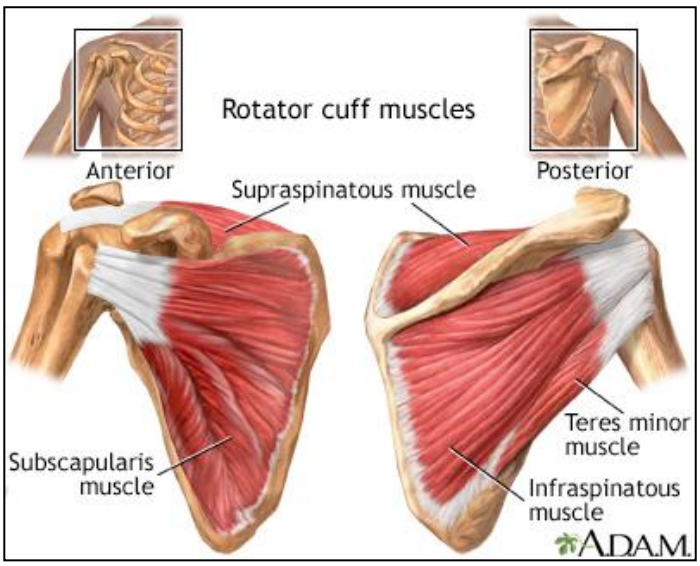

Figure 5: Shoulder rotator cuff muscles anterior and posterior view.
(Website of Medline plus, National Institutes of Health 2011)

The other important structures in the shoulder are the nerves. The shoulder is innervated by the Brachial plexus (i.e: axilary nerve, long thoracic nerve, supraescapular and musculocutaneuous nerve).These nerves bring the orders from the brain to the muscles to move the arm and carry signals back to the brain about sensations as touch, pain or temperature. Information related to shoulder muscles innervations can be found in the APPENDICE 1. (Aszmann, Dellon, Birely & Macfarland 1996,202-207.)

4.2 Shoulder pain prevalence in general population.

Shoulder pain is a common complaint leading patients to visit the healthcare center/hospital. (Van der Windt , Koes , de Jong & Bouter 1995, 959-964).

"According to the centres for Diseases Control and Prevention ,nearly 1'5 million people in US visited an emergency room in 2006 for shoulder problems" (Website of National Institute of arthritis and musculoskeletal diseases and skin diseases; 2010). In the general population, only musculoskeletal complaints of low back pain and knee pain are higher in prevalence than shoulder pain. Furthermore, between 5-47% of the them, the presence of pain last for more than 1 year. In Finland about 4% of the population in between 40-50 years is suffering from rotator cuff pathology. (Website of International Association for the Study of Pain: 2009-2010.)

Subacromial impingement syndrome (SIS) is the most common disorder in shoulder, representing 44-65% of the total shoulder complaints. Nowadays, the last studies suggest that the aetiology of SIS is multifactorial , these causes includes rotator cuff overuse or degenerative tendinopathy, restricted glenohumeral capsule, instability (secondary impingement), posture alteration, scapular instability and mechanical or anatomical causes. (Koester, George & Kuhn 2005,452-455, Lewis, Green & Dekel 2001,458-469, Albuquerque, Camargo, Vieira & Salvini 2012,478-486 .)

The subacromial space (Fig 6) is limited by the inferiorly humeral head, and superiorly by the anterior edge and under surface of the anterior third of the acromion, the coracoacromial ligament and the acromio-clavicular joint (Fig 2). The height of the subacromial space oscillates from 1 to 1'5cm. The rotator cuff tendons, long head of biceps tendon, the bursa and the coracoacromial ligament are placed inside the subcromial space. (Umer, Qadir & Azam 2012,79-82.)

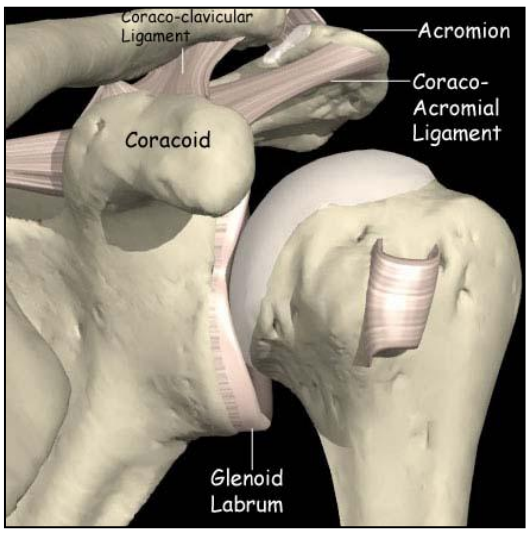

Figure 6: The subacromial space.
(Website of the London Shoulder Partnership 2010)

Two types of SIS can be divided :primary and secondary SIS. The first one, is related to mechanical compromise of the rotator cuff tendons, due to either intrinsic or extrinsic factors or a combination of both. (Kahn,Nagy, Malal & Wasem 2013,347-351.) Intrinsic mechanisms are related to problems in the tendon itself which arise after acute or chronic processes, after partial or full thickness tendons tears happen as a result of the degenerative process that occurs over time with overuse, tension overload, trauma of the tendons or calcified tendinitis. As a contrast, the extrinsic mechanisms are related to reduction of subacromial space due to attachment of the coracoacromial ligament, changes in the acromioclavicular joint (i.e: osteoarthritis), the shape of the acromion, subacromial bursitis or thickened coracoacromial ligament. (Kahn,Nagy, Malal & Wasem 2013,347-351, Hurt & Backer 2003,567-575, Michener, McClure & Karduna 2003,369-379, Lewis, Green & Dekel 2001,458-469.)

The secondary impingement is associated with repeated overhead activities that may cause muscle tiredness leading to micro trauma. It affects the glenohumeral ligaments and tendons of the rotator cuff, in particular the supraspinatus tendon. Moreover near the insertion of supraspinatus in the greater tuberosity, there is an avascular zone that increases in area width as age advances. Deficiency of rotator cuff function can also lead to distorted kinematics and the supraspinatus tendon can be encroached as biceps or rotator cuff tendon. This secondary impingement, is the consequence of encroach the subacromial tissues as a result of narrowing the subacromial space, combined usually with chronic repetitive mechanical process in which the tendon of the rotator cuff experience successive compression or microtrauma as it passes under the coraco-acromial arch. Subsequently, may lead to weakening of the muscles and therefore increases the risk of tendon ruptures.(Umer, Qadir & Azam 2012,79-82, Kahn,Nagy, Malal & Wasem 2013,347-351, McClure & Karduna 2003,369-379, Lewis, Green & Dekel 2001,458-469.)

Frequently, pain is generated with overhead shoulder movements. However in some cases, it can be present in rest as well. More than 45% of the patients still having pain up to 2 years after receiving conservative treatment. In addition, surgical treatment has not show better results than conservative. Consequently some of the patients may develop chronic pain. (Paul, Soo Hoo, Chae & Wilson 2012,2206-2209.)

5 SYSTEMATIC LITERATURE REVIEW

5.1 Information about systematic literature review

Literature reviews are summaries of what have been published on an area by accredited scholars and researchers. A review receives the adjective systematic if is based on a clearly formulated question and is conducted using systematic and explicit methodology with the purpose of minimizing bias by recognizing, appraising and synthesizing all relevant studies in a particular area. This systematic and explicit approach differentiates systematic reviews from traditional reviews and commentaries. (Website of Toronto University, Health Sciences Writing Centre 2013; Kahn, Kunz, Kleijnen & Antes 2003,118-121.) The systematic review is an important element in evidence-based health sciences. They are done in order to filter huge amounts of information that is published every year, through exploration, evaluation and synthesis separating the redundant and insignificant information from relevant and critical studies that are worthy. One of the benefits of analyze more data is the increase in precision of the review. Thanks to systematic reviews the professionals can keep updated quickly about a specific them of their profession. (Website of BMJ, Systematic Reviews 1994; Uman 2011, 57-59; Herbert, Jamtvedt, Mead & Hagen 2005, 32-33.)

To make a systematic review is recommended to follow 5 steps. The first step consists of structuring the research questions. Before that, the researcher has to define the research questions, analyze the existing literature about the topic and determine the need of a systematic review. One to three research questions are needed. Without research questions, the investigator can not find answers to the

research problem. To formulate the research questions is recommended to follow the PICO-model. In this model each letter has a meaning: P= patient or problem(it has to be specified the patient or problem, to get a relevant answer, but if it is too much specified, it will not get any answer), I=Intervention or management strategy and C=comparative intervention (determine the intervention that we are concerned and in what will be compared the effect of the intervention) and O=outcome (what outcomes we are concerned in). If the systematic review can not find any answer to the research questions is not a failure, but it shows the lack of investigation and evidence in the determined topic, and therefore the need further investigation. After that, the material to carry out the seek evidence process is chosen. First of all the search process has to be extensive , determining the databases used to search the evidence (at least 2 or 3) and the keywords used to perform the research. Then the exclusion and inclusion criteria which should flows from the research questions have to be defined and specified. It is important to pay much attention during the research process, because mistakes at this stage can affect the review outcomes from the review. Moreover , the method to search evidence must be registered precisely to make the process reliable.(Khan, Kunz, Kleijnen & Antes 2003,118-121; Uman 2011,57-59; Herbert, Jamtvedt, Mead & Hagen 2005,14-15; Website of Cochrane, about systematic reviews 2006; Website of NYU, health sciences libraries 2013.)

Then, the researcher joins the material from the databases and goes through it according to the guidelines .The investigator analyses the material in line with the research questions, from the ones that are selected they will be assessed by using general evaluation guides and design-based quality check lists (for instance, PEDro scale). After that, the researcher task is to summarize the research results all together. The researcher can do that through tabulation of the characteristics, quality, effects and differences of the studies collected. The last step is to report the outcomes, and come up with the conclusions and suggestions in harmony with the results. It is essential to record all stages in order to make the systematic review reliable.
(Khan, Kunz, Kleijnen & Antes 2003,118-121.)

5.2 Purposes and aims of the thesis

This thesis is carried out in order to review the scientific literature related the presence of central sensitization in patients with chronic shoulder pain, and investigate the prevalence of this phenomenon in the affected population. The thesis was carried out in collaboration with the University of Valencia, and the systematic review aims to be published in a physiotherapy peer-review journal. In this systematic review the research questions were:

1. What is the role central sensitization plays in people with chronic SIS?
2. What is the prevalence of this phenomenon among the affected population due to SIS?

6 RESULTS

6.1 The search strategy.

The database search was done 18.9.2013 and 19.9.2013. The search terms used were the combination of shoulder and " central nervous system sensitization", "sensitization", "central sensitivity", central hyperexcitability", "central sensitization", "pain modulation", "neural inhibition", "hyperalgesia", "nociception", "pain threshold", "algometry" and "hypersensitivity". The databases used to perform the search were Pubmed, Web Of Science and Ebsco. Results from the combination for each database are represented in Table 1.

Table 1. The results for every database and combination of keywords with MeSH terms used in the search strategy.

Entry Terms		**Pubmed**	**Web of Science**	**EBSCO**
Shoulder	AND Central Nervous System Sensitization	5	7	6
	AND sensitization	77	109	45
	AND central sensitivity	65	53	29
	AND central hyperexcitability	6	5	3
	AND central sensitization	25	46	26
	AND pain modulation	28	41	14
	AND neural inhibition	45	15	13
	AND hyperalgesia	48	69	33
	AND nociception	19	33	11
	AND pain threshold	249	269	166
	AND algometry	11	26	39
	AND hypersensitivity	135	65	64
Total hits		**713**	**738**	**449**

6.2 Study selection

The Figure 4 represents the flow diagram of the study selection process including reasons for exclusion at each stage. From the total of 1900 hits found in the different databases, two articles were added after reviewing the reference list. After removing duplicates, 755 hits remained. Then, between, all the titles and abstracts were screened in order to identify relevant articles ,using the predefined inclusion criteria. In case of doubt regarding the appropriateness of the article after reading title and abstract, the full version of the article was screened aiming to check if the inclusion criteria were fulfilled. To be included in this review an article had to meet the following inclusion criteria:(1) to be reported in a peer-review academic journal; (2) to study the phenomenon of CS in human adults (18 years or older) with chronic shoulder pain; (3) to be full-text original research report and (4) to be presented in English. No limitation regarding year of publication was used and all study designs

were eligible. Although review articles were not eligible for inclusion, but their references were screened in order to collect relevant articles which were not initially retrieved by the systematic search. If any of the inclusion criteria was not accomplished the article was rejected. As a result, a total of 11 articles were identified as meeting the inclusion criterion to be included in this review. Methodological assessment and data extraction was thus performed for these 11 articles.

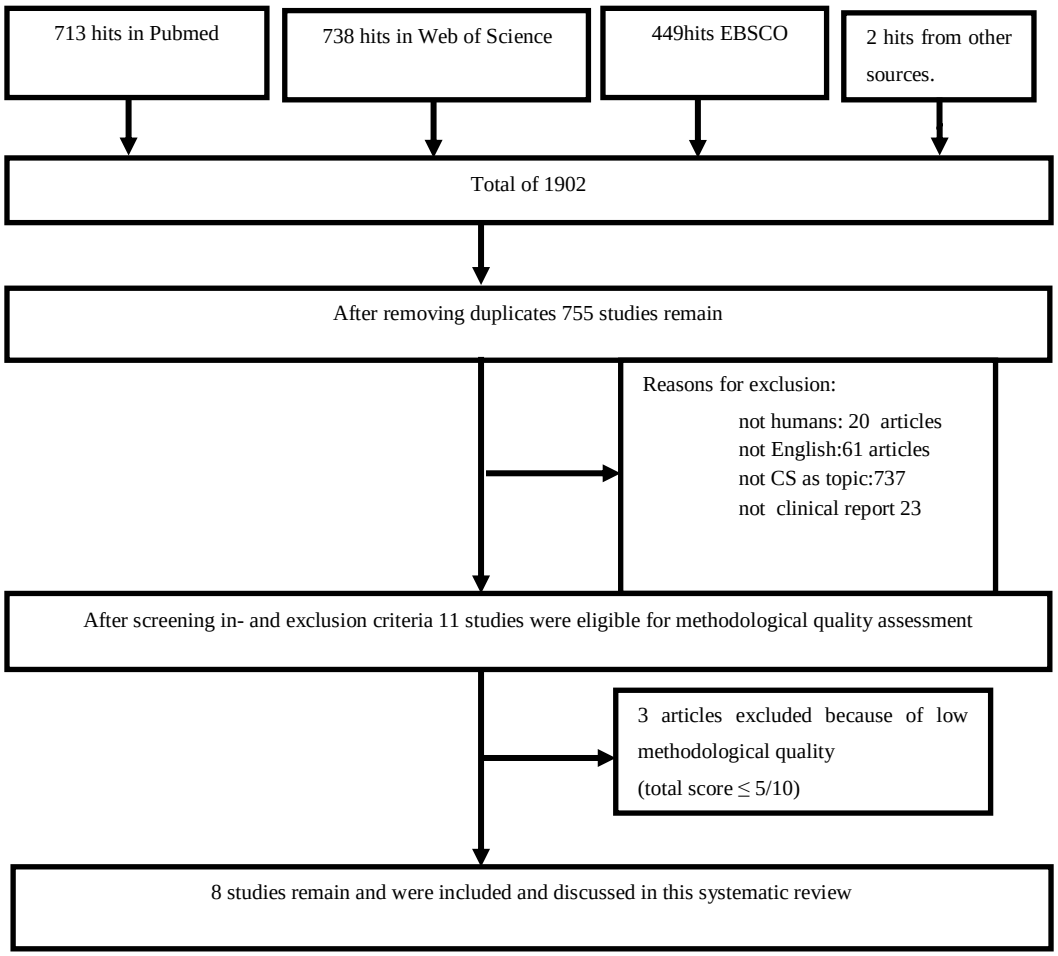

Figure 7: Flow chart of study selection.

6.3 Methodological quality assessment

To determine the methodological quality of the full text articles that were retrieved, the PEDro scale was used, APPENDICE 2. PEDro is the abbreviation of Physiotherapy Evidence Database free online. It has more than 25.000 studies and all of them have been assessed with PEDro scale The PEDro scale uses 11 different criteria to determine the quality of the study, only ten of them are part of the final result. The PEDro scale grades articles getting 6/10 or more points from moderate to high quality. This punctuation was set in this systematic review as the lowest grade for an article to be included. (Website of Physiotherapy Evidence Database free online 1999).

Prior to assess the quality of the included papers a practice trial of scoring was performed by two independent and blinded researchers (MSN and EK) to guarantee understanding of the quality criteria. The two researchers rated independently one article not included in this review. Initially there was 94'5% of agreement (104 of 110 items) between the two researchers on scoring the selected articles. After a second review, the researchers reached consensus in all except 3 items. A third author (EB) was recruited to resolve discrepancy. To be further considered in this review the articles were required to fulfill 6 out of 10 criterions of PEDro's scale. As a result 3 studies were excluded and only 8 were finally included in this review(Figure 7). Table 2 provides information regarding the methodological quality criteria fulfillment of each article analyzed in this review.

Of the 8 studies selected six were categorized as controlled study and two as a cross-sectional study. Five investigated the etiology of SIS, one was classified as a mixed etiology-treatment and the other two were diagnosis studies.

Table 2. Methodological quality assessment of the included studies.

Criteria methodological quality	Criterion 1	Criterion 2	Criterion 3	Criterion 4	Criterion 5	Criterion 6	Criterion 7	Criterion 8	Criterion 9	Criterion 10	Criterion 11	SCORE	ARTICLE
Albuquerque et al. 2012	1	1	0	1	0	1	0	0	1	1	1	6/10	A
Coronado et al. 2011	1	0	0	1	0	1	0	1	1	1	1	6/10	A
Coronado et al. 2013	1	0	0	1	0	0	0	1	1	1	1	5/10	R
George et al. 2008	1	0	0	1	0	0	0	1	0	1	0	3/10	R
Gwilym et al. 2011	1	0	0	1	1	0	1	1	1	1	0	6/10	A
Hidalgo-Lozano et al. 2011	1	0	0	1	1	1	1	1	1	1	1	8/10	A
Paul et al. 2012	1	0	0	1	0	0	0	1	1	1	0	4/10	R
Sjors et al. 2011	1	0	0	1	1	0	1	1	1	1	1	7/10	A
Valencia et al. 2011	1	0	0	1	1	0	1	1	1	1	1	7/10	A
Valencia et al. 2012	1	0	0	1	1	0	1	1	1	1	1	7/10	A
Valencia et al. 2013	1	0	0	0	1	0	1	1	1	1	1	6/10	A

Score: Total score of the article following Pedro scale criteria, the first criterion inclusion and exclusion criteria, is not considered part of the total score.
Criterion: Can be found in the appendices at the end of the thesis.
Article: A(accepted), R(rejected)

Table 3: Summary of the included articles.

Author/publication year.	Purpose	Design	Subjects	Assessment regarding CS	Results regarding CS	Limitations of the study
Albuquerque, Camargo , Vieira & Salvini. 2013	Etiology	Controlled study	27 patients with SIS (Shoulder impingement syndrome) and pain duration of more than 2 months . 20 matched control patients.	MTrPs (myofascial trigger points), were explored bilaterally in both groups in over 10 random muscles (i.e upper trapezius,) following criteria established by Travell and Simons and Gerwin et al. The secondary outcome was the PPTs evaluated bilaterally over several muscle (i.e. levator scapulae) and in a remote site used in previous studies(tibialis anterior) through mechanical pressure algometer.	Increased presence of MTrPs in both involved and uninvolved sides in patients with SIS and increased activity of myofascial pain in the involved side of SIS group when compared with the other group. PPTs was not significantly different between both sides in SIS group and the dominant side of the controls The study reject the presence of CS.	The small sample size employed has probably influenced some of the analyses, especially did not detect statistical differences.
Coronado, Kindler, Valencia & George. 2011	Etiology	Cross-sectional	59 patients seeking operative treatment for shoulder pain, with rotator cuff pathology, adhesive capsulitis or labral lesion.	PPTs was evaluated bilaterally at the muscle belly of(i.e acromion process, supraspinatus) through mechanical pressure algometer. Thermal pain threshold and tolerance, evaluated bilaterally at volar forearms. Thermal temporal summation evaluated bilaterally at the thenar eminence, using pain rating scale (0-100).	PPTs was significantly lower on the involved side compared to uninvolved side. Women lower PPTs than male in the local shoulder areas. Thermal pain threshold and temporal summation, There was no difference between involved and uninvolved sides, there was not interaction between side and sex for threshold and tolerance. Not enough findings	The study did not include a control group, therefore the results cannot be compared to determine if the affected group was more or less sensitive to pain. PPTs were applied to general pain-produce it in anatomical landmarks. It has been suggested that a non-uniform

					to confirm or reject the presence of CS.	of painful points may exist within some muscles of upper extremities which could potentially influence the results of pressure testing. The results are limited to patients with preoperative shoulder pain due to, rotator cuff pathology, adhesive capsulitis or labral lesion.
Gwilym, Oag, Tracey & Carr. 2010	Etiology-Treatment	Controlled-Study	17 patients with unilateral impingement syndrome, awaiting for arthroscopic subacromial decompression 17 matched controls without shoulder pain.	QST(quantitative sensory testing) was underwent by both groups in both shoulders over the insertion of deltoid. Tested to punctuate sharpness threshold and to sharpness of a 265mN punctuate stimulus(VAS 0-10) All participants completed OSS(oxford shoulder score), Pain DETECT and the Brief Pain Inventory pre-operatively , and undertaken 4 weeks after surgery.	Significant improvement of OSS after surgery in patients group. Patients affected shoulders had a lower mechanical threshold which punctuate stimulus was perceived painful. And also compared with the matched controls. Higher ratings of sharpness in the affected side than in the unaffected in the patients group. The presence or absence of referred pain pre-operatively and hyperalgesia was found to have significant role as a predictor outcome of the post-operative score.	The QST was liable to potential confounders as patient motivation, attention and reaction times. This study could not establish a relationship between pre and post operatively measures of pain, because many patients referred pain from sites away of the shoulder that preoperatively were not considered.

					11 patients after the surgery reported referred pain, under arm. The study highlight the presence of CS.	
Hidalgo-Lozano, Fernandez de las Peñas, Alonso-Blanco, Ge, Arendt-Nielsen & Arroyo-Morales. 2010	Etiology	Controlled-Study	12 patients with unilateral shoulder impingement syndrome on the dominant-right side. 10 healthy matched controls	MTrPs were examined in both groups in the affected by the patients and in the dominant side of matched controls in 6 different muscles (i.e: levator scapulae) the diagnosis was performed following the criteria established by Simons and Travell, Gerwi et al. PPTs were examined in the previous 6 muscles and in the tibialis anterior through a mechanical pressure algometer in the affected side of the patients and in the dominant side of the matched controls.	In the patients group there was a presence of active MTrPs in the affected side. In addition patients with impingement syndrome showed a lower PPTs levels when compared with the healthy controls. A greater number of MTrPs and lower of PPTs were related to greater pain intensity. The PPTs were lower in some muscles in patients with MTrPs when compared to those patients without MTrPs. The current study suggests both peripheral and central sensitizations are presents in patients with SIS.	Possible that during the muscle examination of MTrPs a memory bias can be present. Small sample size, even though the results seem robust. The study can not establish a cause-and-effect relationship between MTrPs and SIS, because the design was not longitudinal and because the paper did not report the results of inactivating the MTrPs.
Sjörs, Larsson, Persson & Gerdle. 2011	Etiology	Controlled Study	19 women with chronic non-traumatic neck shoulder pain, without simultaneously widespread clinical pain. 30 age-matched women pain-free control subjects	PPT through pressure algometer over 3 different points bilaterally in the trapezius, and in tibialis anterior . Induced muscle pain, by injection of 0.5ml sterile hypertonic saline (5'8%), inserted in	All PPT's were significantly lower in NSP group than in the control matched group. The differences were smaller between the groups regarding PPT's in tibialis anterior. Induced pain: was significantly higher	Not specified.

				the right tibialis anterior in both groups. Then they reported the pain intensity with (VAS). Clinical pain drawings, the patients with NSP have to draw there painful areas in three different templates, analyzed with, Quantify one. Pain and psychological factors(Questionnaire): -VAS -KSQ -HADS -ASI -PASS-20 -PCS -FABQ -PDI	in the NSP group than in the control group, however timing was similar in between Clinical pain drawings, revealed a significantly larger spreading pain area in sizes in the NSP groups. Questionnaire Scores, NSP generally perceived aspects of their psychological situation, including sleeping problems , the only questionnaire that had similar results between groups was the ASI. The present study suggests that central sensitization mechanisms are involved in chronic non-traumatic neck shoulder pain.	
Valencia, , Fillingim & George. 2011	Etiology	Cross-sectional study.	59 patients with clinical shoulder pain seeking treatment for shoulder pain	Clinical pain intensity -BPI -NRS Experimental pain sensitivity -SPHS (using the 5th pain rating) impulses applied at the thenar eminence of the involved and uninvolved side. -Heat pain threshold and tolerance using NRS to rate the pain. -PPT(with a pressure algometer) Psychological measures	The 5th pain rating scale and a index derived from SPHS, showed the highest association with shoulder pain intensity. The present study demonstrates the SPHR as the strongest QST measure in association with shoulder pain intensity. Catastrophizing and depression as important psychological factors related to	The clinical sample fails to show a robust slope in TS, and may be a reason why the TS did not correlate with clinical pain intensity. Only data from the baseline and not from the postoperative. SPHR was the only dynamic QST measure considered in this study

				-Anxiety (STAI) -Pain catastrophizing(PCS) -Depression (BDI)	clinical pain intensity All of the previous factors are associated with the severity of the experienced pain. The present study suggests that psychological factors and pain amplification represent independent intermediate phenotypes that are associated with clinical pain severity. Therefore, there might be an overlap in the mechanisms that influence the development of chronic shoulder pain	
Valencia, Kindler, Fillingim & George. 2012	Diagnosis	Controlled Study	58 patients with clinical shoulder pain. 56 age and sex matched healthy subjects.	CPM Test stimulus -SPHR at the thenar eminence in the non-affected side of patients and in the not dominant side in healthy matched group. Rating the pain on VAS scale. Conditioning stimulus -Cold pressor pain Immersing surgical hand in the patient group and dominant in the healthy matched group. *CPM procedure was created with consecutive stimuli (test stimulus,	CPM did not differ between both groups in the baseline phase. However SPHR was increased in the clinical group in the baseline phase, may be sensitive to changes in CNS processing of pain during the first 3 month postoperative period. Three months after the surgery the SPHR was comparable to the same levels that the healthy cohort had at the baseline phase. Acute noxious	The study last 3 months post-surgical follow-up period. CPM and SPHR were the only QST assessment measures.

				conditioning stimulus, hand removed from water and then test stimulus) EIMP	stimulation of induced by EIMP over 4 days is not enough to induce measurable changes in central pain processing through CPM and SPHR, but increase the pain reports.	
Valencia, Kindler, Fillingim & George. 2013	Diagnosis	Controlled Study	134 patients with pain limited in anterior ,lateral or posterior shoulder, rotator cuff tendinopathy, adhesive capsulitis or waiting list for arthroscopy surgery. 190 pain free matched controls.	CPM Test stimulus -SPHR at the thenar eminence in the non-affected side of patients and in not dominant in healthy matched group. Rating the pain on VAS scale. Conditioning stimulus -Cold pressor pain Immersing surgical hand in the patient group and dominant in the healthy matched group *CPM procedure was created with consecutive EIMP -MVIC Pain intensity: -BPI -NRS	CPM in the clinical cohort was stable in the females, as a contrast in the healthy group was stable in the males. CPM was not significantly influenced by the pain intensity in between the groups	The paper is a result of a bigger study, therefore the procedures were not designed solely for validate the CPM. Results of the CPM in the clinical cohort group could have been accepted by the drugs took it for the surgery. The present study examined the effect of sex in the CPM, but some aspects as (menstrual cycle or ethnics) were not considered may influenced the results.

CS: Central sensitization, TDT: tactile detection threshold, MTrPs: Myofascial trigger points, PPTs: Pressure pain threshold, CPM: conditioned pain modulation, QST: Quantitative sensory testing, HC: Healthy controls , EST: Electrical sensation threshold, EPT: Electrical pain threshold, EPTT: Electrical pain tolerance threshold, NRS: Numerical Rating Scale, VDT: Vibration detection threshold, VAS: Visual Analogue Scale, NSP: neck-shoulder pain, KSQ: Karolinska Sleep Questionnaire, HADS: Hospital anxiety and depression scale, ASI: Anxiety Sensitivity index, PASS-20: Pain anxiety Symptoms Scale-20, PCS: Pain Catastrophizing Scale, FABQ: Fear avoidance beliefs questionnaire, PDI: pain disability index. SPHR: Suprathreshold heat pain response)

.SPHS: Suprathreshold heat pain stimuli.. EIMP: Exercise induced muscle pain, MVIC: Maxim voluntary isometric contraction ,BPI: Brief pain inventory. STAI: state trait anxiety index. BDI: Beck Depression Inventory. TS: temporal summation.

6.4 Presence of Central Sensitization in Subacromial Impingement Syndrome

In addition to list the search results and the characteristics of the included papers, the objective of this review was to summarize the current evidence regarding CS in people with chronic SIS . Three studies confirmed the presence of CS in patients with SIS using clinical criteria. Gwilym, Oag, Tracey & Carr (2010) evaluated quantitative sensory testing (QST) in a sample of 17 patients with SIS, awaiting for arthroscopic subacromial descompression and 17 age- and gender pain free matched controls, to detect pain thresholds for mechanical stimuli (sharp and blunt punctuate stimuli) and heat pain. In this study, the patients group referred pain radiating down the arm, had significant hyperalgesia to punctuate stimulus of the skin and lower mechanical pain threshold compared to pain free matched subjects. All of these are features are recognized as indicative of CS. (Latremoliere & Woolf 2009, 895-926.) Interestingly, the presence of hyperalgesia before the surgery resulted in a significantly worse outcome 3 months after surgical decompression. In conclusion, this study demonstrated the presence of CS in a proportion subgroup of patients with SIS.

Hidalgo-Lozano, Fernandez de las Peñas, Alonso-Blanco, Ge, Arendt-Nielsen & Arroyo-Morales (2010) explored the presence of myofascial trigger points(MTrPs) in 6 different muscles of the shoulder region in 12 patients with chronic SIS. In addition, they determined if the MTrPs were active or latent in the affected side of patients with SIS and in the dominant side in a matched control group. PPT were assessed at 6 locations (1 at a remote site). Subjects with SIS, showed a greater number of active and latent MTrPs and significant lower PPTs, when compared to matched controls. Moreover they showed widespread hypersensitivity and active trigger points in the shoulder muscles which reproduce their clinical pain symptoms. Pain intensity was greater with active MTrPs and lower PPTs. The findings of this study suggested the presence of both peripheral and central sensitization. Moreover,

the results demonstrated enhanced spatial summation of PPT in patients with SIS compared to control group.

Sjörs, Larsson, Persson & Gerdle (2011) investigated PPTs (bilaterally) and clinical pain drawings and psychological factors (i.e: through questionnaires) in 19 women with chronic non traumatic shoulder/neck pain . In addition, they analyzed the relation of clinical pain drawings and psychological factors to patient response following experimental muscle pain. Presence of CS in subjects with chronic non-traumatic shoulder/ neck pain was inferred because their PPTs were lower and the induced pain was significantly more intense and locally more widespread in comparison to the matched controls after intramuscular hypertonic saline infusion. In addition, sensory hypersensitivity was found in areas distant of current pain. All of these findings were interpreted as reflecting central mechanism (CS) and in particular altered pain inhibitory descending mechanisms in chronic non-traumatic neck/shoulder pain.

Unlike the three above mentioned studies which support the presence of CS, other studies got contradictory results Albuquerque, Camargo, Vieira & Salvini (2013) & Coronado, Kindler, Valencia & George(2011). In a controlled study Albuquerque, Camargo, Vieira & Salvini (2013) 27 patients with SIS and 20 matched controls were assessed bilaterally for MTrPs in 10 shoulder muscles and for PPTs in 8 muscles (-2 of them at remote site). The results showed that the presence of MTrPs was higher in involved/uninvolved sides in patients with SIS when compared with the control group. Furthermore, the mechanical sensitivity was not significantly different between both sides of the patients with SIS compared to the dominant side of the matched controls. In addition, non shoulder PPTs (tibialis anterior and C5-C6) were the most similar data between sides and groups, confirming the absence of widespread alterations, therefore the presence of central sensitization was rejected.

Coronado, Kindler, Valencia & George(2011) investigated the experimental pain sensitivity between the involved and uninvolved sides in 59 patients with unilateral shoulder pain seeking operative treatment, PPTs were measured at the shoulder and forearm, thermal pain threshold and tolerance at the forearm and temporal summation at the thenar eminence. The results showed lower PPTs at the involved

side compared to the uninvolved side. Women PPTs were lower bilaterally at shoulder than men. There was no difference in thermal pain sensitivity between sides and sex. Therefore, these findings were not enough suggestive of the existence of CS in patients with SIS.

All the studies included in this review performed QST as a part of their outcomes measures (Albuquerque, Camargo , Vieira & Salvini 2013 , Coronado, Kindler, Valencia & George 2011 ,Gwilym, Oag, Tracey & Carr 2010, Hidalgo-Lozano, Fernandez de las Peñas, Alonso-Blanco, Ge, Arendt-Nielsen & Arroyo-Morales 2010 , Sjörs, Larsson, Persson & Gerdle 2011 , Valencia, Fillingim & George.(2011), Valencia, Kindler, Fillingim & George 2012 and Valencia, Kindler, Fillingim & George 2013). Different modalities of QST were used for assessing sensory and pain perception, with the mechanical stimulus being the most common form of external stimulation being used (5/8 studies, Table 4). Most of the studies carried out QST at local (i.e: close to the shoulder joint) and distant sites (mostly at tibialis anterior).

Three studies demonstrated the presence of not only local but also widespread hyperalgesia in patients SIS compared to controls (Gwilym, Oag, Tracey & Carr 2010, Hidalgo-Lozano, Fernandez de las Peñas, Alonso-Blanco, Ge, Arendt-Nielsen & Arroyo-Morales 2010, Sjörs, Larsson, Persson & Gerdle 2011). Moreover, a higher degree general sensitization was associated to higher degree of pain perception (Gwilym, Oag, Tracey & Carr 2010, Hidalgo-Lozano, Fernandez de las Peñas, Alonso-Blanco, Ge, Arendt-Nielsen & Arroyo-Morales 2010 , Sjörs, Larsson, Persson & Gerdle 2011, Valencia, Kindler, Fillingim & George 2012 and Valencia, Kindler, Fillingim & George 2013), poor prognosis after surgery intervention (Gwilym, Oag, Tracey & Carr 2010) and distortion of the own body image.(Sjörs, Larsson, Persson & Gerdle 2011). Interestingly, improvements of widespread hyperalgesia, pain and function were reported after surgery only if there was not previous sensitization. (Gwilym, Oag, Tracey & Carr. 2010) .

Descending modulation of pain has been evaluated through the conditioned pain modulation (CPM) paradigm which assesses the activation of the descending endogenous analgesia system Valencia, Kindler, Fillingim & George (2013) & Valencia, Kindler, Fillingim & George 2012, these studies assessed CPM in the

context of SIS. Valencia, Kindler, Fillingim & George (2013) studied the influence of shoulder pain intensity and gender in a subjects with SIS and controls As a result, the article highlighted that CPM was not related to changes in pain intensity. Interestingly, there were sex differences for CPM stability. In addition, Valencia, Kindler, Fillingim & George 2012 performed a controlled study with 58 patients with clinical shoulder pain and 56 age and sex, healthy matched controls to investigate whether central pain processing (i.e:CPM) was altered in these two muscoleskeletal shoulder pain models. The study demonstrated that clinical shoulder pain is associated with measurable changes in central pain processing, but only with longer lasting pain. Authors recommended using thermal stimuli to detect neuroplastic changes. Both studies, shown the presence of CS

Regarding psychosocial factors only two studies take them into account in people with SIS pain. Sjörs, Larsson, Persson & Gerdle 2011 & Valencia, Fillingim & George 2011 confirmed the influence of catastrophizing and depression as a important psychological factors that may be influencing clinical pain intensity. Besides, control over these psychological and psychosocial risk factors predicted postoperative pain reports and the results suggested that there might be an overlap in the mechanism that influences the development of chronic shoulder pain. Sjörs, Larsson, Persson & Gerdle 2011, showed how the sensitivity to chemically induced pain was associated with the psychological status of patients with SIS. Furthermore higher levels of anxiety and depression together with a higher disability level were related to increased pain responses after experimental pain and larger area of the clinical shoulder pain.

6.5 Prevalence of central sensitization in patients with chronic subacromial impingement syndrome

Three articles confirming the presence of CS in patients with chronic SIS highlighted the high prevalence of this phenomenon in the population. Gwilym, Oag, Tracey & Carr 2010 found that 65% of their patients awaiting for subacromial descompression presented features of augmented central pain processing(CS) mentioned as :

extended referred pain areas radiating down the arm, significant hyperalgesia to punctuate stimulus of the skin and lower mechanical pain threshold

On the other hand, Hidalgo-Lozano, Fernandez de las Peñas, Alonso-Blanco, Ge, Arendt-Nielsen & Arroyo-Morales determined over 90% of prevalence of CS in their sample. Clinical manifestations of CS were widespread hyperalgesia and lower PPT in subjects with chronic SIS compared to the matched controls.

Finally, over 80% of the patients presented clinical manifestations of CS as sensory hypersensivity in are distant to site of pain, lower PPTs and more intense and widespread induced pain, in the study conducted by Sjörs, Larsson, Persson & Gerdle 2011.

7 CONCLUSION

In conclusion, the majority of the literature reviewed suggested that central nervous system becomes hypersensitized in patients with chronic SIS, and the phenomenon of CS plays a key role in the frequent pain complaints reported by these patients. In addition, the results suggest that there is a high prevalence of central sensitization in patients with chronic subacromial impingement syndrome.

8 DISCUSSION

Although my knowledge In this area was quite limited before starting the thesis, the assistance received from my tutor from Spain and SAMK was decisive on this thesis process. Moreover, the study plan made up at the beginning and the table of contents, were very helpful to clearly organize the structure of the thesis. The election of the topic was easy for me due to the help of my teacher from València who recommended me this one, as there was not still pre-eliminary evidence of presence

of CS in chronic SIS. Finally, after establishing the research questions the thesis proceeds further.

The two most time consuming parts of the thesis were on the one hand, screening the articles aiming to recognize which ones were relevant for the systematic literature review, and which ones fulfilled the inclusion criteria previously established. On the other hand, summing up the results of the each article included on a table of content. Another challenge I found in this thesis was to narrow the topic , in order to limit the information that would be included . At the beginning, this thesis was going to include the presence of CS in shoulder pain of different ethiologies: SIS and hemiplejic shoulder pain (HSP). However, I decided to exclude the second part HSP, because the topic was too wide to sum up on one thesis. Once, the topic was narrowed to the presence of CS in SIS, the thesis process progressed further.

When making conclusions from this systematic literature review it should be noted that only eleven articles fulfilled the inclusion criteria and were therefore included. In addition the methodological quality assessment of the included articles showed huge variations in the scores, which indicates the need of further research on this topic. From the included articles, there were only four studies considered as high methodological quality researches, three scoring 7/10 and one 8/10. Although these studies provide strong evidence about the presence of CS in chronic SIS, the majority of the studies retrieved were below moderate to low quality scoring below 7/10 failing thus to provide reliable and valid evidence based. There were four articles with scoring 6/10, one with 5/10, one with 4/10 and another with 3/10.

The goal of this thesis was to review and evaluate the existing scientific literature regarding the role of CS in chronic SIS pain. Diverse assessment methodologies were used for evaluating the phenomenon of CS, aiming to understand the different changes in pain sensibility observed in this population. In general, the results from our systematic literature review seem to support the key role of CS in chronic SIS. However, when making conclusions we have to consider the small sample used in those studies. The reduce number of studies, indicates that this topic has not been well studied yet, further research is required with the purpose of make stronger conclusions.

The learning outcome in this bachelor's thesis is extraordinary. Along the review process, I had to read a great deal of new articles , books and find out reliable websites about central sensitization, and therefore about pain, shoulder anatomy and shoulder impingement syndrome. This thesis has improved my knowledge considerably. In addition, this knowledge will be an advantage in my future work as a physiotherapist.

Some limitations need to be recognized in this review. First of all, even though the study selection was carried out by two assessors, some relevant studies may have been excluded. Second, studies including animals models were excluded, due to animal models do not closely reflect the human condition. Finally, this review was focused in subacromial impingement syndrome. In addition, many studies emphasized that the results have been achieved in very specific conditions. Hence, must be taken into account when extrapolating the results of this review to other subjects with different shoulder pathologies. However, this review has been done with the maximum possible reliability since this thesis aims to be published as a part of future article in a physiotherapy journal.

Based on methodological issues recognized in this review, future studies should use a sufficient and justified sample size. Moreover description of the blinding procedure is suggested in order to increase reliability. Finally, many studies failed to confirm the presence of CS due to the follow-up period was not long enough. Therefore future studies, should include a longer follow-up period in order to detect the central alterations in this population.

On the other hand, the majority of the studies of the current review assessed the presence of CS in patients with SIS in laboratory conditions, using costly and inaccessible equipment for most of the clinicians. Further investigation regarding the assessment of CS in SIS is required in order to provide new ways to assess CS, more accessible and less costly for the clinicians.

Some ideas for further research could be narrowing the topic to treatment of central sensitization in chronic subacromial impingement syndrome that has not been

covered in this thesis. Although the idea of this thesis was to include central sensitization in hemiplegic shoulder pain, the topic was to wide to sum it up on this bachelor's thesis. Other topic recommended for a future thesis could be central sensitization in hemiplegic shoulder pain. Until, the moment few literature reviews have been done about that topic.

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APPENDICE 1

Shoulder muscles innervation. (Website of Department of Radiology Washington University Medical Center 1997)

MUSCLE	INNERVATION
Pectoralis major	Lateral and medial pectoral nerves; clavicular head (C5 and C6) sternocostal, (C7,C8 and T1).
Trapezius	Spinal root of accessory nerve (CN XI) and cervical nerves (C3 and C4).
Scalene	Cervical nerves (C4,C5 and C6).
Biceps Brachii	Musculocutaneous nerve (C5 and C6).
Triceps Brachii	Radial nerve (C6, C7 and C8).
Latissimus Dorsi	Thoracodorsal nerve (C6, C7, and C8)
Deltoid	Axillary nerve (C5 and C6)
Pectoralis Minor	Medial pectoral nerves; clavicular head (C8 and T1)
Coracobrachialis	Musculocutaneous nerve (C5, C6 and C7)
Brachialis anticus	Musculocutaneous nerve (C5 and C6)
Subclavius	Subclavius (C5 and C6)
Levator Scapulaes	Dorsal scapular (C5) and cervical (C3 and C4) nerves
Teres major	Lower subscapular nerve (C6 and C7)
Teres minor	Axillary nerve (C5 and C6)
Rhomboid	Dorsal scapular nerve (C4 and C5)
Serratus Anterior	Long thoracic nerve (C5, C6, C7)
Infraspinatus	Suprascapular nerve (C5 and C6)
Supraspinatus	Suprascapular nerve (C4, C5 and C6)
Subscapularis	Upper and lower subscapular nerves (C5, C6 and C7)

PEDro scale

1.	eligibility criteria were specified	no ❑ yes ❑ where:
2.	subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	no ❑ yes ❑ where:
3.	allocation was concealed	no ❑ yes ❑ where:
4.	the groups were similar at baseline regarding the most important prognostic indicators	no ❑ yes ❑ where:
5.	there was blinding of all subjects	no ❑ yes ❑ where:
6.	there was blinding of all therapists who administered the therapy	no ❑ yes ❑ where:
7.	there was blinding of all assessors who measured at least one key outcome	no ❑ yes ❑ where:
8.	measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	no ❑ yes ❑ where:
9.	all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	no ❑ yes ❑ where:
10.	the results of between-group statistical comparisons are reported for at least one key outcome	no ❑ yes ❑ where:
11.	the study provides both point measures and measures of variability for at least one key outcome	no ❑ yes ❑ where:

The PEDro scale is based on the Delphi list developed by Verhagen and colleagues at the Department of Epidemiology, University of Maastricht (*Verhagen AP et al (1998). The Delphi list: a criteria list for quality assessment of randomised clinical trials for conducting systematic reviews developed by Delphi consensus. Journal of Clinical Epidemiology, 51(12):1235-41*). The list is based on "expert consensus" not, for the most part, on empirical data. Two additional items not on the Delphi list (PEDro scale items 8 and 10) have been included in the PEDro scale. As more empirical data comes to hand it may become possible to "weight" scale items so that the PEDro score reflects the importance of individual scale items.

The purpose of the PEDro scale is to help the users of the PEDro database rapidly identify which of the known or suspected randomised clinical trials (ie RCTs or CCTs) archived on the PEDro database are likely to be internally valid (criteria 2-9), and could have sufficient statistical information to make their results interpretable (criteria 10-11). An additional criterion (criterion 1) that relates to the external validity (or "generalisability" or "applicability" of the trial) has been retained so that the Delphi list is complete, but this criterion will not be used to calculate the PEDro score reported on the PEDro web site.

The PEDro scale should not be used as a measure of the "validity" of a study's conclusions. In particular, we caution users of the PEDro scale that studies which show significant treatment effects and which score highly on the PEDro scale do not necessarily provide evidence that the treatment is clinically useful. Additional considerations include whether the treatment effect was big enough to be clinically worthwhile, whether the positive effects of the treatment outweigh its negative effects, and the cost-effectiveness of the treatment. The scale should not be used to compare the "quality" of trials performed in different areas of therapy, primarily because it is not possible to satisfy all scale items in some areas of physiotherapy practice.

Last amended June 21st, 1999