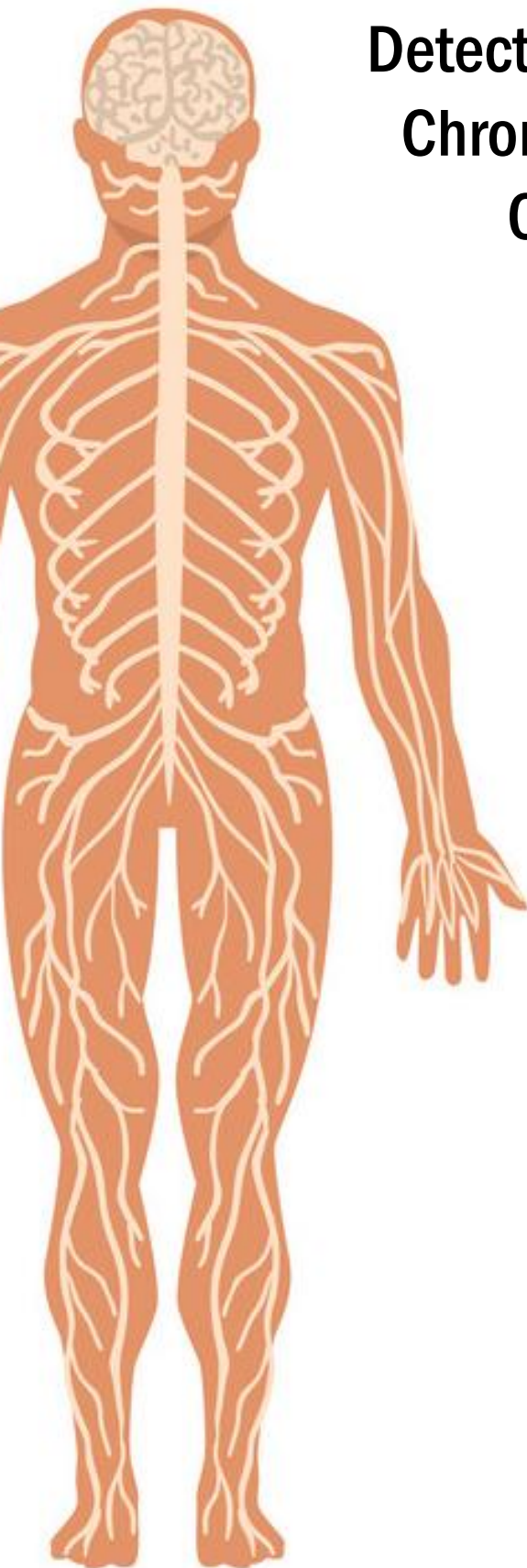


MSc thesis in Technical Medicine

Detection of Central Sensitization in Chronic Pain Patients Visiting the Outpatient Pain Clinic Of St. Antonius Hospital



Lieke Petter
November 2018

**UNIVERSITY
OF TWENTE.**

DETECTION OF CENTRAL SENSITIZATION IN CHRONIC PAIN
PATIENTS VISITING THE OUTPATIENT PAIN CLINIC OF THE
ST. ANTONIUS HOSPITAL

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ABSTRACT

In the Netherlands, 18% of the adults suffer from chronic pain. Chronic pain is not only a burden to the quality of life of the patient, it is also a burden to society due to increased use of medical facilities, and social compensations. The underlying mechanism that is maintaining the pain is thought to be a result of neuroplastic changes in the central nerve system, a phenomenon called central sensitization. In this phenomenon, long-lasting, intense stimuli cause an alteration in the nociceptive pathway, leading to a persistent state of high sensitivity. Detection and monitoring of central sensitization would provide information about the patients nociceptive system that could enable mechanism-based therapy. Unfortunately, appropriate diagnostic tests to monitor patients with signs of central sensitization are not available in current clinical practice.

The aim of this thesis was to set-up a process for the outpatient pain clinic in St. Antonius Hospital for the detection of central sensitization in chronic pain patients with electrical Quantitative Sensory Testing (eQST). This monitoring process was designed, based on current clinical practice in which opportunities for data collection were mapped, existing out of three different phases. The start of the first phase, the validation of the monitoring process was executed by performing an explorative pilot study with eQST in 18 chronic low back pain (CLBP) patients and 79 healthy controls for comparison. The results of the pain thresholds were compared to the scores of the Central Sensitization Inventory (CSI). In addition, expected influencing baseline characteristics were tested.

The preliminary results did not show significant differences in pain threshold for chronic low back patients compared to healthy controls ($t(95)=-0.131$, $p=0.896$). The CSI score did show a significant difference between the two populations ($t(95)=5.395$, $p<0.001$). Regarding of the baseline characteristics, only gender seemed to be an influence related to the pain threshold.

This thesis offers a clinical process aligned with current clinical practice at the outpatient pain clinic to eventually detect and monitor central sensitization. The monitoring process has successfully been implemented at St. Antonius Hospital. So far, no differences between CLBP and healthy controls in pain threshold were seen when using this protocol, however still too few pain patients have been included. Subsequently, it is too early to draw conclusions from these preliminary results. Thereby is recommended to include more patients to evaluate the monitoring process of central sensitization.

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I have really enjoyed working at the department of Anesthesiology at St. Antonius Hospital. My research goal was to set up and perform a clinical study focusing on the monitoring of central sensitization in chronic pain patients. By this project, I had the opportunity to learn much more about pain and the nociceptive system, but also observe the outpatient clinic, and the work flow of the provided health care. This gave me the chance to obtain a different vision towards the organization of the provided health care at the outpatient pain clinic.

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ACRONYMS

ACC	Anterior Cingulate Cortex
AMPA	2-amino-3-(3-hydroxy-5-methyl-isoxazole-4-yl)propanoic acid
BMI	Body Mass Index
BPI	Brief Pain Inventory
CHEP	Conduct Heat Evoked Potential
CLBP	Chronic Low Back Pain
CMAP	Compound Muscle Activation Potential
CNS	Central Nerve System
CRPS	Complex Regional Pain Syndrome
CS	Central Sensitivity
CSI	Central Sensitivity Inventory
DM	Diabetes Mellitus
DNIC	Diffuse Noxious Inhibitory Controls
EMG	Electromyography
EPDT	Electrical Pain Detection Threshold
EPR	Electronic Patient Records
eQST	Electrical Quantitative Sensory Testing
FBSS	Failed Back Surgery Syndrome
GCT	Gate-Control Theory
HC	Healthy Controls
HNP	Hernia Nuclei Pulposi
IASP	International Association for the Study of Pain
IC	Insular Cortex

ICD	Implantable Cardioverter Defibrillator
LBP	Low Back Pain
LEP	Laser Evoked Potential
LTD	Long-Term Depression
LTP	Long-Term Potentiation
MEC	Medical Review Ethics Committee
MPI-DLV	Multidimensional Pain Inventory - Dutch Language Version
NCS	Nerve Conduction Study
NMDA	(N-methyl-D-aspartate)
NRS	Numeric Rating Scale
NS	Nociception-Specific
NSAID	Non-Steroidal Anti-Inflammatory Drugs
PAG	Periaqueductal gray
PIF	Patient Information Form
PM	Pacemaker
POS	Pre-Operative Screening
PP	Pain Patients
RVM	Rostral ventral medulla
SF-36	Short Form Health survey
SG	Substantia Gelatinosa
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
SNRI	serotonin-adrenaline (-epinephrine) reuptake inhibitors
STT	Spino-Thalamic Tract
T	Transmission

TCA	Tricyclic Antidepressants
TENS	Transcutaneous Electrical Nerve Stimulation
TSK	Tampa Scale for Kinesiophobia
QST	Quantitative Sensory Testing
VAS	Visual Analog Scale
WDR	Wide Dynamic Range
WHO	World Health Organization

1 | INTRODUCTION

Over the last decades, chronic pain has become a major healthcare problem for patient and society. A large systematic literature review (with 119 Dutch studies) estimated the prevalence rate of chronic pain in adults to be about 18% in the Netherlands[1]. Among this group of patients, 40% does not receive adequate pain treatment[2]. Contemporary demographic and lifestyle changes lead to the expectation that the number of chronic pain patients will increase even further in the future, resulting in an expansion of the problem around chronic pain [3].

The quality of life of chronic pain patients is seriously affected by pain, since it has a major impact on employment status and daily activities[2]. This is a burden to society and economy, as the use of medical facilities can increase up to five times, and incur social compensation costs and other indirect healthcare costs[4].

The high prevalence and expansion of the problem around chronic pain, emphasize the importance of investigation in developing an adequate manner to prevent or treat chronic pain. However, the underlying mechanisms of chronic pain are still poorly understood and thereby this barrier needs to be conquered. More profound understanding of chronic pain is required to make the development of adequate treatment methods possible.

A major part of the chronic pain population suffers from chronic low back pain (CLBP), which is a highly prevalent health condition and the leading cause of disability worldwide. In Western countries the prevalence of chronic low back pain varies between 12% and 30%[5][6].

Long lasting pain is often defined as chronic pain when it has persisted for three months[7]. The relation between the amount of damage and sensation of pain is not always one-on-one[8]. Moreover, in some cases the pain persists despite removal of the origin of the pain, complicating the determination of the treatment[9][10].

One of the theories that explains chronic pain and why it persists is central sensitization (CS)[11][12]. In CS long-lasting, intense stimuli cause an alteration in the pain signaling pathway in the central nervous system (CNS), leading to a persistent state of high sensitivity. As this process occurs, the peripheral pathophysiology shifts to a central neuroplasticity, resulting in chronic pain. This clinically manifests itself by an increased sense of painful stimuli locally (primary hyperalgesia) and widespread (secondary hyperalgesia), and a painful sense of harmless stimuli (allodynia).

As previously mentioned, major improvement can be achieved in the treatment of chronic pain, since the current adequate treatment numbers are low[2]. However, CS demands a different treatment approach than peripheral injury. In order to set up a patient-tailored treatment, it seems to be necessary to distinguish patients with CS from the group of chronic pain patients. Yet, no simple and fast method is available for testing CS in current practice.

In current practice, pain is mainly monitored using subjective pain scores as the numeric rating scale (NRS) and visual analog scale (VAS)[13][14]. These scores, and thereby the monitoring of the treatment, depend on the self-report of the patient, making the outcome highly subjective. Because of the lack of sufficient, objective measures of pain, pain monitoring of the progress or efficacy of the treatment is difficult. It would be valuable to obtain a more objective method for the evaluation of the effectiveness of the treatment.

A method that is suggested to be more objective to test the presence of CS and to possibly evaluate the treatment could be provided by Quantitative Sensory Testing[15]. With QST the somatosensory function and fluctuations in this function can be tested. As one of the clinical manifestations, widespread hyperalgesia can possibly function as a marker for CS, and can thereby be used to study CS in the chronic pain population [16][17] [18][19][20].

QST has been described as a promising technique to evaluate the patient's pain sensitivity and is suggested to be a good measure for hyperalgesia[15]. Different modalities of QST are known, as mechanical, thermal or vibration. However, most of them are time-consuming and difficult to standardize[21][22]. One of the most easy and fast described QST methods is by electrocutaneous stimulation (eQST). eQST is proposed to be a simple, fast technique for pain monitoring and detection of hyperalgesia to implement in existing clinical practice[23].

Curatolo et al. showed that a high prevalence of widespread hyperalgesia was detected in chronic pain patients compared to pain-free subjects with eQST[23]. They studied pain hypersensitivity and the nociceptive reflex threshold with electrocutaneous stimulation of the sural nerve contralateral to the affected side. The sural nerve is not always a sensory nerve[24], and thereby not the best location to measure the nociceptive reflex threshold. However, with the high prevalence of widespread hyperalgesia, there could still be suggested that this might be a promising technique to detect and monitor CS in chronic pain patients.

Their results have been obtained in a large pain population of a tertiary pain clinic. It would be very interesting to replicate this study in patients visiting the outpatient clinic in the St. Antonius Hospital, and to evaluate whether similar results can be found.

The aim of this thesis was to set up a process to implement eQST measurements in current clinical practice, with the goal of detecting/monitoring CS in chronic pain patients visiting the outpatient clinic the St. Antonius Hospital. Thereby information about the current practices of the outpatient pain clinic was gathered. The long-term goal of this process is to obtain insight in the chronic pain population with respect to hypersensitivity and CS. In this thesis the process was designed, and the first validation of the the process was done with a pilot study.

First, background knowledge obtained from literature that was necessary to set up a clinical process to measure central sensitization is outlined in Chapter 2. The work flow at the outpatient pain clinic in St. Antonius Hospital was analyzed by collecting data from patients visiting the outpatient clinic and by observing the work flow.

With that information, a process was designed, which can be found in Chapter 3. This process was validated with a pilot study suitable for the existing outpatient clinic, Chapter 4.

2 | BACKGROUND

In this chapter, background knowledge essential for understanding the important concepts of this thesis outlined. Information about the mechanisms of pain, central sensitization, and monitoring and treatment of central sensitization is elaborated. In the last section, this information will be combined to form the subject of this research: monitoring CS in chronic pain patients at the outpatient pain clinic in St. Antonius Hospital.

2.1 PAIN

According to the IASP the definition of pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”[25]. The function of pain is essential for the survival and well-being of an organism as it functions as a warning sign for potential tissue damage. Nevertheless, the experience of pain often leads to suffering which is influenced by different factors, as loss of physical function, social isolation, and family distress.

The sensory mechanism allowing organisms to experience pain is nociception. However, one should be aware that nociception and pain are not the same. Pain is the conscious experience, which is in healthy individuals a result of the nociception. Pain is a complex process and the experience is influenced by different factors as the emotional status or duration or extent of the injury. To schematically explain this, pain can be divided into different levels, as is illustrated by Loeser’s model, Figure 2.1[26]. The first level of pain is the nociception. This is the detection of tissue damage by peripheral afferent sensory neurons. The second level is the pain sensation; once the nociceptive signal arrives in the cortical areas, the pain can be observed by the person. On the third level, lies the pain perception which is influenced by e.g. emotions like sadness and fear. And the outer level is the pain behavior; how the person interacts with the world around him.

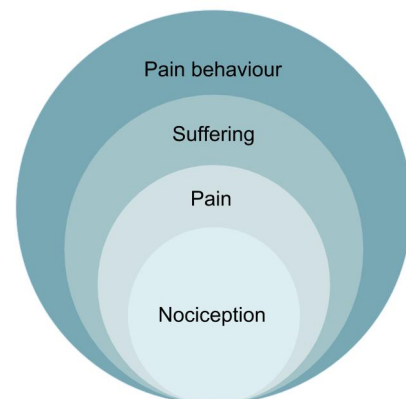


Figure 2.1: Layers of pain defined by Loeser’s modelAdapted from Dingemans et al[26]

Mechanisms of pain

The concept of pain has been a topic of long debate. In Western countries, the first description of pain appeared around the 8th century BC. Yet, since 1800 the concept of pain including involvement of brain activity and nerve fibers is progressively created by experimental sciences. Three main theories are hypothesized about the pain process are the specificity theory, the intensity theory, and the pattern theory. In 1811, Charles Bell introduced the specificity theory. The essence of this theory implies an exclusive pain system with a one-on-one relation between tissue injury and pain sensation: the higher the peripheral stimulus, the more pain is felt. In a healthy nerve system, this theory is more or less applicable. However, for patients in which the damaged tissue has recovered but still feel pain,

this theory can not be correct[27].

The second and the third theory can possibly explain pathophysiologic situations but are not suitable for a healthy nerve system. The second theory suggested is the intensity theory, in which pain occurs when the impulse frequency reaches a certain value. This theory can be applied, for example in neurogenic pain where every (non-noxious) stimulus can be translated into a painful experience. The third, main theory about pain is the pattern theory proposing that pain will arise when stimuli in different nerve fibers fire in a certain pattern. As explained later, wind up and pain inhibition principles could be explained by this theory. Yet still, these theories are helpful for understanding parts of the pain process, but the total process is not fully understood[27].

In 1965 Melzack and Wall introduced a new theory about pain: Gate-control theory[28]. They suggested with this theory that the relation between the perception of pain and the actual damage was not a direct relation. They introduced inhibiting interneurons in the dorsal horn that are activated by earlier painful stimuli, making modulation of pain possible. This theory is nowadays accepted as one of the explanations for modulation.

Pain pathway

The pathway from a noxious stimulus to perceiving pain can be divided into four processes: transduction, transmission, modulation, and perception[29] [30].

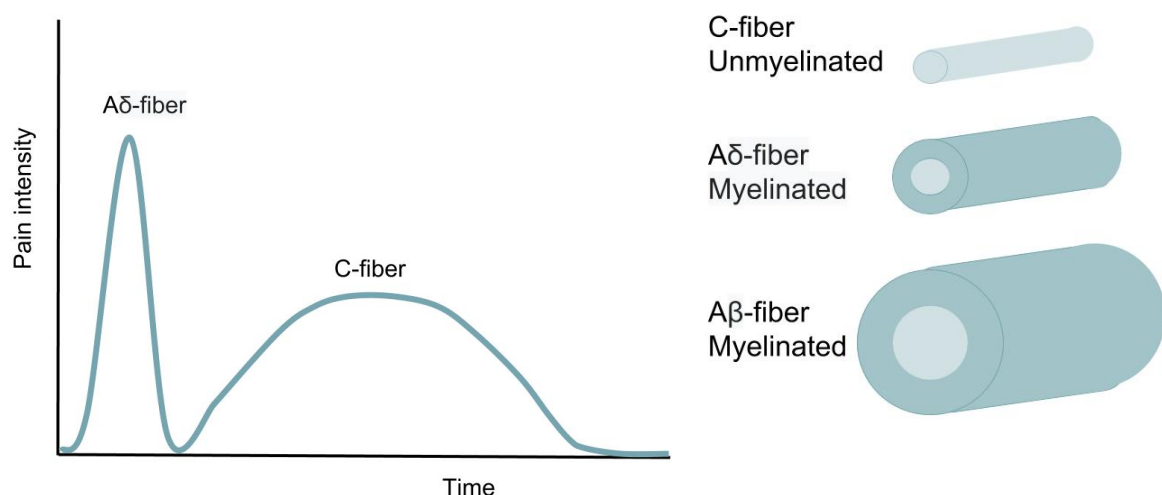
Transduction is the transformation of a noxious stimulus (mechanical, chemical or thermal) into electrical energy by a peripheral nociceptor. Then during transmission, action potentials will be generated and transmitted through the nervous system. Modulation of the signal takes place at different levels of the spinal cord and brain and determines the eventual information reaching the brain. The combined effects of excitatory and inhibitory systems (e.g. the gate control theory) regulate the amount of modulation. Then in the final stage, the neural activity in the somatosensory transmission pathway leads to a perception of pain.

Peripheral afferent neurons can be divided into large myelinated ($A\beta$), small myelinated ($A\delta$) and unmyelinated (C) fibers, as is visualized in Figure 2.2b. With $A\beta$ fibers as the low threshold mechanoreceptive nerve fibers that conduct non-noxious stimuli, these are the thickest fibers with the fastest conduction velocity. $A\beta$ fibers are involved in pain modulation, as described later in this background, by the gate control theory.

$A\delta$ and C fibers transmit both noxious stimuli. Their cell bodies lie in the dorsal root ganglia and project the incoming signals to the spinal cord dorsal horn. $A\delta$ fibers are fast conducting and mechanosensitive, mostly activated by chemical, mechanical, thermal or electrical stimuli. Stimulation of the C fibers works much slower and responds to thermal, mechanical and chemical noxious stimuli (polymodal). C fibers dominate the peripheral afferent fibers, as 75% of the afferent fibers are C fibers [30][31].

As both noxious fiber types have variant conduction velocities, both sensations are different causing a duality of pain[30]. $A\delta$ has the fastest conduction velocity and has the function to make the person aware of the nature of the pain. The second pain arises as a more slow-burning pain sensation with brief intense heat stimulation to the skin that is caused by the C fibers. This second pain is related to the emotional reaction. In most situations, both fiber types are activated, resulting in a combination of the first, sharp pain sensation followed by the second, burning sensation. As shown in figure 2.2a[29].

First order neurons synapse with second-order neurons in the dorsal horn of the spinal cord, where the information is processed and modulated. From the dorsal horn, neurons move through the anterolateral tract of the spinal cord. $A\delta$ and C fibers predominantly terminate in the superficial laminae of the dorsal horn: lamina I (marginal nucleus) and II (substantia gelatinosa), but also in lamina V[32]. Second-order neurons receive input from the primary afferent fibers and process this nociceptive information. Two predominant second-order neurons have been identified: wide dynamic range (WDR)



(a) Duality of pain intensity caused by the different function and conduction velocity of the A δ and C fibers.

Adapted from Ringkamp et al.[29]

(b) Difference in fiber thickness and myelination, causing the different function in pain.

Figure 2.2: Primary afferent nerve fibers thank their difference in function to their difference in thickness and myelination.

neurons and nociceptive-specific (NS) neurons[33]. WDR neurons are mostly found in lamina III-V and receive input from all primary afferent fibers. An important characteristic of these neurons is that they have the capacity to code the intensity of the stimulus and mostly induce a higher response to noxious stimuli. NS neurons lie in the superficial lamina I and II and only respond to noxious stimuli [33].

After interaction with the projection of the neurons in the dorsal horn, the axons of the second order neurons are activated. These neurons project to supraspinal sites in the brainstem, midbrain, and diencephalon, where they end in the hypothalamus and different regions of the thalamus. The axons of the tract cells cross over to the other side of the spinal cord and travel upwards from there to the thalamus where the neurons synapse with third-order neurons[34].

The three major pathways of nociceptive information are spinothalamic, spinoparabrachial and spinoreticular tracts. Most of the nociceptive fibers in the dorsal horn lie contralateral in the spinothalamic tract (STT). The majority of the C-fibers transmit their action potentials through the spinoreticular tract and trigeminal pathways[34].

Dorsal horn nociception can be regulated by local inhibitory interneurons and descending inhibitory pathways in the brainstem. Neurons in the thalamus relay the ascending inputs to several cortical areas. From there, signals are sent to the cingulate cortex (ACC), insular cortex (IC), primary somatosensory cortex (SI) and secondary somatosensory cortex (SII).

Pain perception is the final stage of the process by which the neural activity in the somatosensory transmission pathway results in a subjective sensation of pain [29]. The ACC is the most important region for pain perception. Activation of the amygdala and ACC contribute to pain-related fear memory and pain modulation [34][30]. This perception depends on the summation of incoming signals to the brain, of the nociceptive receptor (primary afferent) and psychophysical (cortical level)[35].

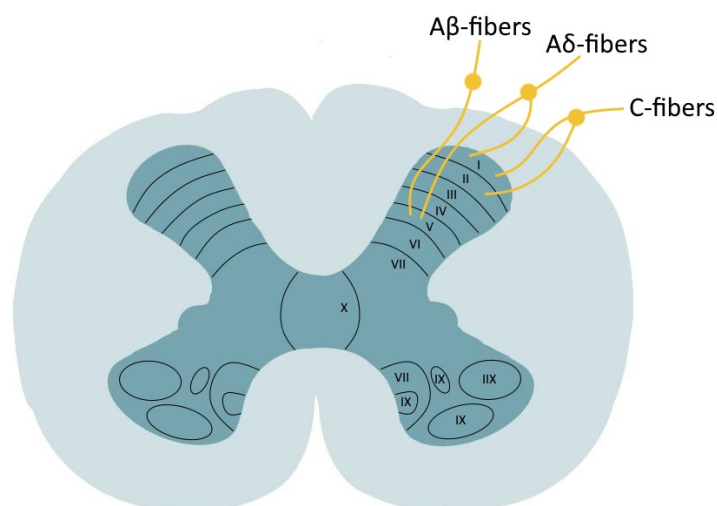


Figure 2.3: Laminae of Rexed. Primary afferent nerve fibers entering the dorsal horn of the spinal cord. Noxious stimuli are mostly processed in the superficial laminae, whereas non-noxious stimuli enter deeper in the dorsal horn. *Adapted from Todd et al. [33]*

2.1.1 Modulation of pain

Pain facilitatory and inhibitory systems are believed to work together in harmony to adjust the pain signal. There are some processes suggested to make modulation of the signal possible.

There is suggested that somewhere in the CNS there is a circuit making modulation of pain possible. One of those circuits in pain modulation is the gate control theory[36].

The schematic representation of this theory can be found in Figure 2.4. The theory proposes that at the first synaptic relay, between primary afferents and transmission (T) cells in lamina II (substantia gelatinosa (SG)) of the spinal dorsal horn the signal is "gated". This gating is mediated by small and large nerve fibers. Neuronal activity via A β fibers will activate inhibitory SG interneurons, which reduce activity from small (A δ and C) nociceptive fibers, causing inhibition of the signal. Activity from small fibers deactivate the inhibitory SG interneurons, which stimulates pain. This is modulated by central control of descending or segmental origin[36].

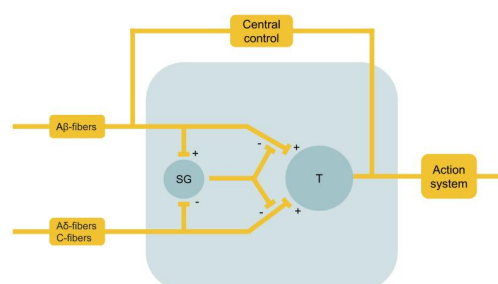


Figure 2.4: Gate control theory making modulation of the pain signal possible. *Adapted from Chen et al. [36]*

Currently, this theory is fundamental for how experts look at pain, with in addition the more recent hypothesis that pain is also modulated through the interaction of certain cortical areas[37][38]. But also for modulation via the descending pathway is growing evidence[39]. This descending modulation involves several brain sites and pathways. Axons of nociceptive spinal neurons terminate in the brain stem where they activate serotonergic, catecholaminergic and GABAergic neurons. These neurons send axons down to the dorsal horn on their turn, providing modulation of the signal[40]. Broadly, three different descending pathways can be defined. The best known pathway is the circuit from the midbrain periaqueductal gray (PAG), rostral ventral medulla (RVM) and spinal cord (PAG-RVM). This system contains nerve endings projecting ON or OFF cells to the dorsal horn. The second system is diffuse noxious inhibitory controls (DNIC), and consists out of the spinal-medullar-spinal route. When the nociceptive nerve endings are stimulated, DNIC can be activated. From the subnucleus reticularis dorsalis the pain signal in the WDR is modulated, resulting in a

generalized inhibition of the pain sensitivity and higher pain threshold. [41] [42]

Another system affects the cognitive and affective factors on the pain sensitivity, this is the case in e.g. the placebo-effect. Higher structures as the prefrontal cortex, cingulate cortex, amygdala and hypothalamus connect with the PAG-RVM system, influencing this modulation system.[41]

2.1.2 Peripheral sensitization

In the excretion of mediators released by tissue injury, prostaglandin products of arachidonic acid metabolism, bradykinin, cytokines, serotonin, and growth factors are present. As a result, the nociceptor threshold is decreased and the responses to suprathreshold stimuli are increased, causing primary hyperalgesia. This peripheral sensitization is a process that contributes to the increased pain from the site of injury and has the function of protecting the tissue for more damage and giving it time to recover.

The increased expression of voltage-gated sodium channels and decreased depression of potassium channels contribute to peripheral sensitization. In hyperalgesia, ion channels of the receptors get activated, causing generation of a brief potential by sodium channels. Activation of neighboring sodium channels triggers an action potential to transfer the nociceptive information into the CNS. Via potassium channels, the signal can be modulated by inhibition.

Activation of nociceptors by the nociceptive input is reversible. With noxious stimuli, postsynaptic glutamate is released binding to AMPA- (2-amino-3-(3-hydroxy-5-methyl-isoxazole-4-yl) propanoic acid) and NMDA- (N-methyl-D-aspartate) receptors. As glutamate binds to these receptors, Na⁺ and Ca²⁺ can flow into the cell, mediating fast synaptic transmission. After stimulation of the nociceptors, secondary neurons in the dorsal horn will be sensitized. Glutamate and substance P cause activation of NMDA receptors in the cell membrane leading to phosphorylation[12].

2.1.3 Central sensitization as a physiological process

The definitions of "central sensitization" that are used in literature are not always entirely compatible. The proposed definition by the IASP describes "central sensitization" as the "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input"[25]. However in some forms it means a disproportionate experience of pain unrelated to the injury. Physiologic mechanisms that lead to an increased responsiveness in the CNS are thereby called by their more specific terms in this thesis. Examples of physiologic mechanisms leading to hyperexcitability are long-term potentiation (LTP) and windup[43][44].

Windup is a physiological aspect of the conductance of dorsal horn neurons and is temporal. The phenomenon occurs after repeated stimulation of C fibers. As C fibers have a relatively slow potential that lasts up to 20 seconds, repeated stimulation with a low frequency causes a temporal summation, resulting in a cumulative depolarization. This results in a progressive increase in response of the dorsal horn neurons, leading to an increase in pain[43].

LTP is an activity-dependent process and has the association with learning and memory of the neuronal network. In nociceptive pathways, increased synaptic activity, may lead to LTP. Amplification of the transition from afferent C fibers to secondary neurons occurs during LTP[44].

Early phase LTP will last up to three hours. In late phase LTP, calmodulin-dependent protein kinase II (CaMKII) stimulates the production of protein to keep AMPA-receptors in their place. This late phase can exist for 24hr till lifetime[43].

Long-term depression (LTD) is also possible in nociceptive pathways, meaning that synaptic strength is decreased for a period after conditioning stimulation.

Windup is not a form of neuroplastic change or hyperalgesia, however neuroplastic changes, like LTP can change the properties of wind-up by amplifying the effect[43]. Windup phenomenon and LPT are physiological changes and reversible. Both mechanisms are thought to be homosynaptic, but there is some uncertainty for LTP, for which some indications might lead to heterosynaptic changes[43]. However, in some cases hypersensitivity persists despite the fact that the stimulus is removed, indicating that there is an additional process causing the hypersensitivity.

2.1.4 Central sensitization as a pathophysiological process

With long-lasting pain, modulation carries through and transforms into modification. This means that a new neural connection in dorsal ganglion root is created, and thereby the neuronal structure is changed[8].

One theory that might explain this ongoing pain and increased sensitivity is the pathophysiologic version of central sensitization: chronic pain can be the result of an ongoing pathology, but can also become autonomous and independent of the trigger that initiated the pain in the first place[45]. In this case, the neuroplastic changes in the nervous system have become the pathology.

Central sensitization differs from the windup and LTP phenomenon in the fact that more factors influence sensitization than the increased excitability[46]. The dominant form in persistent neuroplasticity contributing to central sensitization appears to be heterosynaptic potentiation: activity in one pair of synapses activates non-activated synapses, leading to allodynia and spreading hyperalgesia (secondary hyperalgesia) [47].

More detailed, central sensitization refers to an increase of excitability of spinal neurons, partly caused by activation of NMDA receptors in the dorsal horn. Neurotransmitters are able to activate intracellular signal routes, leading to an increase of the excitability of different nerve fibers of the neurons in the dorsal horn. As a result, the receptive field size of these neurons expands and their spontaneous activity increases. In addition, also A β fibers are activated, so the sensation of pain can be initiated by harmless stimuli[30]. After nerve injury, it appears that pre-existing polysynaptic pathways from deep laminae to laminae I and II are disinhibited and A β fibers are thought to sprout into laminae I and II, where they make synaptic contact with the nociceptive specific neurons (A δ and C), both mechanisms causing A β fiber mediated pain; allodynia[43].

But also in cortical areas, neuroplastic changes occur, so additional symptoms as insomnia, tiredness and cognitive problems are known as well as signs for CS.

These changes lead to primary (local) and secondary (widespread) hyperalgesia, and allodynia[48].

2.1.5 Chronic low back pain

As mentioned in the introduction, a major part of the chronic pain population consists of chronic low back pain patients. Chronic low back pain (CLBP) is a highly prevalent health condition and the leading cause of disability worldwide[5]. Low back pain is not a disease, it is a symptom and may arise from different anatomical structures, like bones, intervertebral discs, joints, ligaments, muscles, neural structures, and blood vessels. Some examples of common spinal mechanical syndromes that cause low back pain are musculoligamentous strain or sprain, herniated disc or foraminal stenosis. Nevertheless, in CLBP the etiology is unknown or nonspecific, which has a prevalence of approximately 23%[49]. This sort of pain is defined by the IASP as nociplastic pain: "Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain".

For low back pain syndromes, the most common tests are imaging, as plain lumbar radiography or MRI, to reveal abnormal findings or to determine the site of surgical or minimal invasive intervention of LBP. However, the nerve function cannot be determined with imaging studies[50][51].

When properly applied, electrophysiologic testing could be a useful tool to measure pain and the effect of mechanical LBP. Options as electromyography (EMG), nerve conduction studies (NCS) and compound muscle action potential (CMAP) can be very useful for evaluation of the peripheral nervous system. Also, laser-evoked potentials (LEPs) or contact heat evoked potentials (CHEPs). They all have their advantages and disadvantages[50]. With these techniques, it is still not possible to measure the nociplastic pain or CS.

A systematic review showed that patients with chronic low back pain show differences in specific cortical and subcortical areas, and altered connectivity to noxious stimuli, suggested an altered pain system, CS [52]. And other studies recognized central sensitization as a potential pathophysiological mechanism that may contribute to the development and maintaining of chronic low back pain[17][18][19][20]. With CLBP increase in sleep disturbance, fatigue and widespread pain seem to appear, which are also signs of CS[16]. The examination of generalized or widespread hyperalgesia is commonly used to detect central sensitization. It is shown that spreading hyperalgesia can possibly be measured on the contralateral side to the affected side[53]. However, also hypoexcitability is seen [41].

The methods for treatment of low back pain, are initially mostly conservative since the pain disappears by itself in many individuals. It is mainly focused to decrease pain by its mechanical cause. However, since many individuals do not have an identifiable mechanical cause, it would be advantageous to know whether central sensitization has occurred. In that case the presence of CS would imply that the brain causes pain, fatigue, and other warning signs. So a more central treatment approach could be tried; the brain would be an important target [54].

2.2 MONITORING OF CENTRAL SENSITIZATION

Pain is time dependent and relative per individual, and thereby difficult to measure objectively. Adequate measurement of pain requires valid and reliable tools and the ability to communicate with the patient. This perception can vary between individuals, and moreover within an individual where, for example, stress or fear can alter the perception of pain[55].

Even more complicated is the measurement of central sensitization. Since pain exists out of different levels, it is not possible to monitor central sensitization or the nociceptive function with just the pain experience, thereby no “golden” standard is available for measuring central sensitization.

Some methods have been developed to get more insight in pain and CS. Widely used tests to score the pain, are visual analog scales (VAS) and numerical rating scales (NRS). Both of these pain scores have been shown valid and are used among many populations[13][14]. The pain rating score is supposed to reflect the intensity of the patient’s physical (sensory) pain. However, it has been shown that the score is not only influenced by the somatosensory process of pain but also affected by cognitive and emotional processes[30].

To properly use these scales, patients should be capable of accurately score their pain without being confused about the interpretation. To overcome this, the Brief Pain Inventory (BPI) was developed, which measures both the intensity of the pain and interference of the pain in the patient’s [30]. These are the most frequent used tests to identify pain, but are both very subjective.

It would be useful to obtain numeric, objective values for assessment of pain and central sensitization. Since the researchers are looking for an easily implementable measurement tool to use in the consulting room, an interesting method would be quantitative sensory testing (QST). With QST signs of change in somatosensory function can be examined, by studying the relation between physical stimuli and perception. QST is widely used to investigate peripheral and central sensitization in chronic pain states [56], and offers numeric results[57]. Since the measurements rely on patient self-

report, the cooperation of the patient is required and the outcome is not fully objective. However, this psychophysical method has been shown to improve the diagnostic accuracy in peripheral neuropathy and chronic pain (BRON).

Although different modalities of QST are known, as mechanical, thermal or vibration, some of them are not implementable in current practice since they are time-consuming and difficult to standardize [21][22]. The best known modality to stimulate nociceptive nerve fibers, is heat stimulation using a CO₂ laser. It achieves specific A δ fiber stimulation. However, peripheral sensitization and heat build-up make the inter-stimulus interval relatively long; one stimulus per 5 to 20 seconds, making the measurements unworkable long [58].

QST by determination of the electrical pain detection threshold (EPDT) with electrocutaneous stimulation is an upcoming method. With electrostimulation, a shorter inter-stimulus interval can be used, leading to a good control of timing. A shortcoming of electrical cutaneous stimulation could be the co-activation of A β -fibers. Nevertheless, results of some trials pointed out that the electrical pain detection threshold has a predictive value for chronic pain and a discriminative value for healthy subjects. These values were only measured in laboratory setup and still need to find its' place in the clinical practice [23][41][59][60].

Although there is evidence that QST might be helpful to distinguish CS from nociplastic pain, more knowledge is necessary about the development of CS and QST measurements. Shorter QST protocols should be developed, in order to add the diagnostic tool in current practice [61].

Another method to diagnose CS that was been found over the last years was described by Nijs et al. They suggested an opinion-based-algorithm with three criteria to identify central sensitization in patients with pain [62]; (1) The patient has a disproportionate pain experience, meaning that the severity and related reported or perceived disability are disproportionate to the injury. (2) The patient shows a diffuse pain distribution, allodynia, and hyperalgesia. (3) There are signs of hypersensitivity of senses unrelated to the musculoskeletal system.

For this last criteria, the signs can be evaluated with the Central Sensitization Inventory (CSI). In this CSI pain-related, psychosocial, cognitive and functional items are questioned. In addition, eight different central sensitivity syndromes (CSS) are asked and two central sensitization related disorders [63]. This questionnaire is validated in Dutch in different chronic pain populations vs healthy subjects [64]. No tests have been found for CSI testing on other study populations.

2.3 PAIN TREATMENT

The aim of pain treatment is to decrease the pain sensation to a tolerable level. Unfortunately, the knowledge about the pathogenesis of chronic pain is still partly speculative, so it is difficult to predict the clinical effectiveness of the medication per individual. This can lead to long trials of different therapy methods, while testing the side effects in absence of efficacy [65]. Pain medication can influence different processes present in the pain pathway from afferent peripheral fibers to perception in the brain. For instance, the first step in the pain process, transduction, can be best inhibited by NSAIDs, opioids and local anesthetics. In 1986 World Health Organization presented the analgesic ladder as a framework to reach adequate pain relief (WHO-ladder) [66]. This is a three-step ladder, in which at every step is evaluated whether adequate pain relief is reached. In case of inadequate pain relief, the next step should be considered. This is done in the order of non-opioids, mild opioids, strong opioids, see Figure 2.5.

The WHO-ladder was initially developed for chronic cancer-pain, however the approach is widely used in chronic

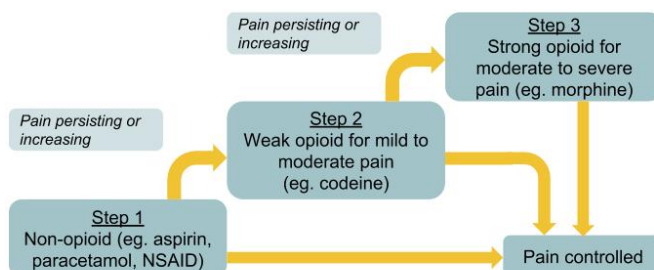


Figure 2.5: Representation of the WHO-ladder by which incrementally pain medication can be prescribed. Adapted from [66]

non-cancer-pain. The WHO-ladder sets the first base of recommendations for pain relief in chronic pain and steps after these propose more invasive techniques or other pharmacologics[67][66].

The first step in the WHO-ladder contains NSAIDs and paracetamol. NSAIDs is a varied group of compounds analgesic that has an antipyretic and anti-inflammatory working. [68] Paracetamol is almost universally accepted as routine treatment in acute and chronic pain since it has minor side effects, is cheap and available in oral, intravenous and rectal administrations. It is an analgesic and antipyretic medication that inhibits central prostaglandin synthesis with minimal inhibition.

The following steps in the ladder are first weak and then strong opioids. Patients with moderate to severe acute and/or chronic pain and still in pain after non-opioid administration are potential candidates for a therapy with opioids. Opioids have an agonistic effect on μ -receptors on the cell membranes in the dorsal horn, causing an inhibition of the ascending pathway and a stimulation of the descending pathway of the CNS.

Only a small group of patients with chronic pain do benefit from opioids. Commonly used oral preparations are codeine, tramadol, morphine, oxycodone, tapentadol and transdermal patches with buprenorphine and fentanyl [69].

2.3.1 Pain treatment of chronic low back pain

The current first- and second-line recommendations in Europe for CLBP are (in combination with the WHO-ladder) paracetamol, NSAIDs, COX2 inhibitors, muscle relaxants and tramadol. Third line options are opioids, antidepressants, anticonvulsants[70].

The evidence for the use of paracetamol in chronic back pain is limited with only small and inconclusive data available[71][68]. NSAIDs and muscle relaxants have been shown to be effective for symptom relief, while opioids have been shown to not improve activity levels and had more side effects than NSAIDs[72].

Transcutaneous electrical nerve stimulation (TENS) is widely used in treatment of different types of acute and chronic pain conditions. Health care professionals use it often as a firstline treatment, however the effectiveness of TENS is still questionable[73][74].

As an addition to the pharmacological treatment, intensive exercise and physiotherapy has shown to reduce pain and improve function in chronic low back pain[75][76].

Since there is no objective way to monitor the origin of the pain and the effectiveness of the treatment a major group of patients goes through long phases of trial and error with different pharmacology's and their belonging side effects[2].

2.3.2 Pain treatment of central sensitization

The upcoming method for treatment of central sensitization is to start with good education of explaining the neuroscientific mechanism behind CS. This method has been proven effective in some chronic pain disorders[77][75]. It would give patients a chance to understand the mystery around their pain and the need for a more time-consuming approach[78].

As pharmacological treatment central sensitization it is preferred to use anticonvulsants, tricyclic antidepressants, weak opioids and opioids, because of their central working principle[62]. Contradicting results arise concerning pharmacotherapy targeting CS, however one must notice that most of these studies are done in animals. Very little is known about the treatment strategy of CS in human subjects[62].

Opioids are frequently used analgesics, for example tramadol would be useful in CS [30] [79]. However, one of the most feared side effects that has recently shown to have bigger impact than initially thought is addiction[80]. So cautious prescription of opioids is necessary.

Anticonvulsants as gabapentin and pregabalin are commonly used as calcium channel blockers. The analgesic effect of anticonvulsants is thanks to the inhibition of voltage-gated calcium channels. Anticonvulsants as gabapentin and pregabalin are commonly used as calcium channel blockers. The main common side effects are dizziness, sedation, lightheadedness, somnolence, and weight gain [81]. Pregabalin and gabapentin show some mixed outcomes in clinical effectiveness[82]. Microgabalin is a new promising calcium channel blocker. A more specific target, causes fewer side effects, so a higher dose can be provided which can lead to improved efficacy. A significant reduction was shown in a study with diabetic neuropathy, where pregabalin was shown not effective[30].

Antidepressants up-regulate the noradrenergic and serotonergic systems and thereby affect the thalamic burst firing activity. Tricyclic antidepressants (TCA), like amitriptyline or nortriptyline, are commonly used in post-herpetic neuralgia, painful diabetic neuropathy, and fibromyalgia. Some studies showed that nortriptyline has similar analgesic effects with fewer side effects[83].

Also serotonin-adrenaline (-epinephrine) reuptake inhibitors (SNRI) have analgesic effects and are used in chronic pain. However, comparing studies found that TCA are more in favor to use in chronic pain than SNRI[83]. Duloxetine is one of the SNRI's used for some chronic pain and shown effective[84].

2.4 OUTPATIENT PAIN CLINIC ST. ANTONIUS HOSPITAL

St. Antonius Hospital is one of Netherlands' major pain centers with approximately 2000 new pain patients annually. The outpatient pain clinic is situated in Nieuwegein and Leidsche Rijn and is instituted in the St. Antonius Hospital. Physicians at the outpatient pain clinic provide pain treatment to patients suffering from difficult pain disorders and cancer-related pain. The outpatient clinic is visited by patients with different pain syndromes, such as fibromyalgia, complex regional pain syndrome (CRPS), facial pain, and low back pain. These patients are referred by general practitioners or specialists like neurologists or orthopaedics, when standard care, as the WHO-ladder, cannot provide adequate pain relief.

The mission of the outpatient pain clinic in St. Antonius Hospital is to reach maximal pain relief in all of their patients. Meaning that a patient-tailored treatment is desirable for every patient. Thereby in the most ideal situation, mechanism-based therapy is given to the patient.

Treatment is thereby determined by an intake and a pain questionnaire. Most patients visit the outpatient clinic only for intake, and only reappear if the treatment is inadequate. Thereby follow-up of some patients after treatment is lacking, since not all patients are easy to follow when therapy is going well.

Contemporary, the outpatient clinic comprises eight consultant anesthesiologists with advanced training in acute and chronic invasive pain management, one resident, pain nurse practitioners and doctor's assistants. St. Antonius Hospital has outpatient pain clinics at two locations: Nieuwegein and Leidsche Rijn (Utrecht). Two specialists are present at both locations with two to four outpatient clinic employees.

The outpatient pain clinic is part of the department of Anesthesiology. Under this department a lot of research is executed, and also at the outpatient pain clinic several studies are currently performed. More explicit, some studies in for example hernia nuclei pulposi (HNP), failed back surgery syndrome (FBSS), and complex regional pain syndrome have been executed with eQST.

2.5 CLINICAL IMPLICATIONS

With a prevalence rate of 18% in the Netherlands[1] and an inadequate treatment in 40% of the cases[2], chronic pain has become a major health care problem. Even though knowledge about the nociceptive system and pain is expanding, still no satisfactory explanation is found of the persistence of chronic pain. This lack of knowledge complicates diagnosis and treatment of chronic pain. Currently it is believed that the phenomenon central sensitization plays a role in maintaining chronic pain[11]. Awareness of the presence of CS would enable mechanism-based pain therapy with analgesics engaging the CNS instead of the peripheral injury. However, factors causing or related to CS are still uncertain.

Available measurement options of pain, (e.g. the NRS, VAS, and BPI) are limited and interpretation of the pain rating scores are difficult. The different levels at which pain can be observed and the cognitive and emotional processes complicate the results from these measurement methods[30].

The aim of this thesis was to set up a process to monitor the prevalence of CS among the chronic pain patients visiting the outpatient pain clinic in St. Antonius Hospital. A measurement technique proposed in this thesis for monitoring of CS is eQST

With the decreased inhibitory modulation, hyperexcitability of peripheral afferents, heterosynaptic potentiation and changes in cortical areas occurring in CS, there can clinically be reasoned that widespread hyperalgesia can function as a biomarker of CS[46][47][48]. The body side chosen to perform eQST measurements should thereby be distant from the affected body side to prevent measurement of peripheral sensitization.

The secondary aim of this work was to validate and evaluate this process by including the first patients of a chronic pain population and obtaining a reference value of the electrical pain threshold in healthy controls. One of the chronic pain populations in which widespread hyperalgesia is frequently shown is chronic low back pain[17] [18][19][20]. And since it is a more or less homogeneous group of chronic pain patients with a high prevalence, CLBP patient population can function as an acceptable population to validate the process with.

One of the recently validated methods for detection CS in chronic pain patients is the Central sensitization Inventory[62]. It measures the signs of senses that are unrelated to the musculoskeletal system, but expected to be increased by CS as well. This method is subjective and relies completely on the patients' self-report, but has shown to be valid[62][64][63]. Thereby this test could function as an extra validation of the outcomes of the eQST measurements.

The hypothesis stated is that CS in chronic pain patients can be detected by measuring widespread hyperalgesia determining the electrical pain detection threshold. It is expected that determination of the electronic pain detection threshold in CLBP will give lower pain thresholds, because of the widespread hyperalgesia. In addition, these results are expected to correlate to the CSI scores. Since the outpatient pain clinic in St. Antonius is a major clinic where already studies have been performed with eQST, this seems to be the location of choice to implement such a process.

The aim of this work is to design a clinical process with which the work of Curatolo et al. could be replicated at the outpatient pain clinic in St. Antonius Hospital[23]. To set up such a major research, it is necessary to align the study perfectly with the current workflow at the outpatient pain clinic. Thereby it was necessary to study and map the current workflow at the outpatient clinic and determine data sources and people involved. To evaluate eventually the possibilities to obtain more insight in the pain population visiting the outpatient pain clinic. A short and simple protocol, that is aligned with current clinical practice, was set up in order to enroll a large patient population in the study. This study should provide more insight in the patient population visiting the outpatient clinic

regarding their widespread hyperalgesia, related patient characteristics and their CSI-score. The end-goal of this monitoring process is to be able to distinguish patients who show signs of CS.

This monitoring process was set up and was started with an explorative pilot study, necessary to evaluate the implementation and the information gathered. The aim of this pilot study was to evaluate whether differences in chronic pain patient compared to healthy subjects could be obtained with this method and whether baseline characteristics appeared to be of influence.

In chapter 3, the design of the process to have an ongoing enrollment of patients in the study in St. Antonius Hospital. The first step in this process, a pilot study, was started in Chapter 4.

3 | DESIGN OF A PROCESS TO MONITOR CENTRAL SENSITIZATION

3.1 INTRODUCTION

In the background chapter, it was proposed that it is desired to monitor central sensitization in chronic pain patients. In this chapter a clinical process to monitor central sensitization is designed, based on current clinical practice at the outpatient pain clinic in St. Antonius Hospital. The monitoring process that was introduced in this chapter is evaluated.

In order to set up such a major study, enrollment of the patients in the study should become part of the current clinical process with as little effort as necessary.

Criteria for a good and efficient designed process can be described as[85]:

- (1) Be of value to someone/something outside the process,
- (2) Create value to the organization, and
- (3) Align with the organization.

The value for patient and organization is the main goal for this project and is described under “Goal and objectives”. Further in this chapter, the currently existing clinical process, workflow, and currently available information sources are described. These are necessary to identify in order to align with the current practice. Thereafter, requirements and efforts necessary were formulated to set up the study.

3.2 GOALS AND OBJECTIVES OF THE MONITORING PROCESS

The objective of monitoring patients with eQST measurements is to eventually be able to distinguish patients who show central sensitization from chronic pain patients in such a way that treatment can be adjusted to that specific patient. The method to make this distinction should be a fast and easy diagnostic tool to use in the consulting room and should be effortlessly aligned with current clinical practice.

At the end of the project, a database filled with information of chronic pain patient characteristics, eQST values and signs of central sensitization should exist, from which can be derived what factors correlate/may be a marker/give a higher chance to CS. Factors correlated with an increased chance in developing CS could then be highlighted.

3.3 OVERVIEW OF THE OUTPATIENT PAIN CLINIC ST ANTONIUS HOSPITAL

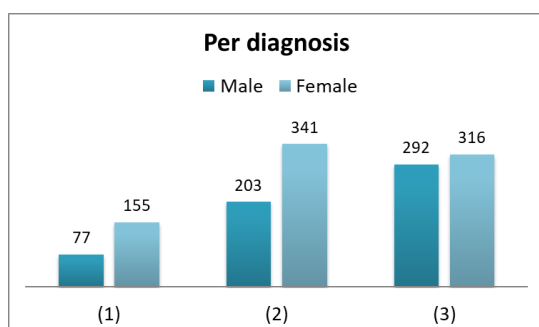
St. Antonius Hospital is one of Netherlands’ major pain centers with approximately 2000 new pain patients annually. The outpatient pain clinic is situated in Nieuwegein and Leidsche Rijn and is instituted in the St Antonius Hospital. Physicians at the outpatient pain clinic provide pain treatment to patients suffering from difficult pain disorders and cancer-related pain. The outpatient clinic is visited by patients with different pain syndromes, such as fibromyalgia, complex regional pain syn-

drome (CRPS), facial pain, and low back pain.

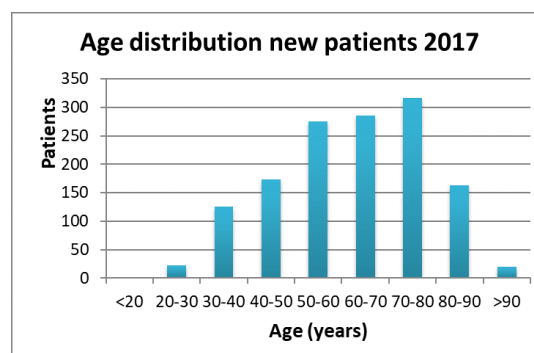
Among the newly diagnosed pain patients a major group of low back pain patients is seen. The mechanical low back pain disorders are mainly included in the following three diagnoses:

- (1) Mechanical/discogenic low back pain
- (2) Chronic neurogenic low back pain
- (3) (sub) acute neurogenic low back pain

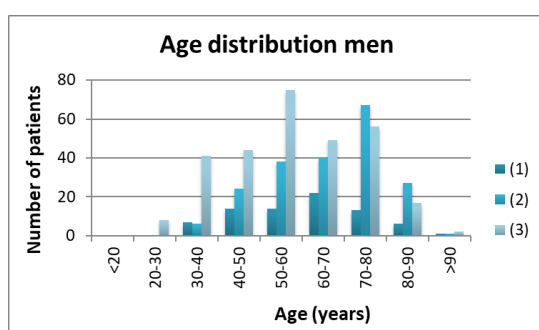
Divided over these three diagnoses, 1384 newly diagnosed pain patients were seen in 2017 by one of the pain physicians in Nieuwegein and Leidsche Rijn. The largest group was “(sub)acute neurogenic low back pain” (608 patients), followed by “chronic neurogenic low back pain” (544 patients) and “mechanical/discogenic” low back pain (232 patients). With 712 women newly visiting and 572 men, the men:women-ratio was approximately 4:5 in the newly diagnosed low back pain. The mean age of these patients was 61 years old, with a spread from 23 to 93 years old (displayed in Figure 3.1b).



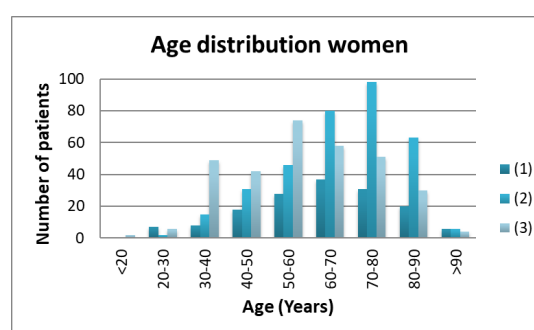
(a) Male and female per diagnosis



(b) Age distribution over all patients



(c) Age distribution divided over the diagnoses for men



(d) Age distribution divided over the diagnoses for women

3.3.1 Patient flow

Only patients that follow a physician's referral are accepted to the outpatient pain clinic (i.e. by general practitioners, orthopedics, neurologists, and geriatrists). A schematical representation of the patient flow in the outpatient pain clinic is given in figure 3.2. Once referred, the patient contacts the outpatient clinic to make an appointment. The secretariat will register the patient and schedules an appointment with one of the pain physicians. Following this phone call a pain questionnaire, designed for all new visiting pain patients, is send to the patient by mail. This questionnaire functions as a standardized self-report assessment battery, in which different factors (e.g. amount of pain, limitations, mood and environment) that might influence the pain experience of the patient are measured. These factors may influence the pain and are thereby important to know in advance of determining

the treatment. Patients complete this pain questionnaire at home prior to the visit and bring this with them on the day of the visit.

The first appointment at the outpatient clinic is the intake with the pain physician which will take 20 minutes. The pain physician reviews the patient's chart, assesses the patient (both in person and through the questionnaire), and sets up a treatment plan tailored to the patient's needs. This plan may include medication, TENS or referral to a physiotherapist. The main goal of this pain therapy is to reduce the patient's pain and distress. Adequate explanation about the treatment and side effects is necessary to give the patient guidance in their expectation of the possible results from the treatment. Currently, no (minimally) invasive methods are used for CLBP patients. When chosen for analgesics, follow up by pain physician is done via a phone call after three to six weeks. In this call is decided in consultation with the patient, whether analgesic medication or therapy needs to be optimized. In case a treatment with TENS is tried, the patient will be registered and the TENS device will be sent to the home address of the patient. An appointment is scheduled with a TENS nurse for adjustment of the settings, where after the patient will continue the treatment until no longer satisfied.

3.3.2 The role of the team members

As can be found in the flowchart, Figure 3.2, different employees are involved in the patient flow. First the secretariat answers the phone call and schedules an appointment, where after they send the pain questionnaire six weeks before the appointment if possible. When the patient arrives at the outpatient clinic on the day of the visit, the secretariat announces the patient in Epic while the patient takes place in the waiting room.

The consult with the physician or resident will take 20 minutes, in which a complete description of the patient's complaint of the patients is tried to understood. Afterwards the treatment plan is decided and confirmed with the patient. When there is chosen for TENS, the patient will get an appointment with the pain nurse practitioner and follow up is done with them. In the case medication is tried, follow up will be with the pain physician.

3.3.3 Data sources

Patient information is gathered at different moments in the patient flow. In the pain questionnaire, questions are asked about the pain and experience of this pain. The questionnaire is specifically set up to evaluate the factors that may influence the treatment negatively. The questions are a mix of the Short Form Health survey (SF-36)[86], the Tampa Scale for Kinesiophobia (TSK)[87], the Multidimensional Pain inventory - Dutch Language Version (MPI-DLV) (environmental factors)[88], the Pain Catastrophizing Scale (catastrophize)[89], Hospital Anxiety Depression Scales (fear and depression)[90], and different VAS-scores.

During the consult additional information about the nature, history, and duration of the pain is obtained and reported in the electronic patient records (EPR).

The follow-up provides information about the success of the treatment.

3.3.4 Location

In current practice, the patient only visits the outpatient clinic for intake, and at request of the patient. The questionnaire is answered from home and follow-up after analgesic medication is done by a phone call. When TENS is chosen, the patient will visit the outpatient pain clinic once for installing and checking the settings of the device. Only when the patient is no longer satisfied with the pain relieve, the patients visit the outpatient clinic again.

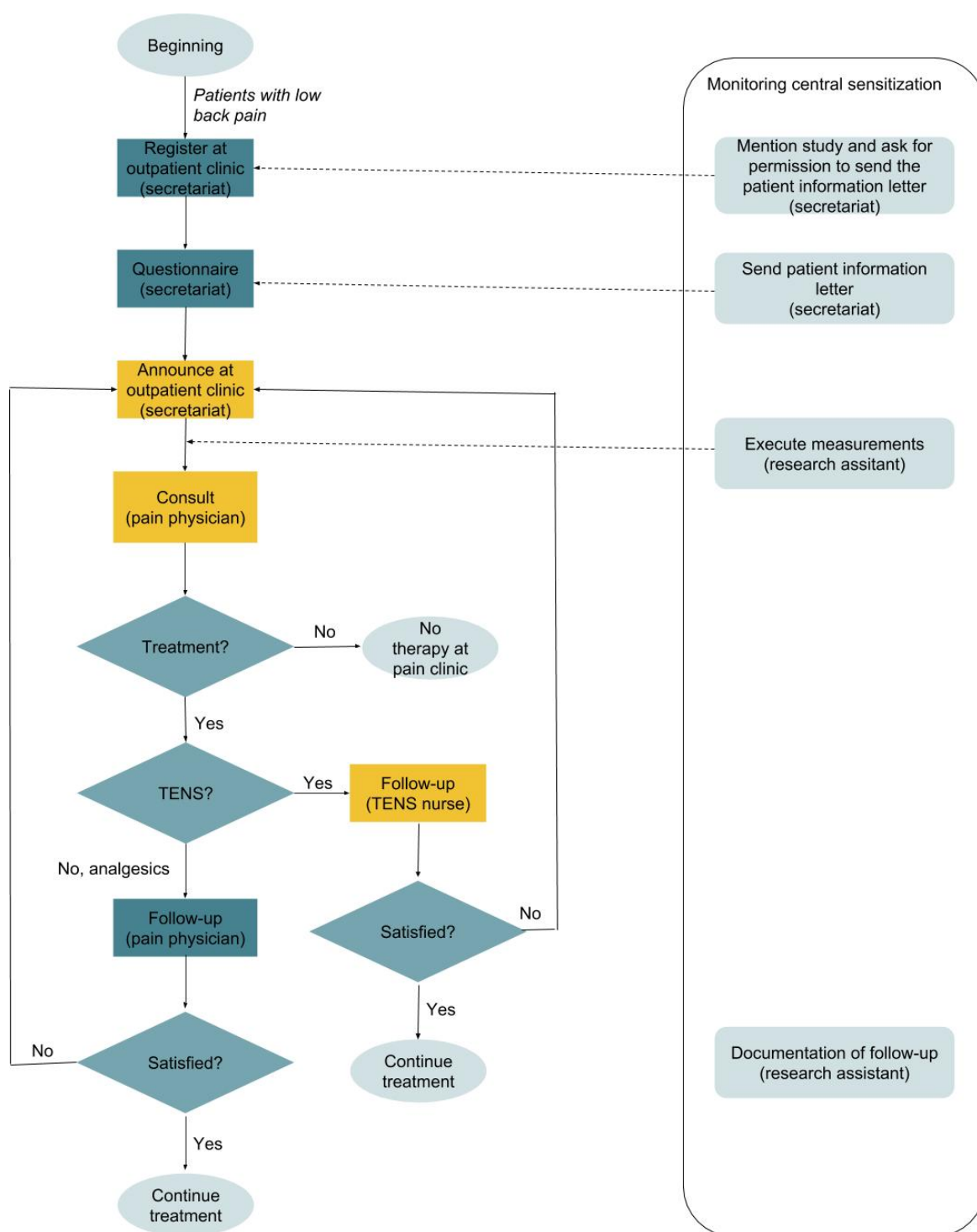


Figure 3.2: The pathway followed by the patient when referred to the outpatient pain clinic, at "beginning". In the framed column on the right are the additional activities shown to add with the monitoring process.

3.4 QUANTITATIVE SENSORY TESTING AT THE OUTPATIENT PAIN CLINIC ST. ANTONIUS HOSPITAL

Electrical quantitative Sensory Testing (eQST) is proposed to be a good measurement method to monitor or detect central sensitization in chronic pain patients. In current practice, determination of the pathophysiology is done by the patient's charts, intake and self-reported questionnaire. There is a growing call for an easy and fast method to help detecting central sensitization in chronic pain patients to obtain mechanism based therapy. In order to organize a monitoring process that fits the current outpatient clinic, the process should be aligned with current clinical practice. The necessities for the process set up are:

- A. Measurement materials
- B. Procedures: Align with organization
- C. Executors: research assistants
- D. Measurements
- E. Data storage and processing and analysis
- F. Quality of measurements

A. Measurement materials

Widespread hyperalgesia is measured with determination of the pain threshold far distant from the pain origin. An Electrical Pain Detection Threshold (EPDT) is measured with the Ambustim PT.

The Ambustim PT is a small device developed by the University of Twente (Nocitrack B.V. University of Twente, Enschede) which enables electrical quantitative sensory testing (eQST) in an easy and non-invasive way. To date, Ambustim PT does not have a CE mark, however, it is used in other clinical trials and is proven to be safe for experimental use by the Department of Medical Physics (St. Antonius Hospital, Nieuwegein). With the Ambustim PT, the one responsible for the stimulation is the subject by pressing the "stimulation"-button, and thereby determine their own EPDT.

The EPDT is compared to the validated Central Sensitization Inventory (CSI) to evaluate the results of the EPDT on accuracy. The CSI is a two-part questionnaire, containing 25 questions that assess the frequency of health-related symptoms that are associated with central sensitivity syndroms (Part A) and 10 questions asking if patients are diagnosed with specific disorders in the past (Part B)[91]. The Dutch CSI is validated by several studies [92] and has shown good test-retest reliability and internal consistency. [93][64][63][91][94]. The full questionnaire can be found in Appendix B.

From the patient charts the use of analgesics, and clinical characteristics (e.g. pain duration, location, and history) can be obtained. In addition to the patient charts and questionnaires, some patient characteristics should be collected, as the baseline characteristics. These are characteristics that might be an influence on the EPDT, as BMI, age, gender, smoking habits, working status and dominance in hands. The NRS scores of the previous 24 hours (highest, lowest, average) and current should be taken into account.

B. Procedures: Align with organization

Recruitment and inclusion should be properly aligned with the outpatient clinic, in such a manner that employees do not have too much difficulties with the extra procedure, next to their normal activities.

Notification of the study is done by the secretariat directly when the patient is scheduled for intake. The patients are noted about study when they call to make an appointment for intake. Then permission is asked to send the Patient-Information Form (PIF) simultaneously with the pain questionnaire. This will give the patients enough time to read the information and to decide whether they would like to participate.

Once arrived at the outpatient clinic, patients get the opportunity to ask questions and during consult the pain physician determines whether the patient fits the in- and exclusion criteria of the study. The patient is asked whether they want to participate and if agreed, the patient can be included in the study, directly after intake.

After informed consent is signed, the eQST measurements are executed by a research assistant, which will take about five minutes. The results are entered directly in REDCap and marked “complete”. Then the online system automatically sends out an e-mail with the additional questions and CSI, which the patient can complete at their own favorable moment and location.

C. Executors: Research Assistants

Employees of the secretariat will recruit and include patients. Research assistants are employees of the secretariat and interns from the outpatient pain clinic who are capable and interested in performing the measurements. There is an overview of all the assigned research assistants available in the study folder at the outpatient pain clinic. Processing of the data and responsibility of the project is the principal investigator.

D. Measurements

As mentioned in the Clinical Background, it is shown in different studies that widespread hyperalgesia can function as a marker for CS and has been shown in chronic low back pain. Widespread hyperalgesia in chronic low back pain is measured on the lower forearm. Ambustim PT uses electrocutaneous stimulation. This device has shown good test-retest reliability in previous studies. Since the measurements are instruction- and placement-dependent, an agreement on the instruction and placement should be obtained in advance.

Electrodes that should be used are: 3M™ Red Dot™ Soft Cloth Monitoring Electrode 2238. When electrode types change, this should be noted and taken into account in data analysis. Placement of the electrodes should be placed with a distance of approximately 5 cm to each other on the most muscular part of the m. brachialis[95].

Since the subject is responsible for the determination of the EPDT, adequate instructions of the assignment should be given. Important for the instruction is to keep track of the exact instructions given, since the measurement outcomes depend on the exact phrasing. After a small explanation about the measurements, phrasing of the instruction of the measurement of the EPDT should be:

“When the feeling starts to feel uncomfortable for the first time, not painful or unbearable, but uncomfortable, we ask you to release the button.”

An important keynote in this instruction is that the button should be released from the moment the sensation starts to feel “uncomfortable”, and not painful.

E. Data storage and processing

All study data can be collected and managed using REDCap electronic data capture tools hosted at St. Antonius Hospital. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources[96]. By this application, data is securely saved and can easily be transferred to statistical programs like SPSS and R.

F. Quality of measurements

An important consideration in the measurement procedures is that measurements are executed in such a manner that the outcome of the measurements is reliable.

To guarantee quality of the performance of the measurements, research assistants that assigned for measurements are qualified by educating them. Thereby a training document was set up, which was saved in a folder belonging to the study. Research assistants should be qualified before they are allowed to perform the measurements. In this training document the device manual, installation, instruction and data collection in REDCap are explained. The research assistants are instructed on how to perform the measurements and received a certificate for completing the training. The principal investigator is responsible to make sure that the research assistants are qualified and are able to deliver reliable data. The principal investigator is also responsible for measurement evaluation and to make sure that measurements of different observers are aligned. Thereby, analysis should be done on the tested data to test on structural differences, and research assistants should perform some measurements together. The education forms need to be updated and reformulated after new devices, and methods are implemented. The principle investigator is responsible to keep track of this updating.

Differences in measurements between observers should be checked with analysis of the data during every analysis.

In addition risk analysis is one of the essential project management areas, and should be executed regularly to identify and analyze the response to projects risks. This evaluation and reflection on the process is necessary to overcome potential bugs in the system that may evolve over time. The executed pilot was evaluated with the people involved in the pilot (subjects, assistants and researchers) for different aspects of the study.

3.5 VALIDATION QST MONITORING PROCESS

Three different phases were set up to structurize the implementation of the process in aligning with the current clinical workflow at the outpatient pain clinic. The first phase is performed to get an overview of the (im)possibilities of the outpatient pain clinic and the measurements, where after different aspects of the monitoring process should be studied and implemented in following phases. The pathway to fully implement the eQST measurement as monitoring of CS was divided in three different phases to create a structure and different steps to take. Objectives and research goals of all these phases were drafted. In the following phases the study should be extended. Some requirements and goals were set up for each phase. After every phase, different requirements to continue were set up.

Phases

Phase 1a: Explorative pilot study (Part I)

The goal of the first phase is to map the (im)possibilities of the outpatient pain clinic in St. Antonius Hospital. This is done with a major and homogeneous pain population: chronic low back pain. In this population, widespread hyperalgesia has already been shown, and would thereby be an acceptable starting point[17] [18][19][20]. During this phase there is studied whether differences between healthy subjects and chronic pain is seen. In addition is evaluated whether the study set-up can be a self-standing process in clinical practice.

The homogeneity should be secured, and thereby disorders that appear with polyneuropathies should be excluded, e.g. diabetes mellitus. Still, there can be expected that an inclusion rate of ten patients a week can be reached.

The aim of this pilot study was to explore whether differences between healthy subjects and chronic pain could be seen in widespread hyperalgesia, baseline patient characteristics and Central Sensiti-

zation Inventory (CSI). It is necessary to determine what the parameters of interest are for following research.

Requirements for success are:

- ◇ Differences between chronic pain and healthy subjects can be found with the QST measurements. Otherwise, change the location of measurements or measurement method.
- ◇ The study is a stand-alone study, or has the potential to become one with a few adaptations.

Phase 1b: Explorative pilot study (Part II)

In Part II of the explorative pilot study, the population of chronic low back pain patients should be filled till 100 patients are included. The differences found between chronic low back pain and healthy subjects can be studied and by studying and determining cut off values of the reference pain threshold it is expected to be able to study the prevalence of CS in the CLBP population.

- ◇ A cut off value is obtained for CS in the chronic low back pain population.
- ◇ The enrollment is still possible with the available research assistants.
- ◇ There can be hypothesized what patient specifics are interesting for detection of CS.

Phase 2: Broaden to more pain populations

The chronic low back pain population should be compared to other prominent pain populations. More research is necessary to determine what population would be best suited to compare those, to eventually include all chronic pain patients in the study to obtain a complete inventory of the presence of CS in the chronic pain population visiting the outpatient clinic in St. Antonius Hospital.

The criteria for success for this part were:

- ◇ A database with patient information of different pain syndromes is obtained.
- ◇ Patient specifics that seem to have high correlation with developing CS are visible.
- ◇ The enrollment is still possible with the available research assistants.

Phase 3: Broaden to treatment monitoring

The aim of monitoring over treatment is to determine whether widespread hyperalgesia is decreasing, and can be concluded that CS is decreasing.

Once figured out what specific patients with what specific characteristics might experience advantage of monitoring their CS, the CS patients could be followed up with QST measurements in order to evaluate the treatment and whether the amount of CS maintains. The follow up with NRS-scores is shown to be inefficient, since pain experience can be forgotten and dynamic; patients start to do several of their daily activities again and overburden their body again, which can again lead to pain. They may not recognize that that is an effect of their activities and score their pain as high as before treatment had started. The criteria for success for this part were:

- ◇ A database with patient information is filled with follow-up/monitoring.
- ◇ Monitoring of CS and the effect of the treatment is possible.
- ◇ The enrollment is still possible with the available research assistants.

3.6 EVALUATION OF THE MONITORING PROCESS

After performing the explorative pilot study to implement the monitoring process in current clinical practice that is outlined in the following chapter, evaluation of the monitoring process was done. The most important points are described.

The alignment of the study with the organization is an important part of making the process a self-standing process. At the end of the first phase, one requirement was that inclusion of subjects can continue without interference of the researchers, except the parts of monitoring and analyzing the results. Thereby special attention was given to the evaluation of the study set-up, the enrollment of

study subjects and research assistants. The enrollment of patients is not going as fast as expected. Currently, 80 patients have been screened for enrollment, and only 24 were measured. As visible in Figure 4.2, the predominant part of the screened patients was not interested in participating, due to time limitations, stress or too much pain. A solution suggested is the moving the measurement to before intake. The measurements can take place in the waiting time of the patient and less effort is asked from the patients.

The materials and storage of the data seem to function properly. For the Ambustim PT is an evaluation point that storage of measurement results would be more easy and user friendly when the data was saved and sent directly in the computer. In the current version measurement results are copied from the tablet and inserted into the computer. Meaning that more attention is given to the tablet, and less attention is given to the patient. In addition, more procedures often lead to more mistakes.

It is important to study the data collection forms, especially when the patient has to self complete the form or when several different assessors will be collecting data. Forms were evaluated by letting different assistants fill in test forms and compare their ways of filling them in and how they interpreted the forms. Important is that questions in the forms are well defined, clearly understood and presented in a consistent manner. A few test surveys were filled in by test subjects, to evaluate whether there were uncertainties in the questions. In addition the import of data of the measurements in REDCap was evaluated in its' ease of use by the researchers and assistants. Filling in the questionnaires were found very easy, and the response rate was 80%. After corrections of some bugs that led to an impossibility of filling out the "age", the reactions were positive. The length was just about right, most people took 5-10 minutes to complete the form. Some patients had the preference to complete the forms directly after the measurements at the outpatient clinic. One question about "ongoing ligitations" made it difficult for some patients to fill out the questionnaire. Since this might also be of influence of the QST-measurements, but it is not preferable that patients get scared away from the questionnaire. So it should be a clear option that an answer is not required to continue.

Research assistants seem to find it acceptable to implement the measurement in their routine. However, it is possible to miss out some patients, because of their unpredictable workload. A possibility would be to perform measurements in the waiting room. An option would be to perform the measurement while waiting, so no extra time or location is asked. When the measurements are completed, the questions are presented on the tablet for the patient to complete.

So far, the education of the measurements seemed clear. Following education and training should be checked with the principal investigator to guarantee proper measurements. In addition the training documents can always be read. One of the drawbacks of the current status of the device is that it is not completely bug-free. For research assistants from the secretariat, this was a problem, and they directly panicked. It is included in the information documents that the tablets and devices need a switch ON/OFF once in a while.

3.7 CONCLUSION

In previous chapter a process to monitor central sensitization in chronic patients has been set up in several different phases. There is attempted to align this process to current clinical practice, in order to create an almost effortless process. In the next chapter there is started with Phase 1a to validate this monitoring process. After the validation, the conclusions and recommendations of this work will be outlined.

4

EXPLORATIVE STUDY TOWARDS EQST AS A POTENTIAL MONITORING METHOD OF CS

4.1 INTRODUCTION

In previous chapter, a monitoring process of CS was set up. As a first step of implementing the monitoring process of CS in current practice of the outpatient pain clinic, exploration of the characteristics and electrical pain detection threshold in healthy controls and chronic pain patients is necessary. Thereby the process that was outlined in previous chapter, is started with an explorative pilot study in chronic low back pain (CLBP) patients and healthy controls in this chapter.

To eventually make a reliable distinction between chronic pain and central sensitization, it is necessary to evaluate whether differences can be measured. Some research has been done in laboratory setting with the Ambustim PT and earlier studies in the St. Antonius Hospital has shown differences in EPDT between healthy subjects and hernia nuclei pulposi (HNP) patients.

The aim of this pilot was to explore whether differences between healthy subjects and chronic pain could be seen in widespread hyperalgesia, patient characteristics and Central Sensitization Inventory (CSI). It is necessary to determine what the parameters of interest are, for further research.

4.2 METHOD

4.2.1 Study design

An explorative, cross-sectional pilot study was executed. METC approval was given by de MEC-U, Nieuwegein on 15/08/2018. Approval is also given by the local committee of the St. Antonius Hospital and the University of Twente. The most important parts of the protocol are discussed in this method section.

4.2.2 Population

The study population existed out of 18 new chronic low back pain patients with mechanical low back pain and 79 healthy controls.

Eligible healthy control subjects had to be free of any acute or chronic pain. To overcome a selection bias of students only in the controls, the control group is formed by escorts of patients attending the Pre-Operative Screening (POS) of the St. Antonius Hospital.

Inclusion criteria for healthy subjects were:

- ◇ Pain free
- ◇ >18 years old
- ◇ Signed informed consent

Inclusion criteria for pain population were:

- ◇ Chronic low back pain, lumbar spine related (>3 months)
- ◇ >18 years old
- ◇ Signed informed consent

For all subjects were the same exclusion criteria applicable:

- ◇ Pregnancy
- ◇ Diabetes Mellitus
- ◇ Polyneuropathies
- ◇ Implantable cardioverter defibrillator (ICD) or pacemaker (PM)
- ◇ Incapable to control the device
- ◇ Alcohol or drug abuse
- ◇ Language barrier

All included subjects met the inclusion and exclusion criteria.

4.2.3 Materials

Ambustim PT

Ambustim PT provides a simple and short method to monitor pain by eQST. This device was used to measure an electrical pain detection threshold. Ambustim PT is a small device developed by the University of Twente (Nocitrack B.V. University of Twente, Enschede) which enables electrical quantitative sensory testing (eQST) in an easy and non-invasive way to quantify pain thresholds. To date, Ambustim PT does not have a CE mark, however, it is used in other clinical trials and is proven to be safe for experimental use by the Department of Medical Physics (St. Antonius Hospital, Nieuwegein).

The Ambustim PT (displayed in Figure 4.1) is an electrical one-channel stimulator. Electrical stimulation runs through two Ag/AgCl ECG electrodes attached to the skin with a distance of approximately 5 cm to each other. The device contains a current generator which generates current pulses with a pulse width of 210 ms and a pulse frequency of 100 Hz. The subject controlled the Ambustim independently by pressing the red button on top. By pressing this button, stimulation was started and the amplitude increases gradually with 0.4 mA/s to a maximum of 20 mA. The stimulation stops immediately when the button is released. The final current, representing the electrical pain threshold, was displayed on a tablet, which was connected to the device via Bluetooth.

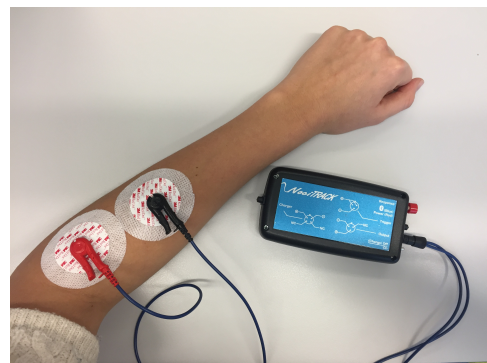


Figure 4.1: AmbuStim PT

Central Sensitization Inventory

Currently, one of the validated methods to evaluate central sensitization is the Central Sensitization Inventory (CSI). The CSI is a two-part questionnaire, containing 25 questions that assess the frequency of health-related symptoms that are associated with central sensitivity syndromes (Part A) and 10 questions asking if patients are diagnosed with specific disorders in the past (Part B).^[91] Part A is divided in four factor groups, found by the factor analysis of the Dutch CSI^[64]:

- (1) General disability and physical symptoms: items 2, 6, 8, 9, 17, 25.
- (2) Higher central sensitivity: items 4, 7, 10, 13, 18, 19, 20.
- (3) Urological and dermatological symptoms: 11, 14, 21.
- (4) Emotional distress: 3, 12, 13, 15, 16, 17.

Each of the questions asked in the CSI is scored on a 5-point temporal Likert scale: never (0), rarely (1), sometimes (2), often (3), and always (4). With 20 questions, the score is from 0 to 100 points. The Dutch CSI is validated by several studies ^[92]. Kregel et al. showed that a cutoff score of 40 points

Table 4.1: Patient specifics

Demographics	NRS-score (0-10)	Clinical	Use of medication
Gender	Before measurement	Pain location	Frequency
Age	Mean score last 24hr	Affected side	Use of NSAIDs, or
BMI	Highest score last 24hr	Pain origin	Paracetamol, or
Smoking habits	Lowest score last 24 hr	Pain duration	Opioids, or
Working status			Antidepressants, or
Highest level of education			Anticonsulvants
Ongoing litigation			
Dominant hand			

as a definition for central sensitization in the Dutch CSI[64]. The CSI has shown good test-retest reliability and internal consistency [93][64][63][91][94]. CSI was digitally sent to the subjects, the full questionnaire can be found in Appendix B.

Patient characteristics

Patients specifics of interest that were researched are displayed in table 4.1. These specifics were collected by an online survey that was set up in REDCap (Research Electronic Data Capture). The surveys can be found in Appendix ..

4.2.4 Protocol procedures

In order to assure a voluntary participation in this study, potential study subjects were not approached by the principal investigators. For healthy controls this was done via a recruitment poster (Appendix...) at the counter of the POS. With this recruitment poster, people were informed about the study and could sign up with the secretariat behind the counter. Recruited were escorts of patients visiting the POS. Once applied, they were directed to the researchers where more information was given and questions could be asked. If agreed, the subject read and signed informed consent.

Chronic pain patients were recruited at the outpatient pain clinic. Again, to assure a voluntary participation in this study, potential study subjects were not approached by the principal investigators. While making an appointment to see the pain specialist, the study was mentioned by the secretary and additional information was sent to them by mail. On the day of the visit, the patients decided if they wanted to participate in the study or not. The measurements were executed directly after intake at the outpatient clinic. All subjects read and signed informed consent prior to undergoing any data collection.

Once enrolled, healthy controls and chronic pain patients completed the same procedures. They were screened on exclusion criteria, where after measurements were executed. Afterwards, online surveys were sent automatically by email.

For all subject the EPDT was measured on the flexor carpi ulnaris on the most muscular part. In the pain population, the measurement side was chosen contralateral to the affected side, and in case of equal pain on both sides by computerized randomization. For the healthy controls the measurement side was randomized.

Observers during this preliminary study were two technical medicine students. In future research, more observers will be trained and qualified to perform the measurements.

4.2.5 Measurement protocol

Once included, the measurements were started with an explanation of the measurements with in addition the following instruction (the Dutch version of the instruction and short explanation of the measurements given can be found in Appendix A.1:

“When the feeling starts to feel uncomfortable for the first time, note that it is not painful or unbearable, but uncomfortable, you may release the button. Remember, it is not a contest.”

After the instruction, two electrodes were applied on the brachioradialis to which the Ambustim was connected, as visualized in Figure 4.1. Via the Nocitrack application on the tablet, connection was made between the tablet and the Amubstim PT. Then the Ambustim was handed over to the subject. To execute the measurement, the subject pressed and held the red button (Figure 4.1) until the sensation became uncomfortable for the first time. This first sensation of “discomfort” was identified as the Electrical Pain Detection Threshold (EPDT). Prior to the measurements, a familiarization session was done for all subjects. This familiarization existed out of an exercise trial, in which the subject could experience the sensation and had to note the first moment of discomfort. When the stimulation was noted as familiar for the subject, the real measurements were executed. The EPDT determination existed out of three trials from which the average value was taken afterwards. This mean EPDT was defined as the EPDT of that subject. One session took five minutes per subject.

Directly after completing the measurements, additional questions about the patient characteristics and the CSI were sent by an online survey via an email.

4.2.6 Data analysis

All data was directly entered in REDCap (Research Electronic Data Capture), where it was coded and saved. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources[96]. By this application, data is securely saved and can easily be transferred to statistical programs like SPSS and R. Statistical analysis was done in SPSS, version 26. Subjects were anonymized by subject numbers in order of enrollment (e.g. subject 1 = 1, subject 2 = 2). In the analysis, the association between hyper-sensitivity and the patient specifics was researched.

With help of histograms and Q-Q plots, collected data was tested for its' normal distribution. For normally distributed data, data were compared using the Student's T-test (continuous variables) or Chi-Square test (categorical variables). Non-parametric tests were executed for non normal distributed data (Mann-Whitney U Test)

Demographic variables were summarized by descriptive statistics to compare the baseline characteristic between both groups and compared with the appropriate statistical tests. Continuous data: mean \pm SD (parametric data) or medians and percentiles (non-parametric data) was calculated.

The difference in EPDT between healthy controls and pain patients was tested with Student's T-test, with a significance level of 5%.

Further, the association between the different characteristics and hyperalgesia was studied. In both populations was determined whether age, gender, BMI and observer had a significant influence on the EPDT outcome. With Student's T-test or Chi-Square tests, the differences between groups were determined. To compare age and BMI, these variables were split in groups. Age was divided in

groups being, <49.99, and >50 years old. The influence of BMI was tested within four groups, underweight(<18.5), normal(18.5-25), overweight(25-30) and obese(>30).

The scores of the EPDT were observed per question and per factorgroup (1-4), and difference between both populations was tested with Student's T-test. The correlation between EPDT and CSI was tested with Pearson's Correlation Coefficient for both populations.

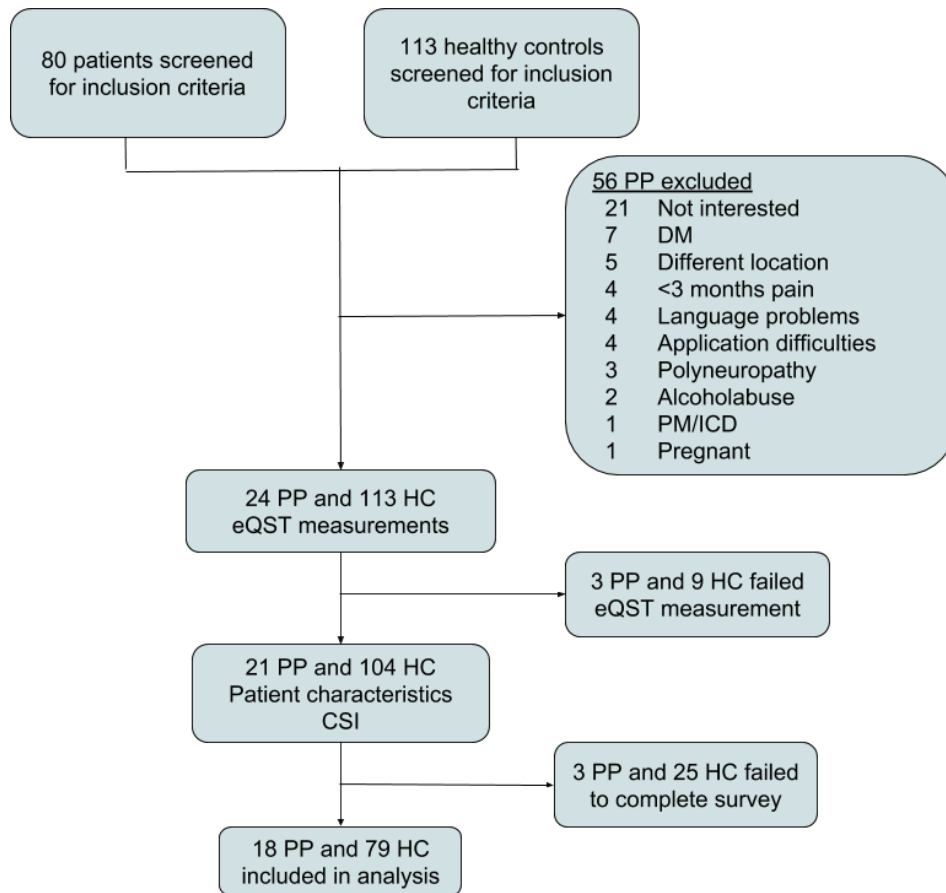


Figure 4.2: Inclusion of Healthy controls (HC) and Pain patients (PP).

4.3 PRELIMINARY RESULTS

A schematic overview of the inclusion can be found in Figure 4.2. For the control group 113 healthy subjects were considered for inclusion, and all were enrolled. Nine of these controls reached the maximum value of the device (20mA) and 20 controls failed to complete the online survey, so were excluded for analysis.

Five control subjects did report pain symptoms, which were arthrosis, fibromyalgia, scar fracture, inguinal hernia, and comminuted fractures of the feet, and were thereby also excluded for further analysis.

A total of 80 patients were considered for inclusion in the study. Among these patients, 56 were not included (reasons in parentheses): 21 (Not interested), 7 (Diabetes Mellitus), 5 (Present at other location), 4 (<3 months pain), 4 (Language problems), 4 (Difficulties with application of electrodes), 3 (Polyneuropathy), 2 (Alcohol abuse), 1 (ICD), and 1 (Pregnant). As a result, 24 patients were enrolled

for measurements and signed informed consent. Three patients reached the maximum value of the device (20mA) and three additional patients failed to complete the survey, and were thereby excluded. The study population consisted out of 18 pain patients and 79 healthy controls that completed the entire study.

4.3.1 Baseline characteristics

A summary of the baseline characteristics of all included subjects in both study populations can be found in Table 4.2.

The healthy population consisted out of 36(45.6%) men and 43(54.5%) women. The mean age was 49.8(\pm 15.5) years old and the BMI was 24.9(\pm 4.6). The main part of this population was highly educated with a level of HBO/WO in the Dutch education system.

In the patient population 6(33.3%) men and 12(66.7%) women were included. The population had a mean age of 54.8(\pm 18.1) and a mean BMI of 25.4(\pm 4.5). One third of the pain population were smokers in the pain group. The level of education was diffuse, with VMBO/MAVO/LBO and HBO/WO as the most common. Six patients still worked full time, five patients reported to reduced their working hours because of their pain, and four patients (22.2%) reported being disabled for work. However, only two patients received a disability pension as compensation for their pain.

Between both populations, no statistically significant differences found regarding age ($t(90)=1.199$, $p=0.234$), BMI ($t(93)=0.352$, $p=0.726$), and gender ($\chi^2(1)=0.894$, $p=0.344$).

Significant differences in education level and working status were found among both groups, $\chi^2(4)=11.219$, $p=0.024$, and $\chi^2(5)=19.335$, $p=0.02$ respectively. These differences are visualized in the piecharts in figures A.1 and A.2, in Appendix A.2.

4.3.2 Electrical Pain Detection Threshold

Inspection of histograms and Q-Q plots of the averaged EPDTs showed that the data was normally distributed in both, the healthy controls and in patient population (shown in Figure ??). The averaged thresholds of both groups can be found in table 4.4. The mean threshold of the healthy controls was 9.6(\pm 4.2) and in the pain population 9.4(\pm 3.9) (see Table 4.4), comparison of the mean EPDT's of both groups did not show statistical significant difference ($t(95)=-0.131$, $p=0.896$).

Gender

Both populations were split in male and female compare the EPDT in men and women 4.4.

In the healthy controls, the distribution of the EPDTs was normal for both groups, the corresponding histograms can be found in Appendix A.2, Figures A.3e and A.3f. The mean EPDT in men was 10.7(\pm 4.5) mA and in women was 8.6(\pm 3.6) mA. Statistical analysis of this difference by an independent T-test showed a significant difference between men and women ($t(77)=2.306$, $p=0.024$), the corresponding test can be found in Appendix ??.

In the chronic pain population 6 men and 12 women were present. The men showed a mean EPDT of 11.1(\pm 3) mA and the women a mean of 8.6(\pm 2.8) mA. No significance between both groups were found ($t(16)=3.261$, $p=0.090$).

Age

The effect of age was tested by comparing the mean EPDTs for two age groups, <49.99 and >50 years old. In the control population, the groups consisted an equal number of patients, N=39 for both groups. The mean EPDT divided over the different groups were normally distributed, Figure A.3a. With the Students T-test the averaged EPDT of the two different groups were

Table 4.5: Mean EPDT for pain patients and healthy controls.

Population	N	Mean[SD] (mA)
HC		
<49.99	39	8.8(4.0)
>50	39	10.5(4.1)
PP		
<49.99	7	9.3(4.0)
>50	11	9.5(4.0)

Table 4.2: Baseline characteristics: Sociodemographic characteristics

Baseline characteristics		
Mean (SD) or nr. of patients (%)	Pain population (n=18)	Healthy controls (n=79)
Sociodemographic characteristics		
Gender		
Male	6(33.3%)	36(45.6%)
Female	12(66.7%)	43(54.5%)
Age (years)	54.8(±18.1)	49.8(±15.5)
BMI (kg/m ²)	25.4(±4.5)	24.9(±4.6)
Smoking habits		
Yes	6(33.3%)	9(11.4%)
No	12(66.7%)	70(88.6%)
Highest level of education		
No/primary education	1(5.6%)	0
VMBO/MAVO/LBO	6(33.3%)	10(13.0%)
MBO(MTS/MEAO)	4(22.2%)	13(16.5%)
HAVO/VWO(HBS/MMS)	0(0%)	9(11.4%)
HBO/WO (HTS/HEAO)	7(38.9%)	45(58.4%)
Working status		
Full time	6(33.3%)	25(32.9%)
Part time	4(22.2%)	25(32.9%)
Disabled	4(22.2%)	0
Unemployed	0	2(2.5%)
Retired or studying	4(22.2%)	24(31.8%)
Changes in working status		
Regular work as usual	4(22.2%)	-
Reduced work due to pain	5(27.8%)	-
Disabled due to pain	4(22.2%)	
Inapplicable	5(27.8%)	79 (100%)
Disability pension		
Yes	2(11.1%)	11(14.7%)
No	16(88.9%)	64(85.3%)
Ongoing litigation		
Yes	0(0%)	1(1.3%)
No	18(100%)	74(94.9%)

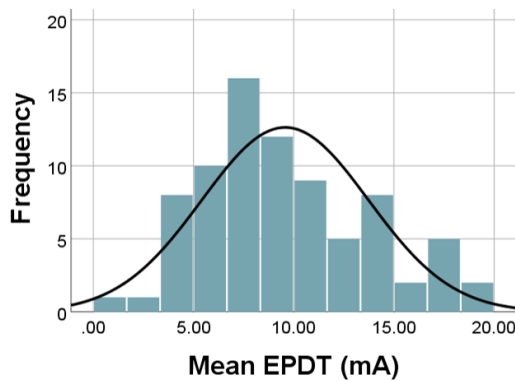
Table 4.3: Baseline characteristics: Clinical characteristics

Baseline characteristics Mean (SD) or nr. of patients (%)	Pain population (n=18)	Healthy controls (n=78)
Clinical characteristics		
Origin of the pain		
History of trauma related to pain	1(5.9%)	1(1.4%)
History of surgery related to pain	0(0%)	0(0%)
Spontaneously	16(94.1%)	2(2.7%)
Affected side		
Right	9(50.0%)	-
Left	6(33.3%)	-
Bilateral	3(16.7%)	-
Pain duration (years)		
<1	7(38.9%)	1(1.3%)
1-2	1(5.6%)	1(1.3%)
>2	8(44.4%)	3(3.8%)
Maximum pain over the last 24hr (NRS 1-10)	7.0(±2.6)	0
Minimum pain over the last 24hr (NRS 1-10)	3.3(±2.1)	0
Average pain over the last 24hr (NRS 1-10)	5.5(±2.3)	0
Pain intensity before testing (NRS 1-10)	4.2(±2.6)	0
Frequency intake pain medication		
Never	3(16.7%)	88(100%)
Daily	10(55.6%)	0(0%)
Weekly	3(16.7%)	0(0%)
Monthly	1(5.6%)	0(0%)
Daily intake of		
NSAIDs/paracetamol	11(61.1%)	0(0%)
Opioids	3(16.7%)	0(0%)
Antidepressants	0	0
Anticonvulsants	0(0%)	0(0)

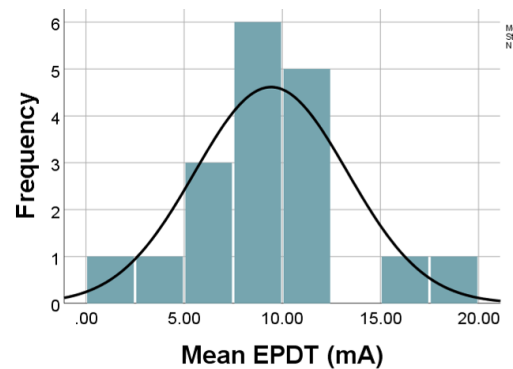
Table 4.4: Mean EPDT for pain patients and healthy controls. Differentiation for gender shows significant difference for man and women in the control group.

Population	N	Mean (mA)	St.Dev.	Min (mA)	Max (mA)
Healthy Controls	79	9.6	4.2	1.36	19.13
Men	36	10.7*	4.5	3.5	19.1
Women	43	8.6*	3.6	1.4	18.7
Pain Patients	18	9.4	3.9	1.98	17.96
Men	6	11.1	5.4	4.1	18.0
Women	12	8.6	2.8	2.0	12.0

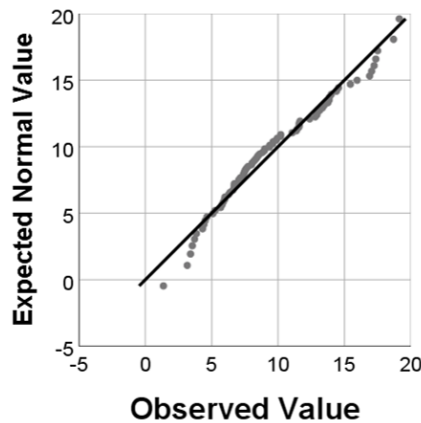
*Significant test $p < 0.05$



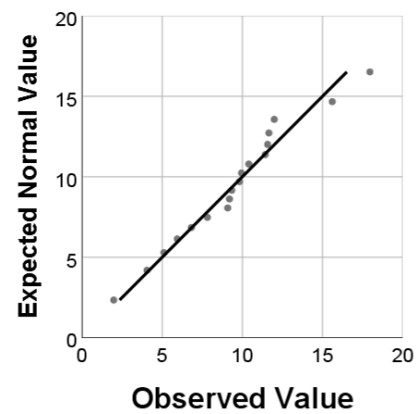
(a) Histogram of the mean EPDT in the healthy controls (N=79). The mean of the healthy population is at $9.6(\pm 4.2)$ mA.



(b) Histogram of the mean EPDT in the pain patients (N=18). The mean of the patient population is at $9.4(\pm 3.9)$ mA.



(c) The Q-Q plot of the EPDT in the healthy control population.



(d) The Q-Q plot of the EPDT in the patient population.

Figure 4.3: The distribution of the data for both populations.

compared. The groups <49.99 and >50 had mean EPDTs of $8.8(\pm 4.0)$ mA, and $10.5(\pm 4.1)$ mA, respectively. This difference was not significantly different ($t(76) = -1.812$, $p = 0.074$).

EPDTs for the agegroups in the PP groups were for <49.99 and >50 were respectively $9.3(\pm 4.0)$ mA and $9.5(\pm 4.0)$ mA, in which no significant difference was found as well ($t(16) = -0.099$, $p = 0.922$).

BMI

The subjects were divided in four subgroups:

(1) underweight (<18.49), (2) Normal (18.5-24.99), (3) Overweight (25-29.99) and (4) Obesity (>30).

In the HC population, no statistical analysis could be performed on group (1)(N=3, EPDT=10.3±5.1mA), because of the low subjects numbers in that group. Mann-Whitney U tests were performed to determine the difference between the groups (2) (9.2±3.7mA), (3) (9.2±4.2mA) and (4) (11.1±5.01mA). These tests showed that no significant difference was visible between the different BMI classes comparing (2) vs. (3) (U=322.00, p=0.808), (2) vs. (4) (U=265.00, p=0.217), and (3) vs. (4) (U=102.00, p=0.317).

For the pain patients, the same BMI division was obtained as in the healthy subjects. N=11 for group (2) Normal, 6 in group (3) and 1 patient was present with (4) Obesity. The mean EPDT's were respectively 10.6(±4.0)mA, 7.6(±3.4)mA, and 7.8(-)mA. These groups were too small for statistical testing.

Table 4.6: Mean EPDT for pain patients and healthy controls.

Population	N	Mean[SD] (mA)
HC		
<18.49	3	10.3(5.1)
18.5-24.99	42	9.2(3.7)
25-29.99	16	9.1(4.2)
>30	16	11.1(5.0)
PP		
<18.49	0	-
18.5-24.99	11	10.6(4.0)
25-29.99	6	7.6(3.4)
>30	1	7.8(-)

Observer

The differences between observers was tested in the healthy controls. The two groups were compared with the students T-test. Observer (1) had a mean of the averaged EPDT of 8.6(±4.2)mA and observer (2) had a mean of 10.3(±10.3)mA. No significant difference in observers was found (t(75)=-1.907, p=0.060).

Table 4.7: Mean EPDT for pain patients and healthy controls.

Population	N	Mean[SD] (mA)
HC		
(1)	38	8.6(3.8)
(2)	39	10.3(3.8)

4.3.3 Central Sensitization Inventory (CSI)

The CSI was evaluated for both parts of the inventory (Part A and Part B). Part A existed out of 25 question, for each question a score was given on a scale from zero to four. The mean answers given per question of part A are visualized in the bar diagram in Figure 4.4. The total results per question for Part A and B can be found in Appendix B.

Since the populations did not differ significantly on gender ($\chi^2(1)=0.894$, p=0.344) or age (t(90)=1.199, p=0.234) compared to the control group, it was not necessary to control for gender or age for the CSI[64]. For healthy controls, the mean CSI-score was 18.4(±9.6), while pain patients, had a mean score of 33.8(±15.6). The mean scores of both groups can be found in Table 4.8.

The difference in CSI score between both groups was significant, tested with a Student's T-test (t(95)=5.395, p=0.009).

The answers were arranged into four different factor groups. Comparison of HC to PP was done with Independent T-tests. The comparisons were significant for all four factors, as visible in Table 4.9.

In part B, different CS syndromes have been noted in the healthy population. Fifteen healthy subjects noted to be diagnosed with at least one of the CS syndromes in their lives, and were compared to the group without CS syndromes. Also in the patient population, ten patients recorded at least one CSS.

CSI score vs. EPDT

The CSI score in relation to the EPDT was visualized in a scatterplot in Figure 4.5. The Pearson Correlation Coefficient was computed to assess the relationship between the outcome of the EPDT and the CSI. There was no significant correlation between the two variables (r=-0.282, n=18, p=0.258). No significant difference in EPDT between the healthy control group who noted zero CS syndromes,

and one CS syndrome ($t(75)=0.416$, $p=0.678$). The CSI score from Part A, did show significant differences between those groups ($t(75)=2.374$, $p=0.020$).

In the pain population this difference was neither significant for EPDT ($t(16)=0.520$, $p=0.603$), nor CSI score ($t(16)=2.210$, $p=0.785$).

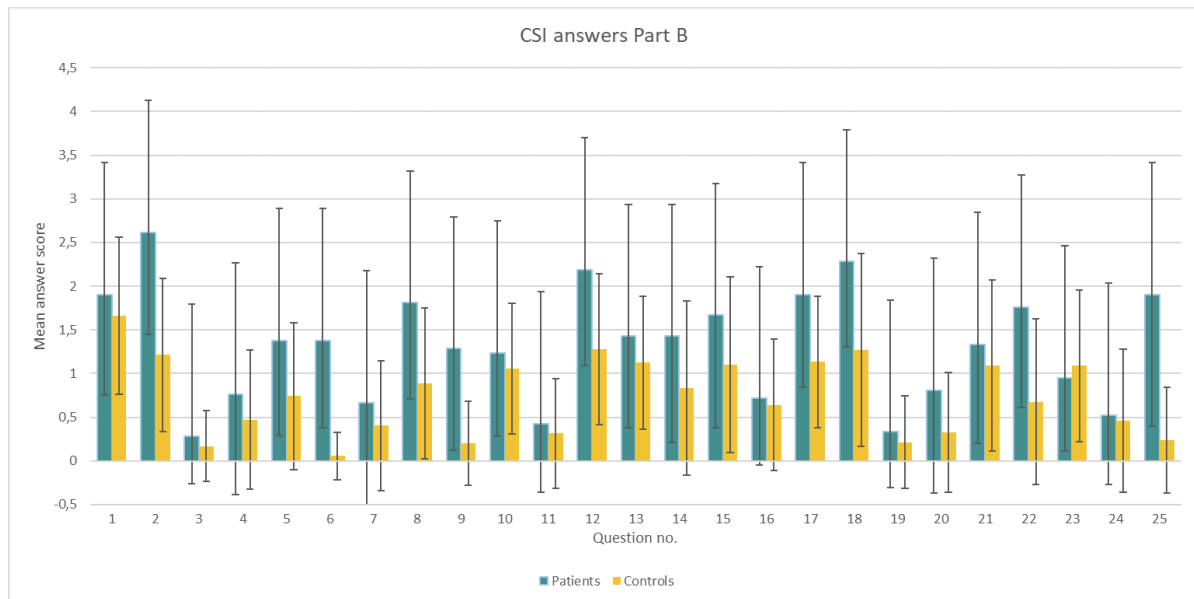


Figure 4.4: The mean scores per question in both populations

Table 4.8: CSI results

Population	N	Part A mean(SD)(range)	Part B mean(SD)	Age mean(SD)	gender (% Female)
Chronic pain	18	33.8** (15.6)(11-64)	0.8 (1.2)	57.9 (17.1)	14 (73.7%)
Controls	79	18.4** (9.6)(0-47)	0.5 (0.79)	50.4 (15.3)	50 (55.6%)

**Significant test $p < 0.001$

Table 4.9: CSI results averaged per factor

Factor group	Pain patient N=18	Healthy control N=79
Factor (1): General disability and physical symptoms	1.8**(0.8)	0.7**(0.5)
Factor (2): Higher central sensitivity	1.1*(0.7)	0.7*(0.5)
Factor (3): Urological and dermatological symptoms	1.1*(0.7)	0.7*(0.6)
Factor (4): Emotional distress	1.4*(0.8)	0.9*(0.5)
Remaining questions	1.4*(0.8)	0.9*(0.5)

*Significant test $p < 0.05$ **Significant test $p < 0.001$

Table 4.10: CSI Part B - The number of CSS reported in the CSI in both populations

Diagnosis	N	CSI-A	CSI-B	EPDT
CSS (N=..., ..%)	(%)	M(SD)	M(SD)	M(SD)
Controls				
Restless Leg Syndrome	3(3.4)	20(.7)	1(0)	15.9(3.4)
Chronic Fatigue Syndrome	0(0)	7	-	-
Fibromyalgia	1(1.1)	34(-)	1(-)	14.4(-)
Jaw symptoms	1(1.2)	36(-)	2(-)	15.96(-)
Tension Headache/Migraines	10(11.5)	28.3(10.1)	1.8(1.1)	9.0(4.9)
Irritable Bowel Syndrome	4(4.4)	30(17.9)	2.3(1.5)	6.6(1.9)
Multiple Chemical Sensitivity	1(1.2)	36(-)	2(-)	16.0(-)
Neck injury (incl. whiplash)	3(3.5)	16.3(3.8)	1.3(0.6)	7.8(3.0)
Anxiety/panic attacks	3(3.3)	28.7(19.0)	2.7(1.5)	9.5(8.1)
Depression	5(5.7)	26.8(14.3)	2.4(1.3)	9.4(6.4)
Patients				
Restless Leg Syndrome	1(5.3)	39(-)	1(-)	10.4(-)
Chronic Fatigue Syndrome	0(0)	-	-	-
Fibromyalgia	0(0)	-	-	-
Jaw symptoms	1(5.3)	61(-)	2(-)	5.9(-)
Tension Headache/Migraines	3(15.8)	51(11.1)	2(1)	6.6(3.0)
Irritable Bowel Syndrome	4(21.1)	46.8(15.1)	2.5(1.3)	10.0(1.1)
Multiple Chemical Sensitivity	0(0)	-	-	-
Neck injury (incl. whiplash)	3(15.8)	47(20.7)	2.7(1.5)	12.4(4.9)
Anxiety/panic attacks	1(5.6)	41(-)	2(-)	11.6(-)
Depression	2(10.5)	42(31.1)	2.5(2.1)	5.6(5.1)

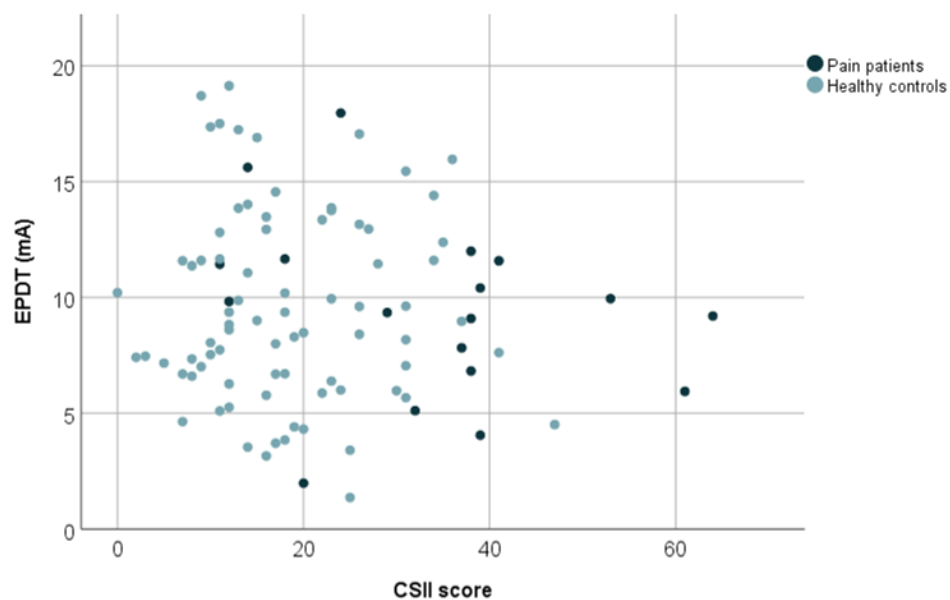


Figure 4.5: EPDT vs. CSI score in healthy subjects and pain patients. The cut off value of the CSI score is at 40.

4.4 DISCUSSION

In this explorative pilot study a psychophysical experiment was performed to study the prevalence of hypersensitivity in CLBP patients with the EPDT on the lower forearm. This study was performed to validate the monitoring process, set up in Chapter 3, and to evaluate whether similar results can be obtained as Curatolo et al.[23]. The normative values of the electrical pain detection threshold were determined with data of 79 healthy controls. During the study, patient characteristics were collected that could have influenced the EPDT. Of the independent parameters gender, age, BMI and difference in observer were studied. In addition, the CSI was collected to compare to the EPDT. Using these demographics and CSI, the population visiting the outpatient pain clinic can be studied and compared to the normative data. With the CSI-scores the detection of central sensitization can be compared and researched.

The normative data could be used as reference value when alterations in pain sensitivity are explored in individual patients. The most straightforward application would be the determination of bounds of the percentiles to assess central pain hypersensitivity. However, with the low number of included patients so far, these bounds cannot be tested.

The EPDT was measured with electrocutaneous stimulation of the lower forearm. With current method is believed that first A β -fibers are stimulated, and from the start of the "uncomfortable" sensation A δ -fibers are activated.

4.4.1 Clinical implications

Demographics

The baseline characteristics were collected for of both populations only showed significant differences in education level and working status. Thereby is was not necessary to compensate for differences in parameters. A major group highly educated healthy controls were included in the study. No relations between education level or work status and pain threshold has been found in literature. However, the education level of patients visiting the outpatient pain clinic is more diffuse. When completing the chronic pain population this might be an interesting parameter to observe, since there could be argued that level of understanding of the measurements might be of influence in the outcome.

Differences in Electrical Pain Detection Threshold across healthy controls and pain patients

This study suggests a normative value of the EPDT in the lower forearm with a value around $9.6(\pm 4.2)$. The value of chronic pain patients has a mean value of $9.4(.9)$, which is approximately the same pain threshold. As a result, the included pain patients up to now, there is no difference in EPDT found compared to the healthy controls.

Stimulation was performed contralateral to the affected side, far distant from the site of pain. In patients with unilateral symptoms can therefor be clinically argued that widespread hypersensitivity could have been measured[53]. This is thought to reflect the hyperexcitability of central pathways. The range of the electrical pain threshold seems very wide, suggesting a wide variety in pain thresholds. However, in Curatolo et al. a standard deviation of 3.3 was seen as well. More patients should be included in the pain population to draw conclusions on this difference.

Furthermore, these results differ from Curatolo et al. who found a lower pain threshold of $6.1(\pm 3.3)$ mA in pain patients and a slightly higher $10.8(\pm 2.5)$ mA in healthy controls[23]. Because of the different body side used for measurements, no direct conclusions can be drawn from these differences. Nevertheless, the difference in mean pain threshold in chronic pain, compared to healthy controls is so far not visible in our results.

Differences in Electrical Pain Detection Threshold across gender, age, and BMI.

The EPDT in women was significant lower than in men in the healthy control population. This result is consistent with results of most studies of pain threshold on healthy subjects comparing different genders[97][98][99][100][101][15]. Higher pain sensitivity in women might be due to biological gender differences in ascending pain transmission pathways, descending pain modulation pathways and/or any number of psychological phenomena that affect pain[102][103][104][105]. The effect of gonadal hormones seems to be major[106][107][108][109][110], however the effect of the menstrual cycle has also been debated in literature[104]. The parameter "gender" is thereby an important factor to compensate for in analysis and in further research.

Contradictory to literature, there were no direct significant differences found for age groups and BMI[15]. However, after diving over gender, and then over age, a significant difference was seen in the healthy population for woman of <49.99 years old and >50 years old, for which the pain thresholds were $7.6(\pm 3.2)$ mA and $10.0(\pm 3.8)$ mA respectively. This difference was not found for men. Neziril et al., was one of the first studies to compare the relation of age to gender, and suggested that the decrease in sensitivity over the years in women has a bigger effect than in men[97]. Thereby could be explained that the difference in gender possibly reduces for elder patients.

The EPDT did not show any direct relation to the BMI and no significant differences between the different groups was found. In addition, when observing the results in a scatter plot, also no linear relations between any of the characteristics was visible. This is contradictory with the literature, where some researchers did found significant effects[111][112]. However, other researchers already stated that the relation between BMI and chronic pain, is not likely to be direct[113], and is body side dependent[114]. Which might explain why no correlations were observed in the data of age or BMI with the EPDT.

However, in the study of Curatolo et al., also there was limited association of demographic, psychological, and clinical characteristics with electrical tests. They eventually concluded that an explanation for that might be that the electrical modality may explore only a limited part of the complex pain experience. Which is thereby similar to the results obtained with our correlations.

Central Sensitization Inventory score

The CSI was scored and analyzed for the different factor groups. Kregel et al. showed that factor (1) had the most difference for healthy and control group[64], which is also shown in our populations. The CSI scored significant higher for the patients with chronic low back pain, compared to the healthy controls.

According the CSI scores, in the patient group, five patients with signs of CS were present. They had CSI scores of 41, 42, 53, 61 and 64, with the number of reported CSS respectively, 2, 0, 3, 2, and 4. Their origin of CLBP had gradually emerged in all cases. Their BMI's were three in groups (2), one in (3) and one in (4), and three were smokers. They were three female and male from 35-57 years old. Although four patients were identified with CS according the inventory, these CSI scores did not correlate to the EPDT. When more patients are included, it would be interesting to observe what parameters may be of influence of these differences.

CSI testing on other patient groups than in pain populations (and healthy controls) was not found. It could be questioned what the accuracy of the questionnaire is, in populations which might include different syndromes or stress periods. However, in these results, it is remarkable that the CSI did show such a high scores in the chronic pain population, compared to the healthy controls.

With a cut-off score of 40 for the CSI results, two controls showed CS, with scores of 41 and 47. The control with the score 41, did not score any of the CSS, had a mean EPDT of 7.62. The control with the score of 47, did score four of the CSS, and a mean EPDT of 4.5. Both of the scores are below the mean value of the pain threshold measured in the HC population. However until more pain patients are included, nothing can be said about the pain thresholds discriminative value.

4.4.2 Limitations

There are some points of discussion that might have influenced the results. One of the major limitations of the study is the low number of measured pain patients. Thereby conclusions cannot be drawn on the results in this population, and statistical tests on this population is not completely reliable.

The nerve stimulated by Curatolo et al. was the sural nerve[23]. Since our measurements have been executed on the innervation area of the lateral cutaneous nerve, the absolute values of the measurements cannot be compared to each other, since it is already shown that QST is body side dependent. Nevertheless, a similar difference when comparing both populations in pain threshold would have been expected. However, affecting baseline characteristics cannot be studied with the limited number of pain patients currently measured.

Since this was an explorative pilot, there was chosen for the measurement location of the forearm. In previous studies executed at the outpatient pain clinic in patients with HNP, compared to healthy subjects, the eQST measurements did show differences in measurements executed on the hand. Very low thresholds were obtained then, but there could be concluded this was because of the measurements executed on bone, instead of on muscular parts[15]. Thereby, the measurement side was moved to the m. brachialis in current study. Still, too few patients have been included in these preliminary results to compare the thresholds.

In addition to the location of the measurements, co-activation of the muscle made the measurement for a lot people uncomfortable. It can thereby be questioned whether the nociceptive threshold, or the muscle activation was measured in patients in which this occurred. It is possible that since the measurements were executed on the lower forearm, activation of the muscle, and thereby movement of the hand was experienced as uncomfortable, instead of the real activation of the nerve fibers. This would be an argument to change the location of the measurements to, for example the suprascapular region, which has also been shown to be a good measurement side[60].

Within our chronic low back population, there might be a possibility that not only hyperexcitability is measured, but hypo-excitability is a phenomenon in CLBP as well[41]. In previous studies at the outpatient pain clinic, this phenomenon has been observed. This would mean that the average pain threshold of chronic pain patient population might split in three when more patients are included. Currently, the pain population is too small to test this hypothesis, however, this might have been an influence on the results.

In addition, the patients and healthy controls were not asked to stop their medication before execution of the measurements. The intake of pain medication was reported, however the group of subjects that used daily pain medication, was too small to compare with the non-medication group. With visual observation of the data no clear differences in pain threshold were visible so far, but nothing could be said about it.

The method is a semi-objective measurement method and is depending on the subject self-report, which had possibly an influence on the results. Although instructions were very explicit to release the button when the sensation became uncomfortable, some subjects continued until the sensation became painful. Once the subject had reached the maximum value, they might have been tempted to reach this maximum again and were thereby stressing there threshold.

The feeling of “discomfort” and “pain” is different. With saying “discomfort”, the intention is that the history of pain is not measured. However, it will never be a complete objective measure.

Some subjects reached the maximum of 20 mA of the Ambustim PT and were still not reaching their limit. If there had not been a maximum, a higher value was reached, and more differences could have been made. The subjects that reached that maximum (>19.5) were excluded for further analysis for the reason that their threshold was not reached and so, their measurement “failed”.

And although previous studies showed a good test re-test variability with these measurements, it is possible that the measurement of the EPDT was influenced by mood, rush, available time, and energy level of the subject. These are some variables that are hard to measure or to collect, but since the

patient is responsible for the outcome of the measurements, the mood swings or harassment might affect the measurements.

All the healthy controls were recruited at the preoperative screening. This was chosen to overcome the bias of measuring only students or hospital employees. However, the reason for the subjects' (or their partners') visit of the hospital was not reported. The stress that might have been caused by the visit of the hospital, but could have caused a change in the results. There might have been a major surgery scheduled for the subject's partner, causing stress. Despite the fact that there was expected that people with too much stress, would not apply in the first place, this still might have been an influence.

The determination of "healthy" has shown to be difficult when recruiting healthy subjects. A lot of subjects said to be healthy and pain free. However, during analysis appeared that there were some CSS syndromes in the healthy population. It is explainable that at moment that e.g. the migraine is suppressed, the experience having a pain syndrome is suppressed as well. The researchers decided to not exclude these subjects from the population, since they were the representation of the group. Additionally, they were visually analyzed separate from the chronic pain patients as well, but no clear difference in the EPDT was found.

Not all measured patients completed the online survey and thereby information about the demographics and their CSI was missing. This is unfortunate, because their results were not useful. There might have biased the result.

There was no significant difference found between the measurements of both observers, the measurements were executed by two different observers that might have influenced the results. The instructions could have been slightly different. In addition, the placements of the electrodes could have been a fraction different. This was tried to oppose by some measurements that were executed together, and all the documentation for the measurements.

4.5 CONCLUSION

With these preliminary results of the explorative pilot study it was shown that an electrical pain detection threshold can be obtained in an healthy subject population. This EPDT is significantly different for gender, and does not seem to vary significantly for different ages, or BMI. In addition, despite different observers, measurements can be executed without significant differences in the outcome. The hypothesis to find a lower electrical pain detection threshold in chronic pain patients based on findings in Curatolo et al was not found in these preliminary results. Since the CSI has been validated on pain patients, the correlation between EPDT and CSI was expected to be low in healthy subjects. However, too few patients have been included in current study to research the differences between the populations and to take into account the affecting factors. More patients need to be included to perform further statistical testing.

5 | CONCLUSIONS

The aim of this work was to provide a monitoring process for central sensitization in chronic pain patients at the outpatient pain clinic in St. Antonius Hospital. This was done by setting up a monitoring process to measure widespread hyperalgesia with electrical quantitative sensory testing in patients visiting the outpatient pain clinic. The process was aligned with current clinical practice to create a self-standing process.

The monitoring process was validated with an explorative pilot study in CLBP patients and compared with a healthy control group. The hypothesis stated was that CS in CLBP can be detected by measuring widespread hyperalgesia determining the electrical pain detection threshold. Since widespread hyperalgesia was already shown in CLBP[17][18][19][20], the hypothesis was that the pain threshold in the pain population would be significant lower in comparison to healthy controls. In addition, these results were expected to correlate to the CSI scores.

This thesis offers a clinical monitoring process aligned with current clinical practice at the outpatient pain clinic to eventually detect and monitor central sensitization. The monitoring process has successfully been implemented at St. Antonius Hospital.

With the preliminary results of this pilot study it was shown that an electrical pain detection threshold can be obtained in an healthy subject population. This EPDT varies significantly for differences in gender, and does not seem to vary significantly for different ages, or BMI. In addition, despite different observers, measurements can be executed without significant differences in the outcome.

So far, findings similar to Curatolo et al. were not found in these preliminary results. Also, no correlation with the CSI has been found. However still too few pain patients have been included in current study to research the differences between the populations and to take into account the affecting factors. Subsequently, it is too early to draw conclusions from these preliminary results. Thereby is recommended to include more patients to evaluate the monitoring process of central sensitization.

5.0.1 Recommendations

The work presented throughout this thesis is the beginning of the determination of the monitoring of CS in chronic pain patients with electrocutaneous stimulation.

Evaluation of this process pointed out as the most important evaluation points that the inclusion rate could be enlarged by executing the measurement in the waiting time of the patients. Additionally, the measurements could be simplified by automating the input of the results to the computer.

An important consideration could be, whether measurements should be moved towards the suprascapular nerve to prevent the uncomfortable sensation co-activation of the muscle. The first step would be to complete the inclusion of CLBP patients in the pain population. As mentioned in the design Chapter 3, once the cut off bounds for signs of CS could be obtained, the correlation of the pain thresholds with baseline characteristics and CSI could be studied.

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A | APPENDICES

A.1 DUTCH INSTRUCTIONS

We gaan zo dadelijk bij u een pijndrempelonderzoek uitvoeren, het is niet de bedoeling dat dit u pijn zal doen. Ik plak deze twee stickers op de bovenkant van uw onderarm. Daarna geef ik dit apparaat aan u. U mag dan, zodra ik dat aangeef, deze rode knop indrukken en ingedrukt houden. Wanneer u dit doet zal er een stroompje gaan lopen en deze zal steeds iets oplopen. Dit zal u een beetje een vreemd, tintelend gevoel geven; een beetje alsof uw arm slaapt. Wanneer u het gevoel als eerst als vervelend ervaart, dus niet pijnlijk of ondraaglijk, maar vervelend, dan laat u de knop los en kan ik de waarde aflezen. U mag dit eerst een keer oefenen om het gevoel te ervaren dat het geeft. Daarna zullen we de meting drie keer uitvoeren.

ECG elektroden opplakken en proefpersoon het apparaat overhandigen.

Nogmaals herhalen: Belangrijk is dat dit niet pijnlijk of ondraaglijk word, maar loslaat als het gevoel voor u voor het eerst vervelend wordt.

A.2 PIECHARTS DEMOGRAPHIC DIFFERENCES IN EDUCATION LEVEL AND WORKING STATUS.

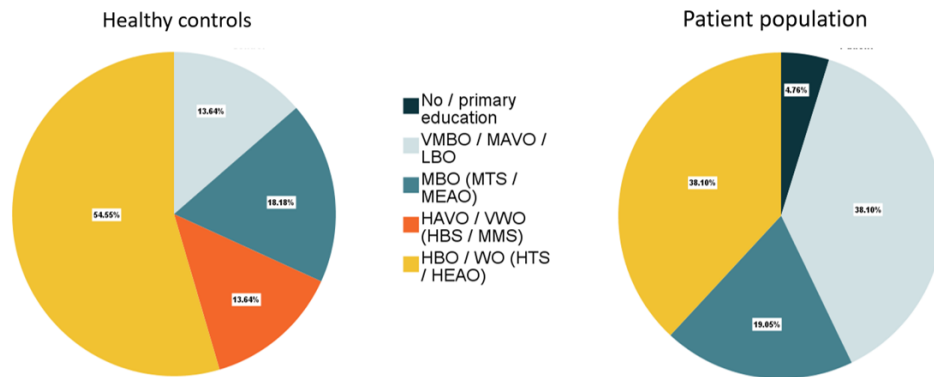


Figure A.1: Educationlevel

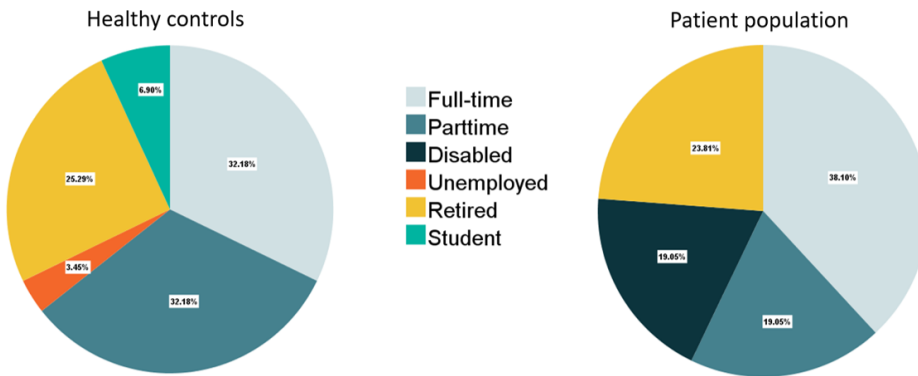
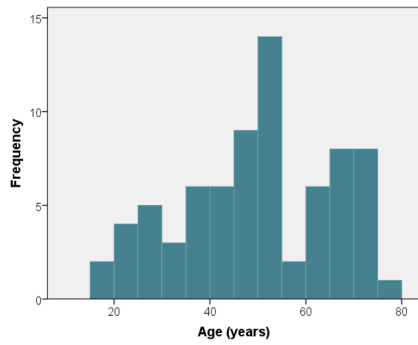
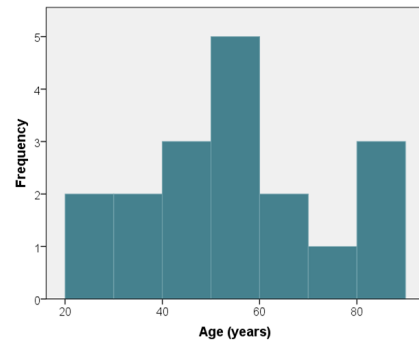


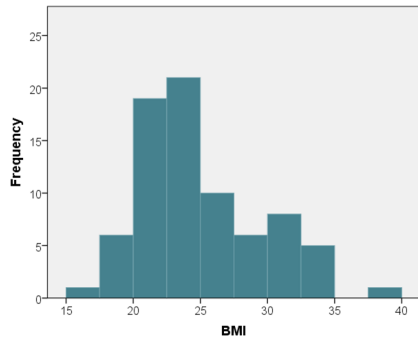
Figure A.2: Workingstatus



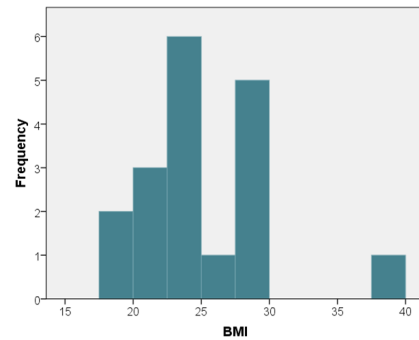
(a) Histogram of the age distribution in HC



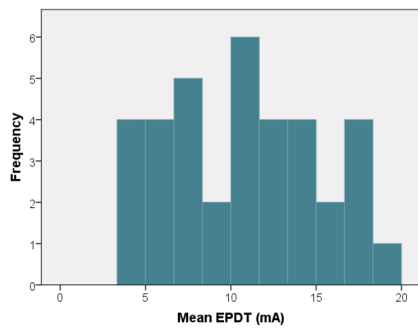
(b) Histogram of the age distribution in PP



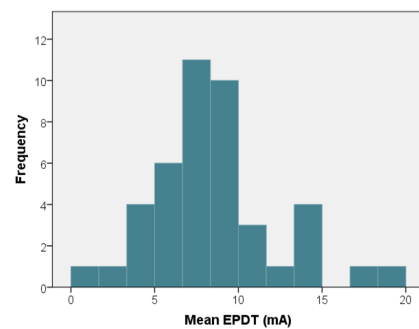
(c) Histogram of the BMI distribution in HC



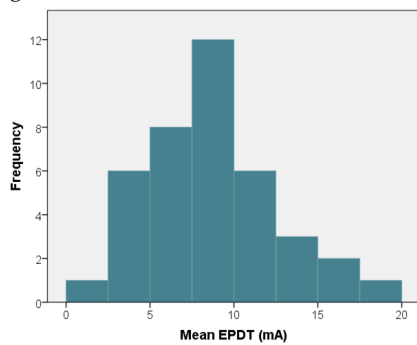
(d) Histogram of the BMI distribution in PP



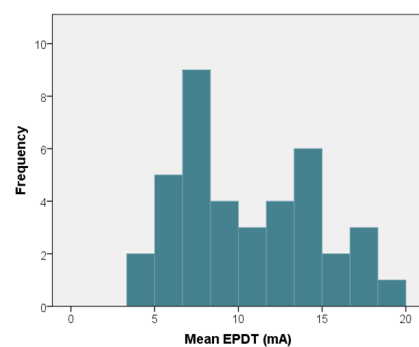
(e) Histogram of the EPDT in men HC



(f) Histogram of the EPDT in women HC



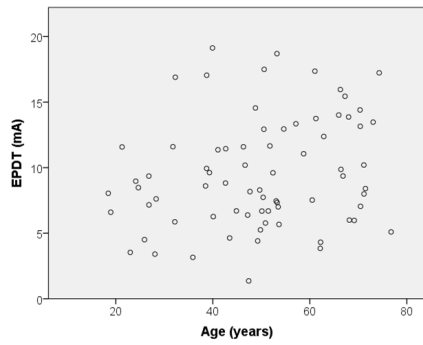
(g) Histogram of the EPDT HC with age <49.99



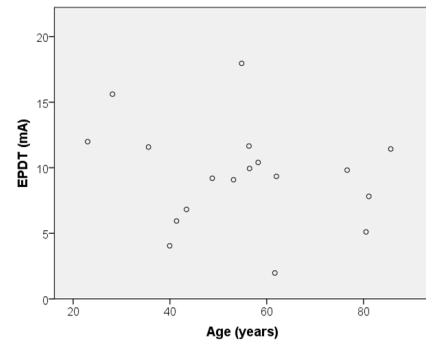
(h) Histogram of the BMI distribution in PP

Figure A.3: Histogram of the EPDT HC with age >50

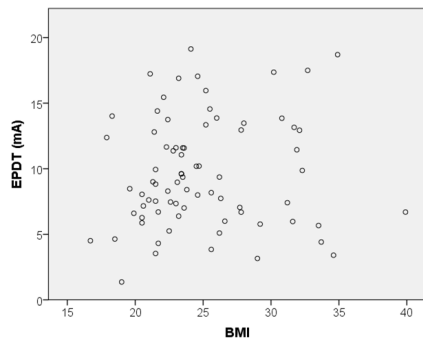
A.3 SCATTERPLOTS OF THE RELATION BETWEEN EPDT AND AGE AND BMI



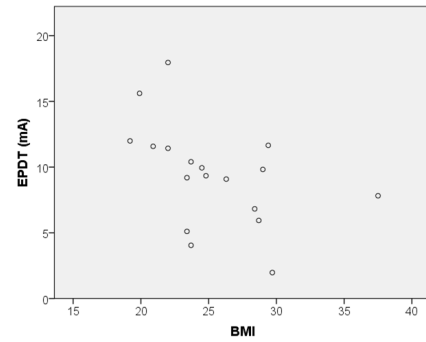
(a) Scatter of the EPDT in relation to the age in HC



(b) Scatter of the EPDT in relation to the age in PP



(c) Scatter of the EPDT in relation to the BMI in HC



(d) Scatter of the EPDT in relation to the BMI in PP

Figure A.4: Scatterplots of Age and BMI, showing no clear correlation for any of the parameters.

Deel A:**Geef aan in welke mate u de volgende klachten heeft.**

Ik voel me niet uitgeslapen 's morgens als ik wakker word

- ☐ Nooit
☐ Zelden
☐ Soms
☐ Vaak
☐ Altijd

Mijn spieren voelen stijf en pijnlijk

- ☐ Nooit
☐ Zelden
☐ Soms
☐ Vaak
☐ Altijd

Ik heb angstaanvallen

- ☐ Nooit
☐ Zelden
☐ Soms
☐ Vaak
☐ Altijd

Ik knars of klem met mijn tanden

- ☐ Nooit
☐ Zelden
☐ Soms
☐ Vaak
☐ Altijd

Ik heb last van diarree en/of constipatie

- ☐ Nooit
☐ Zelden
☐ Soms
☐ Vaak
☐ Altijd

Ik heb hulp nodig bij het uitvoeren van dagelijkse activiteiten

- ☐ Nooit
☐ Zelden
☐ Soms
☐ Vaak
☐ Altijd

Ik ben gevoelig voor fel licht

- ☐ Nooit
☐ Zelden
☐ Soms
☐ Vaak
☐ Altijd

Ik ben snel moe bij fysieke activiteiten

- ☐ Nooit
☐ Zelden
☐ Soms
☐ Vaak
☐ Altijd

Ik heb pijn over mijn gehele lichaam

- ☐ Nooit
- ☐ Zelden
- ☐ Soms
- ☐ Vaak
- ☐ Altijd

Ik heb last van hoofdpijn

- ☐ Nooit
- ☐ Zelden
- ☐ Soms
- ☐ Vaak
- ☐ Altijd

Ik heb een ongemakkelijk gevoel in mijn blaas en/of
branderig gevoel bij het plassen

- ☐ Nooit
- ☐ Zelden
- ☐ Soms
- ☐ Vaak
- ☐ Altijd

Ik slaap niet goed

- ☐ Nooit
- ☐ Zelden
- ☐ Soms
- ☐ Vaak
- ☐ Altijd

Ik kan me moeilijk concentreren

- ☐ Nooit
- ☐ Zelden
- ☐ Soms
- ☐ Vaak
- ☐ Altijd

Ik heb huidproblemen zoals droge huid, jeuk of
huiduitslag

- ☐ Nooit
- ☐ Zelden
- ☐ Soms
- ☐ Vaak
- ☐ Altijd

Stress verergert mijn lichamelijke klachten

- ☐ Nooit
- ☐ Zelden
- ☐ Soms
- ☐ Vaak
- ☐ Altijd

Ik voel me neerslachtig of depressief

- ☐ Nooit
- ☐ Zelden
- ☐ Soms
- ☐ Vaak
- ☐ Altijd

Ik heb weinig energie

- ☐ Nooit
- ☐ Zelden
- ☐ Soms
- ☐ Vaak
- ☐ Altijd

Ik heb spierspanning in mijn nek en schouders

- ☐ Nooit
- ☐ Zelden
- ☐ Soms
- ☐ Vaak
- ☐ Altijd

- | | |
|---|---|
| Ik heb pijn in mijn kaak | <input type="radio"/> Nooit
<input type="radio"/> Zelden
<input type="radio"/> Soms
<input type="radio"/> Vaak
<input type="radio"/> Altijd |
| Bepaalde geuren, zoals parfums, maken me duizelig en misselijk | <input type="radio"/> Nooit
<input type="radio"/> Zelden
<input type="radio"/> Soms
<input type="radio"/> Vaak
<input type="radio"/> Altijd |
| Ik moet vaak plassen | <input type="radio"/> Nooit
<input type="radio"/> Zelden
<input type="radio"/> Soms
<input type="radio"/> Vaak
<input type="radio"/> Altijd |
| Mijn benen voelen ongemakkelijk en rusteloos wanneer ik 's avonds wil gaan slapen | <input type="radio"/> Nooit
<input type="radio"/> Zelden
<input type="radio"/> Soms
<input type="radio"/> Vaak
<input type="radio"/> Altijd |
| Ik heb moeite om dingen te onthouden | <input type="radio"/> Nooit
<input type="radio"/> Zelden
<input type="radio"/> Soms
<input type="radio"/> Vaak
<input type="radio"/> Altijd |
| Als kind heb ik traumatische gebeurtenissen meegemaakt | <input type="radio"/> Nooit
<input type="radio"/> Zelden
<input type="radio"/> Soms
<input type="radio"/> Vaak
<input type="radio"/> Altijd |
| Ik heb pijn in mijn bekkenregio | <input type="radio"/> Nooit
<input type="radio"/> Zelden
<input type="radio"/> Soms
<input type="radio"/> Vaak
<input type="radio"/> Altijd |

Deel B:

Zijn er door een arts in het verleden bij u één van de volgende aandoening gediagnosticeerd?
Vink het vakje aan voor welke diagnose en schrijf het jaar van de diagnose indien van toepassing.

- | | |
|--|---|
| Restless legs syndrome (rusteloze benen) | <input type="radio"/> Ja
<input type="radio"/> Nee |
| Jaar diagnose | _____ |
| Chronische vermoeidheidssyndroom | <input type="radio"/> Ja
<input type="radio"/> Nee |
| Jaar diagnose | _____ |
| Fibromyalgie | <input type="radio"/> Ja
<input type="radio"/> Nee |

Jaar diagnose	<hr/>
Kaakklachten	<input type="radio"/> Ja <input type="radio"/> Nee
Jaar diagnose	<hr/>
Migraine of spanningshoofdpijn	<input type="radio"/> Ja <input type="radio"/> Nee
Jaar diagnose	<hr/>
Prikkelbare darm syndroom	<input type="radio"/> Ja <input type="radio"/> Nee
Jaar diagnose	<hr/>
Overgevoeligheid voor chemische stoffen	<input type="radio"/> Ja <input type="radio"/> Nee
Jaar diagnose	<hr/>
Nekletsel (inclusief whiplash)	<input type="radio"/> Ja <input type="radio"/> Nee
Jaar diagnose	<hr/>
Angst- of paniekaanvallen	<input type="radio"/> Ja <input type="radio"/> Nee
Jaar diagnose	<hr/>
Depressie	<input type="radio"/> Ja <input type="radio"/> Nee
Jaar diagnose	<hr/>

eQST metingen

Onderzoeksnummer _____

Pijn over 24hr voor meting

Scoor uw pijn met een cijfer dat het best de gemiddelde pijn van de afgelopen 24 uur omschrijft _____

(waarin 0 helemaal geen pijn is en 10 de allerergste pijn ooit)

Scoor uw pijn met een cijfer dat het best de ergste pijn van de afgelopen 24 uur omschrijft _____

(waarin 0 helemaal geen pijn is en 10 de allerergste pijn ooit)

Scoor uw pijn met een cijfer dat het best de minste pijn van de afgelopen 24 uur omschrijft _____

(waarin 0 helemaal geen pijn is en 10 de allerergste pijn ooit)

Pijn op het moment vóór de meting

Scoor uw pijn met een cijfer dat het best pijn van dit moment voorafgaand aan de meting omschrijft _____

(waarin 0 helemaal geen pijn is en 10 de allerergste pijn ooit)

Pijnlijke zijde

☐ Links
☐ Rechts

eQST metingen

Meting 1 (mA) _____

Meting 2 (mA) _____

Meting 3 (mA) _____

Gemiddelde

Gemiddelde (mA) _____

Overige opmerkingen

Dominante hand

- ☐ Links
- ☐ Rechts

Meting uitgevoerd op

- ☐ Links
- ☐ Rechts

Opmerkingen
