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Improving the clinical assessment of pain processes in pediatric patients with chronic musculoskeletal pain

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ABSTRACT

Chronic pain is common affecting 11-38% of children and adolescents with musculoskeletal (MSK) pain being one of the most common types of pain. In the pediatric population, pain is much more complex due to different factors that come into play as they grow into adults. Understanding chronic pain in youth is crucial because about 20% of children and adolescents living with chronic pain, have persistent pain in adulthood. The adequate assessment of pain offers a first step to better understand and improve the management of it. Several tools and approaches have been developed and validated for the study of mechanisms involved in pediatric chronic pain such as self-reported questionnaires, quantitative sensory testing (QST) and neuroimaging.

Pain assessment in youth is an inferential process in which all information should be taken into account. To address this problem, this project was developed better understand chronic pain in youth to improve the clinical assessment of pain processes in youth with chronic musculoskeletal pain. The main aims were to 1) identify psychosocial and psychophysical profiles in a population of pediatric patients with chronic pain, and 2) investigate distinct electroencephalographic characteristics underlying acute or chronic pain.

Using a combination of self-reported questionnaires, and static and dynamic QST, we demonstrated that clinically relevant subgroups pertaining to their psychosocial characteristics, somatosensory function and/or pain modulatory responses can be identified in three different samples of youth with chronic pain. Moreover, using a dry electroencephalography headset, we observed differential changes in brain activity during rest and tonic painful stimuli in youth with chronic MSK pain.

The work in this thesis provides evidence that children and adolescents have their own way of integrating and experiencing pain, and distinct subgroups of patients with chronic MSK pain can be identified in a clinical context. Moreover, the underlying pain mechanisms characterizing these subgroups can be targeted and may ultimately contribute to personalized therapy.

RÉSUMÉ

La douleur chronique touche 11 à 38 % des enfants et des adolescents, dont la douleur musculosquelettique étant l'un des types de douleur les plus courants. Dans la population pédiatrique, la douleur est beaucoup plus complexe en raison de différents facteurs de développement. Comprendre la douleur chronique chez les jeunes est important, car environ 20% des enfants et adolescents aux prises avec de la douleur chronique continuent de souffrir à l'âge adulte. L'évaluation adéquate de la douleur offre une première étape pour mieux la comprendre et améliorer sa gestion. Plusieurs outils et approches ont été développés et validés pour l'étude des mécanismes impliqués dans la douleur chronique pédiatrique tels que les questionnaires auto-administrés, les tests sensoriels quantitatifs (TSQ) et la neuroimagerie.

L'évaluation de la douleur chez les jeunes est un processus inférentiel dans lequel toutes les informations doivent être prises en compte. Pour résoudre ce problème, ce projet a été développé pour mieux comprendre la douleur chronique chez les jeunes afin d'améliorer l'évaluation clinique des processus douloureux chez les jeunes souffrant de douleur chronique musculosquelettique. Les principaux objectifs étaient 1) d'identifier des profils psychosociaux et psychophysiques dans une population de patients pédiatriques souffrant de douleurs chroniques, et 2) d'étudier les caractéristiques électroencéphalographiques distinctes sous-jacentes à la douleur aiguë ou chronique.

En utilisant une combinaison de questionnaires auto-administrés et de TSQ statiques et dynamiques, nous avons démontré que des profils cliniquement pertinents basés sur les caractéristiques psychosociaux et/ou les mécanismes somatosensoriels et modulateurs de la douleur peuvent être identifiés dans trois échantillons différents de jeunes souffrant de douleurs chroniques. De plus, à l'aide d'un casque d'électroencéphalographie sèche, nous avons observé des changements différentiels dans l'activité cérébrale pendant le repos et des stimuli douloureux toniques chez les jeunes souffrant de douleurs chroniques musculosquelettiques.

Les travaux de cette thèse fournissent des preuves que les enfants et les adolescents ont leur propre façon d'intégrer et de ressentir la douleur, et différents sous-groupes de patients souffrant de douleur chronique musculosquelettique peuvent être identifié dans le contexte clinique. De plus, les mécanismes de douleur sous-jacents caractérisant ces sous-groupes peuvent être ciblés, et contribuer à une thérapie personnalisée.

ACKNOWLEDGEMENTS

I would like to begin by thanking the Louise & Alan Edwards Foundation's Edwards Ph.D. Studentships in Pain Research 2019 for awarding me funding throughout my doctoral degree. I would also like to thank the McGill University Health Centre Research Institute – Desjardins Studentship in Child Research and the Fonds de recherche du Québec – Santé for awarding me funding during my first year of my master's degree prior to fast tracking into the Ph.D. program. These awards have given me the motivation that my research project is significant in contributing to original knowledge in the field of pediatric pain research.

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This dissertation is dedicated to all children and adolescents. To all children and adolescents with chronic pain that deserve proper pain management. To all pain-free children and adolescents that deserve the protection and prevention from the development of chronic pain. To everyone that needs to understand the impact of children and adolescents on our society.

For my parents;

Words cannot describe how grateful I am

for the sacrifices you have made to give me

a better life. Thank you and I love you

from the bottom of my heart

"Let me tell you the secret that has led me to my goal. My strength lies solely in my tenacity."

Louis Pasteur

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CONTRIBUTION TO ORIGINAL KNOWLEDGE

The results contained in this thesis emphasize that children and adolescents have their own way of integrating and experiencing pain, and distinct subgroups of patients with chronic MSK pain can be identified in a clinical context. To our current knowledge, the results contained in this thesis are some of the first to identify distinct subgroups in large samples of youth experiencing chronic musculoskeletal pain in regard to their psychosocial characteristics, somatosensory function and pain modulatory responses, building on prior studies in adults including only QST, and adult and pediatric studies including only pain descriptors and psychological symptoms. Moreover, this thesis includes one of the first studies investigating EEG findings in a large sample size of children and adolescents with chronic MSK pain and pain-free controls. Original findings contribute to the knowledge base and the discussion surrounding the improvement of the clinical assessment of pain processes in youth.

CONTRIBUTION OF AUTHORS

The entirety of the thesis was reviewed by Dr. Catherine E Ferland and they were involved in developing the methodology for this project as well.

I completed the writing and redaction of the following sections:

- Abstracts
- Introduction
- Chapter 1: Comprehensive review of the literature
- Chapter 2: Rationale, objectives, and hypothesis
- Chapter 4: Discussion
- Chapter 5: Conclusion

The articles in Chapter 3 were completed with the help of co-authors, as detailed below:

- Article 1 was written by me and was co-authored by Allison Loewen and Shajenth Premachandran for their participation in data analysis and manuscript review, by Dr. Pablo M. Ingelmo for their expertise in pediatric chronic pain, by Dr. Neil Saran and Dr. Jean A. Ouellet for their patients and their expertise in spine pathologies and back pain, and by Dr. Catherine E. Ferland who oversaw all parts of the project.
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INTRODUCTION

Pain is one of the common reasons patients visit their general practitioner [1] and is defined as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” [2]. Acute pain, which is felt suddenly and sharply, plays a protective role by making us aware of harmful events and protecting the body from permanent damage. Acute pain can occur in many circumstances such as surgery, trauma, or muscle strain, and, in most cases, disappears when the underlying cause of pain has been treated or has healed. However, when pain lasts for longer than three months or past the time of normal tissue healing, acute pain transitions into chronic pain. Chronic pain does not only have physical effects, but emotional effects as well such as depression and anxiety. Although there has been a lot of advancement in chronic pain management in the past decades, there are still numerous questions unanswered. The major aim of research groups studying chronic pain is to unveil the underlying mechanisms which are at the root of the genesis and maintenance of chronic pain and may become potential targets for pain treatment. However, chronic pain is a dynamic phenomenon, such that it is multidimensional. The transition from acute to chronic pain may include alterations in sensory pain processing and psychosocial processes which promote the development of chronic pain. Moreover, demographic factors (e.g., age and gender) and medical factors may further modulate these changes [3].

Chronic pain is common, affecting 11-38% of children and adolescents with musculoskeletal pain being one of the most common types of pain [4, 5]. Youth with chronic pain also may experience functional disability, higher rates of missed school, poor sleep quality and mental health problems [6-8]. Understanding chronic pain in children and adolescents is crucial because about 20% of them living with chronic pain, have persistent pain in adulthood [9-12]. In

the pediatric population, there are many factors (physiological, psychological, behavioral, and developmental) that come into play as they grow into adults [13-15]. Accurate pain measurements in children are difficult to achieve as the full pain experience and narrative cannot be measured [16].

In the clinic, face-to-face interviews and questionnaires are the standardized clinical way to assess the patient's history on pain experience and their perception of it. Clinicians currently lack the tools to physically examine and objectively examine pain processes underlying the development of chronic pain. The adequate assessment of pain offers a first step to better understand pain and improve the management of it. As such, several approaches have been developed for the study of peripheral and central mechanisms involved in chronic pain such as quantitative sensory testing and neuroimaging.

Pain assessment in children and adolescents is an inferential process in which all information should be taken into account [17]. To address this problem, this project was developed to provide evidence that children and adolescents have their own way of integrating and experiencing pain, and distinct subgroups of patients with chronic MSK pain can be identified in a clinical context.

In the first chapter, a review of the literature is presented. The second chapter presents the rationale, objective, and hypotheses of this thesis. The third chapter presents four research studies that were performed to achieve the proposed objectives of this thesis. The fourth chapter discusses the findings of these studies and their limitations. In the final chapter, the conclusions of this thesis are presented.

CHAPTER 1 COMPREHENSIVE REVIEW OF THE LITERATURE

1.1 Pathophysiology of chronic pain

According to the International Association for the Study of Pain (IASP), pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [2] and is expanded upon by the addition of six key notes and the etymology of the word pain for further context:

- "Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors."
- "Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons."
- "Through their life experiences, individuals learn the concept of pain."
- "A person's report of an experience as pain should be respected."
- "Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being."
- "Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain" [2].

When pain "lasts or recurs for longer than 3 months", it is called chronic pain [18]. Chronic pain is difficult to treat due to the complexity of many potential pain mechanisms involved and the evolution of the disease over time. Furthermore, in the pediatric population, there are many internal and external factors proposed to play a role in the genesis and maintenance of chronic pain such as individual predisposition (age, gender, sex, genetics, etc.), environmental factors (history of previous pain, abuse, stress, poor access to health care, etc.), and psychological factors (anxiety,

depression, catastrophizing, sleep quality, etc.) [13-15, 19-22]. An epidemiological summary of 42 pediatric studies conducted by King et al. (2011) brought to light the prevalence rate of chronic pain in youth ranging from 8-83% for headaches, 4-53% for abdominal pain, 14-24% for back pain, 4-40% for musculoskeletal pain, 4-49% for multiple pains, and 5-88% for other pains [4]. Moreover, chronic pain in children has an important impact on their daily life which may result in increased missed school days, poor sleep quality, poor school performance, and decreased social activities [23-29]. Therefore, more attention is required into understanding the underlying mechanisms leading to the genesis and maintenance of chronic pain in childhood and adolescence.

To understand chronic pain in children and adolescents, it is best to follow the nociceptive signal pathway of the somatosensory system from the periphery to the brain, emphasizing on the integration and modulation of the nociceptive signal at different steps in the central nervous system. The somatosensory system is the network of neural structures in the brain and body that processes information about, and represent, several sensations, such as pain, temperature, touch, position, and movement. Nociception, the neural process of encoding noxious (i.e., painful) stimuli, occurs through four main steps: transduction, transmission, modulation, and perception.

1.1.1 Nociceptive transduction

Transduction is the first step in processing pain and is referred to the "conversion of a noxious stimuli (thermal, mechanical, or chemical) into electrical activity in the peripheral terminals of nociceptor sensory fibers" [30]. It starts with nociceptors, which are free nerve endings of peripheral afferent neurons that are activated by noxious stimuli. Nociceptors can be found in many organs in the periphery, including the skin, joints, and muscles. These specialized sensory receptors can be further subclassed into three main classes: thermal, mechanical and polymodal nociceptors which are widely distributed in skin and deep tissues and are often coactivated [31].

A fourth class of nociceptors are found in the viscera: the silent nociceptors. They are not normally activated by noxious stimuli, but their firing threshold can be reduced by inflammation and various chemical agents. Their activation after tissue injury implicates them in the development and maintenance of hyperalgesia or hypersensitivity which will be described below [31, 32]. Thermal nociceptors are activated by extreme temperatures (greater than 40-45°C or less than 5°C), mechanical nociceptors are activated by intense pressure applied to the skin (noxious pinching, probing with sharp objects, and squeezing), and polymodal nociceptors are activated by high-intensity mechanical, chemical, or thermal (both hot and cold) stimuli. The action potentials are generated by receptors on the membrane of the nociceptors through the conversion of thermal, mechanical or chemical energy of the noxious stimulus into a depolarizing electrical potential [20].

Nociceptor messages are mainly transmitted by two classes of afferent fibers: Aδ and C fibers. The peripheral endings of small-diameter (1-5 μm), thinly myelinated Aδ fibers are mainly thermal and mechanical nociceptors with rapid conduction velocity (5-30 meters per second) involved in transmitting fast sharp pain. In contrast, the peripheral endings of small-diameter (0.2-1.5 μm) unmyelinated C fibers are mainly polymodal nociceptors with slow conducting velocity (0.5-2 meters per second), and therefore involved in slow dull aching pain [19, 20]. The conduction velocity differences between the Aδ and C fibers can be fully understood when isolating the sensation of first and second pain (Figure 1-1). Upon painful stimulation, a first brief, pinprick-like sensation is perceived and well-localized. Following this activity, a second longer-lasting, less-localized, deep dull and aching pain sensation is perceived [31].

A third class of afferent fibers can be found in the periphery: the Aβ fibers. They are large-diameter (6-12 μm) myelinated fibers with rapid conduction velocity (35-75 meters per second) involved in detecting non-nociceptive input, such as vibration, movement, or light touch [20].

However, other than conducting non-nociceptive input, Aβ fibers can play a dynamic inhibitory role by recruiting inhibitory interneurons at the spinal level which will inhibit nociceptive input at the same spinal level, a fundamental component of the gate-control theory [33]. Aβ fibers also seem to play a role in the tonic inhibition of nociceptive input, such that blocking Aβ fibers input will result in an increased response to nociceptive stimuli.

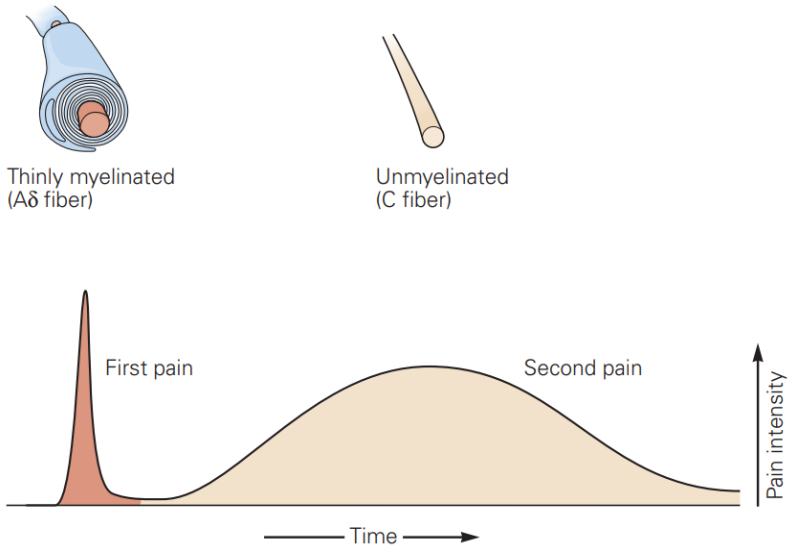

Figure 1-1. First and second pain carried by two different peripheral afferent fibers. Following a brief painful stimulation, the Aδ fibers will rapidly transmit a brief pinprick-like sensation perceived precisely at the point of the stimulation. This activity is followed by C fibers transmitting their information with a relatively long delay resulting in a more diffuse deep pain sensation. Image taken from *Pain. Principles of Neural Science,* Fifth Edition. New York, NY, McGraw-Hill Education. 2014, p.531.

Uncontrolled changes in nociceptor activity are associated with several pathological conditions, such as hyperalgesia and allodynia. In response to an injury or tissue damage, nociceptors can further activate more nociceptors through the release of several pro-nociceptive chemicals (e.g., histamine, bradykinin, acetylcholine, serotonin, and substance P). Hyperactivity of these nociceptors can lead to a phenomenon called hyperalgesia, resulting in an increase in pain sensitivity (i.e. “increased pain from a stimulus that normally provokes pain”) (Figure 1-2) [20, 31, 34, 35]. These sensitized nociceptors will generate an increased number of action potentials to be transmitted to the brain and interpreted as more intense pain [19, 20]. Sensitized nociceptors associated with an overexpression of pro-nociceptive chemicals can lead to pathological spontaneous discharges and a lowered activation threshold for thermal (heat and cold) and mechanical stimuli which is a phenomenon called peripheral sensitization [35]. Peripheral sensitization may persist for prolonged periods past the healing process of an injury or tissue damage and has an important effect on chronic pain. If pain is perceived from normally non-noxious stimuli, a phenomenon called allodynia is reported. In contrast to hyperalgesia, allodynia requires a stimulus to be observed (i.e., not spontaneous).

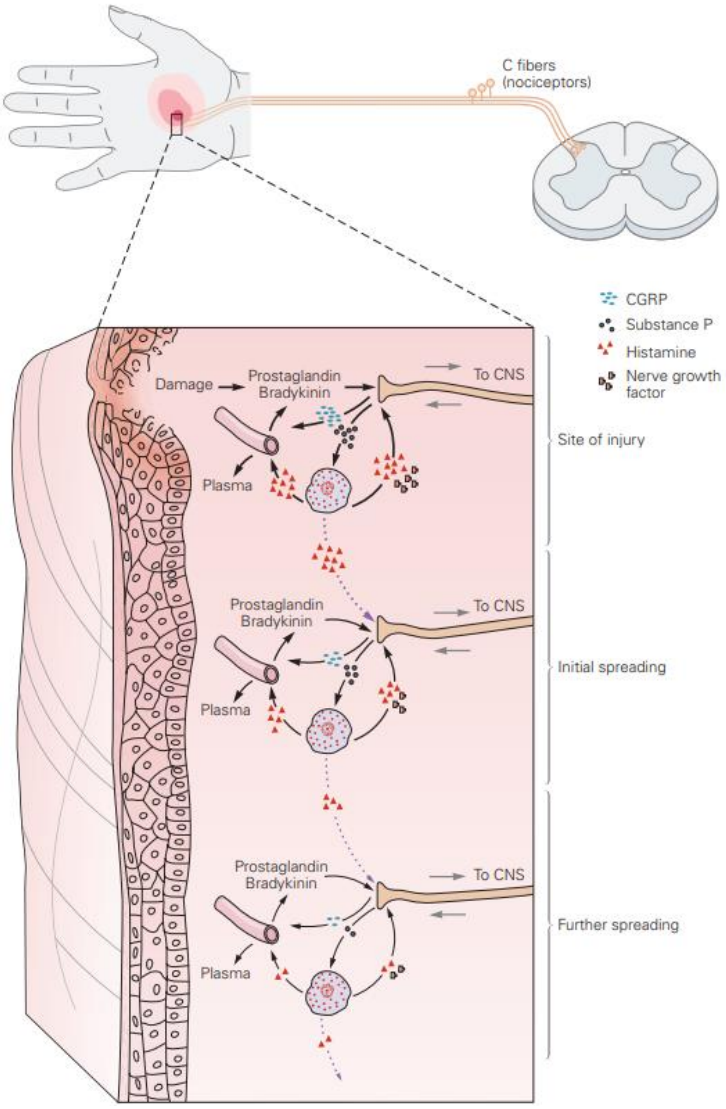

Figure 1-2. Hyperalgesia.

Injury or tissue damage can lead to the release of pro-nociceptive chemicals which sensitize nociceptors and further activates them to release pro-nociceptive chemicals. This mechanism can occur in surrounding healthy tissue causing and spreading hyperalgesia. Image taken from *Pain. Principles of Neural Science,* Fifth Edition. New York, NY, McGraw-Hill Education. 2014, p.540.

1.1.2 Nociceptive transmission

Transmission is referred as “the passage of action potentials from the peripheral terminal along axons to the central terminal of nociceptors in the central nervous system” [30]. Transmission first occurs when the nociceptive action potential is conveyed from the peripheral afferent neurons (first order neurons) to distinct sensory modalities in different laminae of the dorsal horn of the spinal cord (Figure 1-3) [31]. Lamina I contain neurons that respond to Aδ fibers and C fibers which then project towards the thalamus and are called nociception-specific neurons. Another class of lamina I neurons receives input from C fibers that are activated distinctively by intense cold. Other classes of lamina I neurons respond to both innocuous and noxious mechanical stimulation and are called wide-dynamic-range neurons. Aδ fibers and C fibers can also project inputs to lamina II, the substancia gelatinosa, which contains different classes of interneurons that can either be excitatory or inhibitory, and indirectly convey the noxious signal to the thalamus via their dendrites extending to lamina I. Lamina III and IV contain a variety of local interneurons and projection neurons which receive input mainly from Aβ fibers that respond to non-noxious stimuli such as light touch and pressure. Lamina V contains neurons that receive inputs from Aβ, Aδ, and C fibers, but also from nociceptors in visceral tissues [31]. Lamina VI contains neurons that receive input from large-diameter fibers that innervate muscles and joints which are activated by innocuous joint movement. Lamina VII and VIII, the intermediate and ventral regions of the spinal cord, contain neurons that respond to noxious stimuli and have complex response properties, since the nociceptive information are conveyed through many intervening synapses. The neurons in lamina VII are mainly responsive to stimulations from both sides of the body, unlike most unilateral dorsal horn neurons, and are therefore thought to be involved in the diffuse aspect of many pain conditions.

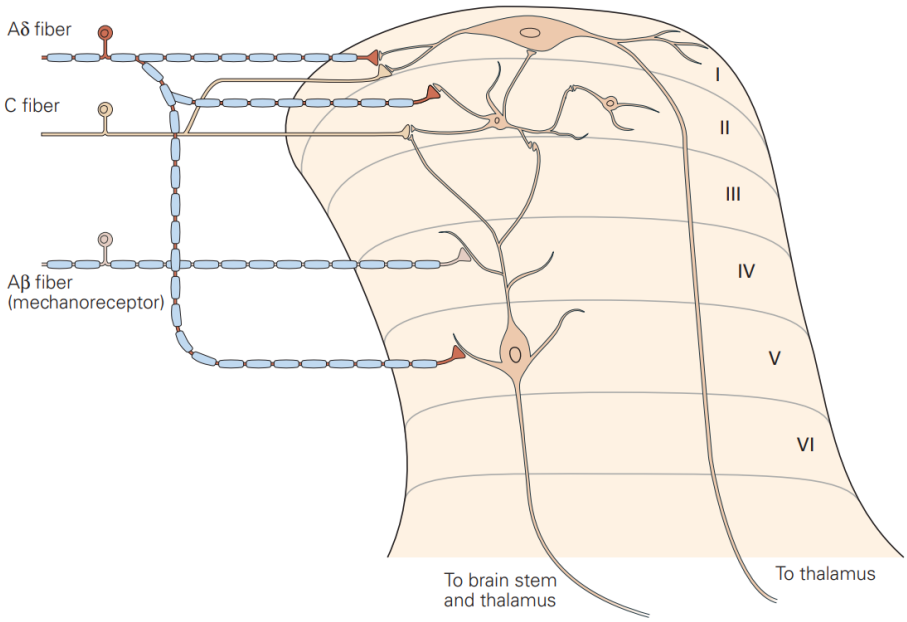

Figure 1-3. Nociceptive fibers terminate in different laminae of the dorsal horn of the spinal cord.

Neurons in specific lamina of the dorsal horn receive direct and/or indirect input via interneurons from other lamina to further relay the information to upper levels. *Principles of Neural Science,* Fifth Edition. New York, NY, McGraw-Hill Education. 2014, p.534.

The convergence of nociceptive inputs from adjacent body regions supplied by the same single spinal nerve onto to the same neurons of the dorsal horn of the spinal cord can lead to a phenomenon called referred pain, in which an injury in one area of the body is perceived in a neighbouring region of the body (e.g., lower back injury/pain perceived in the thighs). This phenomenon occurs due to an individual lamina neuron receiving input from two adjacent tissues, and the nociceptive signal from the neurons of the dorsal horn of the spinal cord does not inform superior centers of the central nervous system of the source of the input [31].

Sensitization can also occur at the spinal level through the repeated recruitment of C fibers after injury or tissue damage leading to a phenomenon called central sensitization. Central sensitization is defined as increased excitability and spontaneous discharge at the dorsal horn neurons. These changes in the spinal cord mainly occur in the wide-dynamic range neurons which,

when sensitized, gives a large response to both nociceptive (i.e. hyperalgesia) and tactile input which is interpreted as a painful signal (i.e., allodynia) [19, 20, 31]. Like peripheral sensitization, central sensitization may persist for prolonged periods past the healing process of an injury or tissue damage and has an important effect on chronic pain.

The neurons from the dorsal horn further send the nociceptive impulse to superior centers by five major ascending pathways all contributing to the central processing of pain: the spinothalamic, spinoreticular, spinomesencephalic, cervicothalamic, and spinohypothalamic tracts (Figure 1-4) [20, 31]. These tracts connecting to superior centers of the central nervous system further project to the somatosensory cortex for interpretation and to other brain areas for an integrated response to the noxious stimuli.

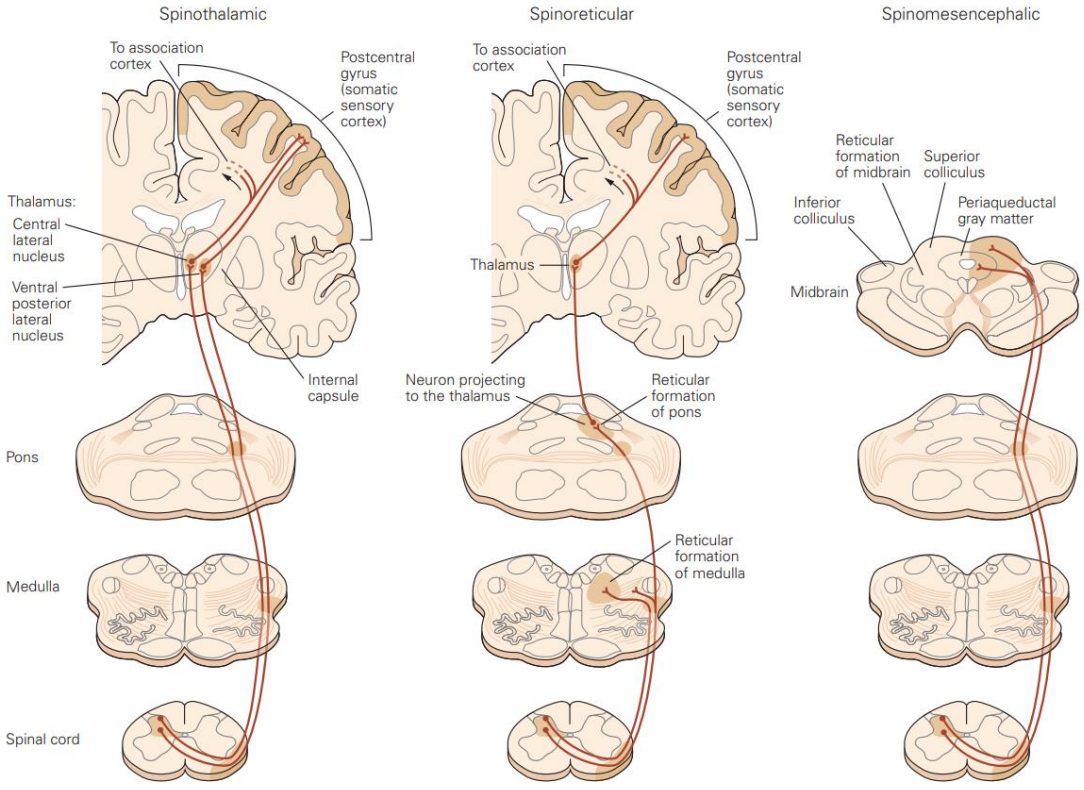

Figure 1-4. Three of the five ascending pathways of pain.
The spinothalamic, spinoreticular and spinomesencephalic tracts. Image taken from *Pain. Principles of Neural Science,* Fifth Edition. New York, NY, McGraw-Hill Education. 2014, p.534.

The most prominent ascending nociceptive pathway in the spinal cord is the spinothalamic tract which includes the axons of nociception-specific, thermosensitive, and wide-dynamic-range neurons from laminae I and V of the dorsal horn. At their spinal segment of origin, these axons cross the midline of the spinal cord and ascend the anterolateral white matter then terminate in the thalamic nuclei. The spinothalamic tract plays an important role in the transmission of the nociceptive impulse, such that electrical stimulation of the tract can elicit the sensation of pain, and contrarily, lesion of this tract results in pain insensitivity on the contralateral side of the body contralateral to the lesion. The spinothalamic tract can be further divided into the neospinothalamic tract and the paleospinothalamic tract, which constitute the lateral and the anterior spinothalamic tract, respectively. The neospinothalamic tract conveys fast impulses for acute sharp pain, while the paleospinothalamic tract conveys slow impulses for dull pain [30].

The spinoreticular tract contains axons of neurons in laminae VII and VIII, and ascends in the anterolateral quadrant of the spinal cord (i.e. does not cross the midline of the spinal cord) and terminates in the reticular formation and the thalamus.

The spinomesencephalic tract contains axons of neurons in laminae I and V, and it thought to transmit nociceptive information contributing to the affective component of pain. The axons in this tract ascend in the anterolateral quadrant of the spinal cord towards the mesencephalic reticular formation, and periaqueductal gray matter. Other axons ascend through the dorsal part of the lateral funiculus towards the parabrachial nucleus, which further projects its neurons to the amygdala, an important player of the limbic system regulating emotional states.

1.1.3 Nociceptive modulation

Modulation is referred as “the alteration (e.g. augmentation or suppression) of sensory input” [30]. To date, we know that modulation of the pain stimuli can occur by either inhibition or

enhancement through supraspinal influences from the pons, medulla, and midbrain. Interneurons can be influenced by ascending pathways from the spinal cord or descending pathways from the brain [30, 36]. Supraspinal stimulation occurs via the release additional chemicals (e.g. bradykinin, substance P, nerve growth factor, histamine, serotonin, prostaglandins, acetylcholine, etc.) to decrease the threshold of nociceptor activation and therefore enhance the progression of the nociceptive impulse from peripheral to central neurons. Supraspinal inhibition occurs via the release of endogenous opiates that limit the release of neurotransmitters from peripheral neurons and hyperpolarize central neurons, so it requires greater stimulation to generate an action potential. Other inhibitory chemicals can be released at the dorsal horn of the spinal cord.

The descending inhibitory mechanism is termed the endogenous analgesia which can be investigated using the psychophysical paradigm of conditioned pain modulation (CPM), previously known as the diffuse noxious inhibitory control (DNIC) [36-38]. DNIC was first introduced by Le Bars in 1979 who observed a reduced pain response in the dorsal horn neurons of rats when noxious stimuli were applied in various parts of the body [39]. Moreover, lesion of the main descending pathway produces hyperalgesia suggesting that the descending endogenous inhibitory mechanisms plays an important role in chronic pain conditions and the reason pain persists [38, 40, 41].

1.1.4 Nociceptive perception

Perception is referred as “the decoding/interpretation of afferent input in the brain that gives rise to the individual’s specific sensory experience” [30]. There are three interactive systems involved in the perception of pain and are referred to as the “pain matrix” as revealed through neuroimaging studies [42, 43]. The sensory-discriminative system is mediated by the somatosensory cortex which is responsible for the conscious awareness of pain by identifying the

presence, type, location, and intensity of pain. The affective-motivational system is mediated by the reticular formation, limbic system, and brainstem. This system is responsible for the individual's conditioned avoidance and emotional responses to pain. The cognitive-evaluative system is mediated by the anterior cingulate cortex, the insula, and the prefrontal cortex which is responsible for the individual's learned behavior in response to pain by taking the context in which pain occurs and the attention given towards the noxious stimulus to modulate the pain experienced [44]. The integration of the three systems highlights the dynamic complexity and subjectivity of pain [30, 31, 43, 45].

1.1.5 Factors influencing pain perception

Each individual applies the term "pain" to a specific experience usually related to injury in their life, leading to different perception and expectation of pain. Therefore, there are many factors that are involved in the perception of pain, even more so in the pediatric population [46]. Childhood and adolescence are crucial periods characteristic of neurobiological and hormonal regulation associated with maturation and many other psychophysical processes [14, 47].

Age plays an important role in pain perception, as an individual's concept of pain are based on life experiences [15]. Studies have shown that older children report more pain and unpleasantness in response to acute pain than younger children [48-50]. Children between 7 to 11 years usually display more abstract thinking in their view of pain and use more vivid qualitative descriptions. Adolescents 12 years and up have a more active view in the concept of pain leading to greater awareness and capacity for introspection. Furthermore, they report to not express demands for relief and mainly sought emotional support from friends to obtain relief [51].

Sex and gender play another important role in pain perception. Females are more frequently affected by chronic pain [21, 22], but they also perceive pain differently than males [52]. Studies

have shown that hormonal changes may influence pain perception because of its minor influential role in inflammation [53, 54]. Studies have investigated whether specific phases during the menstrual cycle influence pain perception or whether menstrual cramps in girls act as a physical stressor that may alter their perception and expectation of pain, but results are still controversial and inconclusive [55]. The influence of gender on pediatric pain perception may be mainly attributed to parental influence [13, 56]. It has been established that fathers play an important role in their child's development that is unique but not entirely independent of the mother's role [57, 58]. However, there is limited data on the differential impact of mothers versus fathers on girls' versus boys' pain either within a clinical or laboratory setting. A study by Evans et al. investigated sex-specific parent-child pain associations, and observed stronger mother-daughter than mother-son relationships [59]. They suggest that girls' pain and functional disability is associated to an overly enmeshed mother-daughter relationship which promotes ongoing stress and recurrent pain. On the other hand, boys' pain and functional disability is associated to male pain behaviors and criticism, as well as maternal worry and solicitous behaviors.

Environmental factors, such as external stressors and history of previous pain, are important in pediatric pain perception. For instance, studies have shown that parental anxiety preoperatively and postoperatively influenced anxiety and pain in children and adolescents undergoing surgery postoperatively [60-62]. Moreover, the social interactions between the clinical team and the child or adolescent plays an important role in pain treatment as well [63-66]. Studies have also observed that children born prematurely, and who receive multiple painful clinical interventions, demonstrated more pain sensitivity later in life [67-69]

Finally, pain-specific cognitive and emotional processes are important in the perception of pain. Psychological factors, such as anxiety, depression, and catastrophizing, play an important

role in pediatric pain perception. Studies have shown that children who report higher levels of anxiety are more likely develop more negative pain memories, which consequently makes them more at risk of experiencing greater distress as subsequent painful experiences [70-72]. Compared to boys, studies have also shown that girls with depressive symptoms are more likely to report more pain than those without depressive symptoms [73-75]. Pain catastrophizing is a pain-specific psychosocial construct indicating the tendency of an individual to overstate negative appraisals of nociceptive stimuli and is described through 3 main constructs: magnification, rumination, and helplessness [76]. Studies have shown that pain catastrophizing in children and adolescents was associated with pain intensity [77-81]. Therefore, the treatment of pain in youth should always take psychological factors into consideration as they affect youth's reactions to a painful experience or their ability to cope with the pain.

1.2 Assessment of chronic musculoskeletal pain

Chronic musculoskeletal (MSK) pain is defined as pain located in the muscles, bones, joints, or tendons [82]. Chronic MSK pain can be primary in nature, such that the pain cannot be better accounted for by another chronic pain condition, or secondary in nature, such that the pain arises from an underlying disease classified elsewhere and are mostly caused by "persisting local or systemic inflammatory illnesses, local structural musculoskeletal changes, or diseases of the nervous system that are not musculoskeletal conditions in themselves but which may cause musculoskeletal problems" [83].

The need for careful attention to pain in children and adolescents has been highlighted by the high prevalence of pain in this population. In order to monitor population health and health system quality, a more standardized approach regarding pain assessment is needed [84]. The

assessment of psychosocial factors and the four main steps of nociception (transduction, transmission, modulation and perception) are described below in relation to pediatric chronic pain.

1.2.1 Self-reported questionnaires

In a clinical context, pain qualities and psychosocial factors can be assessed through standardized interviews or a diversity of self-reported questionnaires.

1.2.1.1 Self-reported pain

There is a diversity of "well established assessment" self-report measures of pain by children and adolescents [86, 87]. These included the 11-point numeric rating scale (NRS-11), the Color Analogue Scale (CAS), the Faces Pain Scale–Revised (FPS-R), the Oucher scales, the Pieces of Hurt/Poker Chip Tool, the Visual Analogue Scale (VAS), and the Wong-Baker FACES Pain Rating Scale. Especially for acute pain, the NRS-11, FPS-R and CAS are strongly recommended [87]. However, weak recommendations at best were made for all measures for chronic pain [87]. Other pain qualities intended to understand the pain narrative can be assessed through face-to-face interviews or self-reported questionnaires. For example, the Adolescent Pediatric Pain Tool (APPT) can assess the pain experience using a list of sixty-seven descriptive words assessing four dimensions of pain (37 sensory, 11 affective, 8 evaluative and 11 temporal descriptive words) [88]. Other self-report questionnaires have been developed to screen for neuropathic pain (i.e., pain caused by a lesion or disease of the somatosensory nervous system), which display distinct pain qualities. For example, the Neuropathic Pain Symptom Inventory [89], pain DETECT questionnaire [90] and the Douleur neuropathique en 4 questions (DN4) [91, 92] are relatively effective tools for identifying neuropathic pain.

1.2.1.2 Anxiety and depression

An example of a tool assessing anxiety and depression is the Revised Child Anxiety and Depression Scale (RCADS) questionnaire. The RCADS is a 47-item scale with subscales including separation anxiety disorder, generalized anxiety disorder, panic disorder, social phobia, obsessive compulsive disorder, and low mood (major depressive disorder). Based on the patient's age and grade in school, their total subscale scores can be calculated and compared to established cut-off scores [93]. The RCADS is not the only psychometrically sound and widely used measure of emotional distress. Other validated self-reported questionnaire such the Hospital Anxiety and Depression Scale [94, 95] or the NIH-supported Patient-Reported Outcomes Measurement Information System can be used.

1.2.1.3 Pain catastrophizing

The Pain Catastrophizing Scale for Children (PCS-C) is the most frequently completed validated self-report questionnaire that can be used to assess the degree to which children or adolescents experienced negative thoughts or feelings while experiencing pain [96]. Recently, it was shown in a pediatric surgical population that pain catastrophizing may not behave as a stable trait-like construct, further providing evidence that psychosocial factors are potentially malleable in response to proper therapeutic approaches [81]. Other measures of catastrophizing are subscales of coping measures, such as the Pain Response Inventory [97] and Pain Coping Questionnaire [98]. Although these measures describe pain-related cognition, they do not consider pain-related behavior or physiological reactions to pain [99].

1.2.1.4 Sleep quality

Children and adolescents with chronic pain commonly experience poor sleep quality [7]. Occurring during critical stages of cognitive development, poor sleep quality can have far-reaching negative consequences on pain intensity [100], functional disability [101], and symptoms of anxiety and depression [102-104]. With patients who can self-report, healthcare providers commonly assess sleep quality by administrating the Pittsburgh Sleep Quality Index (PSQI), one of the most frequently used general measures of sleep quality in clinical and research settings [105]. Another widely used questionnaire is the Epworth Sleepiness Scale [106]. However, this questionnaire mainly consists of situations where the individual assesses how likely they would fall asleep [107]. The PSQI is a 19-item questionnaire that was developed and initially validated in adults by Buysse et al. [108] and recently validated in pediatrics by Larche et al [109] to assess sleep quality over the previous month, yielding a global score that facilitates score comparison between groups or individuals over time.

1.2.2 Quantitative sensory testing

Quantitative sensory testing (QST) is defined as a psychophysical set of methods that neurologically examines the somatosensory function [110]. QST was first brought to light in the mid-1800s as a tool in experimental psychology to further understand our perception of the physical world [111, 112]. Many sophisticated quantitative sensory tests provide information on the nociceptive transduction, transmission and/or modulation from all aspects of the somatosensory system. The parameters tested include mechanical detection threshold [113], dynamic mechanical allodynia [114, 115], vibration detection threshold [116], mechanical pain threshold [117], mechanical pain sensitivity [117], temporal summation of pain [118], pressure pain threshold [119, 120], cold and warm detection thresholds [121, 122], paradoxical heat

sensations [123], and cold and heat pain thresholds [121, 124].The tests can be grouped as 1) thermal detection thresholds for the perception of cold, warm and paradoxical heat sensations, 2) thermal pain thresholds for cold and hot stimuli, 3) mechanical detection thresholds for touch and vibration, and 4) mechanical pain sensitivity including thresholds for pinprick and pressure, a stimulus-response function for pinprick sensitivity and dynamic mechanical allodynia, and pain summation to repetitive pinprick stimuli. In response to an objective sensory stimulus, either thermal or mechanical, an individual's perception and expectation of pain can be measured in a semi-objective manner [110]. Through the understanding of the pathophysiology of pain and the afferent fibers (Aβ, Aδ and C) activated by the test stimuli (mechanical or thermal), QST can aid in the evaluation of hyper- and hyposensitivity phenomena in patients (Table 1-1).

Static QST focuses on the determination of sensory threshold, or the rating of a single stimulus, and the corresponding magnitude of pain. To determine the sensitivity of a subject to the defined test stimuli, perception and pain thresholds can quantified through the "method of levels" or the "method of limits" [125]. The method of levels consists of repeatedly applying a stimulus below and then above the perception or pain thresholds. After each stimulation, the subjects are asked about the perception or painfulness of the stimulus. QST applying the method of levels include mechanical detection threshold (MDT), mechanical pain threshold (MPT), and dynamic mechanical allodynia (DMA) [50]. The method of limits consists of measuring the perception and pain thresholds as the first identified threshold under increasing stimulus intensities. QST applying the method of limits include cold detection threshold (CDT), warm detection threshold (WDT), cold pain threshold (CPT), heat pain threshold (HPT), vibration detection threshold (VDT), and pressure pain threshold (PPT). When pain allodynia or hyperalgesia is observed, excessive neural

activity is reported. In contrast, when hypoesthesia or hypoalgesia is observed, deficient neural activity is reported.

Table 1-1. Static QST and possible underlying pathophysiological pain mechanisms
Modified from Mücke et al. "Quantitative sensory testing (QST). English version." "Quantitative sensorische Testung (QST)." *Schmerz (Berlin, Germany)* vol. 35,Suppl 3 (2021): 153-160. doi:10.1007/s00482-015-0093-2

Test name	Type of test stimuli	Sensory afferents	Response to stimuli	Pain profile
Cold detection threshold	Light cold stimuli	Aβ/C	Decreased sensitivity to non-painful stimuli	Cold thermal hypoesthesia
Warm detection threshold	Light heat stimuli	Aβ/C	Decreased sensitivity to non-painful stimuli	Hot thermal hypoesthesia
Cold pain threshold	Cold thermal stimuli	Aδ/C	Decreased/Increased pain sensitivity	Cold hypo-/hyperalgesia
Heat pain threshold	Heat thermal stimuli	Aδ/C	Decreased/Increased pain sensitivity	Heat hypo-/hyperalgesia
Mechanical detection threshold	von Frey filaments	Aβ	Decreased sensitivity to non-painful stimuli	Mechanical hypoesthesia
Mechanical pain threshold	Calibrate needle stimuli	Aδ/C	Decreased/Increased pain sensitivity	Mechanical hypo-/hyperalgesia
Dynamic mechanical allodynia	Cotton wisp, cotton swab to skin brushing	Aβ	Pain in response to non-painful stimuli	Allodynia
Vibration detection threshold	Tuning fork	Aβ	Decreased sensitivity to non-painful stimuli	Mechanical/vibration hypoesthesia
Pressure pain threshold	Pressure algometer	Aδ/C	Decreased/Increased pain sensitivity	Mechanical hypo-/hyperalgesia

Dynamic QST focuses on the evaluation of pain modulation by means of the temporal and spatial summation of pain, and conditioned pain modulation (CPM) paradigms. The complex central pathways of pain processing can be indirectly assessed through the activation and measuring temporal and spatial summation, and descending modulation of pain.

Temporal summation of pain (TSP) refers to the increased perception of pain from repetitive or tonic noxious stimuli. TSP is a behavioral correlate of wind-up, a phenomenon where

spinal neurons increase their activity due to repetitive C fiber input [20, 126, 127]. TSP can be induced by using different types of test stimuli, such as heat, electrical and mechanical (pressure or pinprick) [50, 126]. Spatial summation of pain (SSP) refers to the increased perception of pain from the integration of nociceptive input from a large area [31, 128]. SSP can be induced by thermal stimuli with increasing area of stimulation [129].

The descending inhibitory pain mechanism can be investigated using the psychophysical paradigm of CPM, which is a behavioral correlate of the diffuse noxious inhibitory control (DNIC) [36-38]. In the experimental setup, CPM is tested using the concept of "pain inhibits pain", in which the intensity of a painful stimulus in one area of the body (i.e., test stimulus) is reduced by the application of a second painful stimulus in another area of the body (i.e., conditioning stimulus) (Figure 1-5) [38, 130, 131]. Assessing CPM in a clinical setting may be a valuable tool to assess any deficits in the descending inhibitory pain response [38].

Figure 1-5. Example of a conditioned pain modulation assessment.
In this experimental setup using the concept of "pain inhibits pain", the intensity of the painful cold water immersion test (conditioning stimulus) on the left forearm may reduce the intensity of the painful stimulus from the warm thermode (test stimulus). Image modified from the Shriners Hospitals for Children – Canada. Consent of the participant was taken before use.

Although QST has been used successfully in clinical settings in the various adult populations, QST is less widely used in the pediatric population. QST poses as an advantage in the

examination of all modalities of the somatosensory function in children and adolescents since it is non-invasive [50, 132-135]. There are numerous pioneer studies highlighting the feasibility of detection and pain threshold testing using different modalities in healthy children and adolescents [132, 133, 136-150]. Furthermore, loss and/or gain of function in the somatosensory system was studied in various pediatric chronic conditions such as diabetes mellitus [143], juvenile fibromyalgia [151], functional abdominal pain [152], peripheral neuropathic pain [135] and complex regional pain syndrome [142]. Although these studies established reference values for various tests, major limitations include small sample size, the inability to stratify results by age and gender, and no protocol was standardized which are all highlighted in McGrath and Brown's editorial in 2006 [153]. Blankenburg et al. (2010) decided to address the issues brought up by McGrath and Brown by investigating the feasibility of applying a QST protocol established by the German Research Network on Neuropathic Pain (DFNS) in children and adolescents, and the impact of age, gender, and tested body sites on all QST parameters [50]. Blankenburg et al. were able to establish reference values for thirteen QST parameters for the face, hand and foot in the pediatric population between the age of 6 and 16 years old [50]. Furthermore, they were able to explore the impact of age, gender, and tested body sites and concluded that further establishment of reference values for other body sites is needed in the literature. In addition, other factors such as attention, anxiety, and coping strategies must be further studied in association with all QST parameters to understand the main effect of age and gender on the QST values reported [50]. Their study highlights that there is still a gap in the literature concerning investigating QST in the pediatric population. The use of QST in children and adolescents has been increasing since Blankenburg et al.'s pioneering study. Hirschfeld et al. (2012) conducted a longitudinal QST study in children and adolescents and observed that short-term QST retesting display reliability, but there

is decreased pain sensitivity after 1 year, which aligns with studies reporting older children report decreased pain sensitivity than younger children [154]. They highlight that age-based reference QST values are important due to the dynamic variability across different age ranges [139, 155]. Furthermore, Tham et al. (2016) conducted a population-based study on QST in adolescents with chronic pain and healthy controls [156]. They observed that pressure pain threshold in the trapezius muscle was significantly lower in adolescents with chronic pain. Furthermore, they reported that female adolescents and patients with more negative affect reported greater pain sensitivity to pressure, heat and cold [156]. Furthermore, Teles et al. (2018) conducted a cross-sectional study using QST in adolescents with idiopathic scoliosis with chronic back pain and they observed that nearly 40% of the patients have at least 50% lower pressure pain thresholds at the back in comparison with a non-affected area which was their forearm [157]. They highlight that QST reference values for other body sites such as the back are needed in the literature, because the patients are used as their own control, but as already highlighted from previous studies, there are slight differences in QST responses depending on the tested body site [50, 158].

In regards to dynamic QST, studies in pediatrics have shown that chronic pain in children and adolescents is associated with altered excitatory and inhibitory endogenous pain modulation systems [12, 152, 159-166]. The endogenous facilitatory phenomenon of pain modulation such as temporal summation and central sensitization have been shown to be involved in the development of some chronic pain conditions such as sickle cell disease, fibromyalgia, migraines, and functional abdominal pain [152, 164-168].

Although CPM has been well studied in adult populations, most of the results cannot generalized to the pediatric population due to different psychological and developmental factors [169]. A deficit of this mechanism was found in some chronic pain conditions such as abdominal

pain and chronic musculoskeletal pain when compared to healthy controls [12, 160, 163, 170, 171]. Hwang et al. (2018) reviewed the results of twelve studies investigating CPM strictly in the pediatric population. They highlight that CPM along with other psychosocial variables should be studied more in depth to understand chronic pain in the pediatric population. In addition, they highlight the lack of consensus in CPM assessment due to the various approaches used for the test stimulus, conditioning stimulus, and the calculation of CPM efficacy similarly to Lewis et al.'s systematic review on CPM investigated in adults (2012) [172, 173].

One of the studies reviewed by Hwang et al. was conducted by Goffaux et al (2008) which investigated whether early physical stress such as preterm births affect the endogenous descending pathways of pain modulation. They observed the children born at full-term and children born prematurely but exposed to few painful interventions possessed normal endogenous pain inhibition unlike children born prematurely and exposed to many painful interventions who possessed an impaired DNIC [69]. Their study highlights that the neonatal period is crucial for the development of the descending inhibitory pain response and early physical stress can alter the DNIC response in children and therefore, put them more at risk to develop chronic pain conditions in adulthood. However, their conclusion can only be validated through longitudinal studies.

Holley et al. (2017) first conducted a controlled cohort study in which they clinically phenotyped youth with new-onset musculoskeletal (MSK) pain and compared them with children with and without chronic pain [169]. They recruited 191 children and adolescents in their study (69 with new onset musculoskeletal pain, 62 with chronic pain, and 60 without chronic pain) and they observed that when analyzing group differences on pain characteristics and pain-related disability, self-reported sleep quality and psychological functioning, and experimental pain responses (i.e. QST), the clinical phenotype of the group with new onset MSK pain fell between

the group with and without chronic pain. However, no group differences were observed concerning CPM [169]. They discuss that their finding on CPM may be due to the impact of age on CPM, since it is postulated that the descending inhibitory pain control develops throughout childhood and adolescence. Furthermore, they discuss that they only used one CPM protocol. Using two CPM protocols to ensure reliability of CPM assessment in future studies may be required to ensure that the reported CPM effect is valid. Holley et al. (2017) followed their cohort through a prospective study to evaluate the persistence of pain at a four-month follow-up and identify predictors of the transition from acute to chronic MSK pain. In their cohort of eighty-eight patients with new onset MSK pain, 35% developed persistent pain at their four-month follow-up. Furthermore, Holley et al.'s logistic regression analysis revealed that CPM and sex significantly predicted the transition from acute to chronic pain in their cohort such that females with lower CPM effect at baseline were more likely to develop persistent pain at their 4-month follow-up [12]. Their results are one of the first to highlight that a deficit in the descending inhibitory pain control in patients with early onset MSK pain are more at risk to develop chronic pain, which extends to adult research findings. However, the follow-up period should be extended to understand if CPM or other factors may influence the development of persistent pain beyond four months. Hence, although more research is needed to understand the transition from acute to chronic pain, Holley et al.'s results highlight that early identification of patients at risk of developing chronic pain may benefit from early intervention [12].

Overall, more QST-based studies in the pediatric population are needed to understand the underlying mechanisms involved in chronic pain in this population.

1.2.3 Electroencephalography

Advances in electroencephalography (EEG) present opportunities to better characterize the neurological processes underlying pain perception in pediatric chronic pain. EEG has been a hot topic for the pediatric population as a non-invasive, safe, and reliable measurement of electrical patterns at the surface of the scalp, which reflect cortical activity. The study of electroencephalographic patterns has recently gained a lot of interest for how the brain processes during a tonic painful stimulus which best mimic clinical pain, especially as age-dependent developmental changes in pediatric pain processing, perception and responses have been identified [154, 174-176]. EEG is a safe, reliable and portable neuroimaging tool that is well-positioned to measure electrical activity patterns on the scalp surface at the point-of-care [177]. Previous studies have identified that adults with and without chronic pain show distinct EEG patterns [178-180]. Spectral power and peak frequency, measures of oscillatory neural activity generated by transforming EEG waves from the time to frequency domain, are the most commonly assessed parameters in the chronic pain literature [181, 182]. There are five widely recognized EEG waves with distinct characteristics: 1) delta frequencies (0.5-4 Hz) usually reflect sleep, 2) theta (4-8 Hz) usually reflect drowsiness, 3) alpha frequencies (8-12 Hz) usually reflect reflective and/or restful states, 4) beta frequencies (12-30 Hz) usually reflect a busy an active mind, and 5) gamma frequencies (>30 Hz) which usually reflect problem solving and/or concentration. Studies have also identified that there are changes in the pain connectome among adult chronic pain patients [183, 184], as measured through altered functional connectivity between the EEG captured over different scalp areas, and that anesthesia alter waveform permutation entropy, a measure of EEG information content quantifying the regularity of the continuous EEG time series [185, 186].

When combining EEG with sensory testing, studies in adults have shown that thermal noxious stimulations seem to modulate activity over orbitofrontal, prefrontal or cingulate regions [187-198] and sensorimotor cortices [187-196, 198-203] (Table 1-2). This modulation in neural activity reflects the flow of information between the sensory-discriminative and affective-motivational systems of pain. Studies in adults using phasic stimuli measured contact heat-evoked potentials [187-192, 199], which are thought to reflect brief noxious stimulation of the A-delta and C fibers. Source localization has associated this activity over the sensorimotor and frontal cortices to the evoked response [187-192]. Spectral analysis in adults over longer noxious stimulations (i.e., tonic stimulations) have revealed changes in cerebral activity over frontal [191, 193-198, 203] and sensorimotor cortices [191, 193-196, 198, 200-203]. On the one hand, researchers found decreased spectral power over the central sulcus, extending from high theta to low beta bands but predominantly in the alpha band [191, 193-196, 198, 200-203]. On the other hand, studies have shown an increasing relationship between frequency bands observed in the frontal regions and pain intensity thought to be independent of stimulus location and attentional resources [194, 195].

There are a limited number of studies investigating EEG patterns children and adolescents with chronic pain. Therefore, there is a need for more studies to investigate whether findings of the adult chronic pain EEG literature extend into pediatric populations to identify objective, dynamic, and age-related cerebral biomarkers of pediatric chronic pain.

Table 1-2. Modulation in Cortical Activity Associated with Principal Examined EEG Features

Modified from Savignac et al. (2021) "Clinical use of Electroencephalography in the Assessment of Acute Thermal Pain: A Narrative Review Based on Articles From 2009 to 2019." *Clinical EEG and neuroscience.*

		Cerebral Regions			
		Frontal	Temporal	Central-Parietal	Occipital
Power Spectra	Delta (0-3.5 Hz)	↑	↑ contralaterally	↓ over sensorimotor regions & ↑ over parietal region	↑ caudally
	Theta (4-7 Hz)	↑ or ↓	↑	↑ or ↓ over sensorimotor regions	
	Alpha (8-12 Hz)	↓ over cingulate region & ↑ over frontal area	↓ bilaterally	↓ over sensorimotor regions	
	Beta (13-29 Hz)	↓ low beta power over cingulate region & ↑ high beta power over frontal and cingulate regions	↑ in temporal, insular and parahippocampal regions	↓ over sensorimotor region	↑ near cerebellum
	Gamma (30-100 Hz)	↑			

↑ represents an increase in cortical activity, while ↓ represents a decrease in cortical activity.

CHAPTER 2 RATIONALE, OBJECTIVES, AND HYPOTHESES

2.1 Rationale and objective of the project

The comprehensive literature review in the previous chapter introduced the basic pathophysiology of pain and mechanisms of chronic pain, as well as the use of different tools (self-report questionnaires, quantitative sensory testing and electroencephalography) to study these mechanisms in pediatric patients. Despite the current knowledge presented, a major limitation in treatment outcomes for chronic pain is still the heterogeneity of the pediatric population. There is a need for a person-centered approach to the assessment of pain in children and adolescents. Due to the heterogeneity within chronic pain conditions and that different chronic pain conditions may share similar characteristics [204], researchers and clinicians have turned to identifying heterogeneous subgroups of pediatric chronic pain patients [135, 152, 205-207]. However, these studies mostly investigated pain and psychosocial characteristics in their cluster analysis and there is limited data evaluating subgroups based on the psychophysical characteristics of pediatric chronic pain patients. Moreover, there is limited data evaluating differences in electroencephalographic characteristics in large samples of pediatric chronic pain patients. Detailed profiling of patients can inform individualized therapy and stratification for strategic therapeutic trials.

The overall objective of this thesis is to better understand chronic pain in youth to improve the clinical assessment of pain processes in pediatric patients with chronic musculoskeletal pain through the inclusion of self-reported questionnaires, static and dynamic quantitative sensory testing, and electroencephalography.

2.2 Main aims

The aims of this project were to:

1. Identify psychosocial and psychophysical profiles in a population of pediatric patients with chronic pain.
2. Investigate distinct electroencephalographic characteristics underlying acute or chronic pain.

2.3 Main hypotheses

The hypotheses were:

1. Distinct subgroups of patients with chronic pain can be identified based on similar psychosocial and psychophysical characteristics.
2. Distinct electroencephalographic characteristics underlying acute or chronic pain will be identified in pediatric patients with chronic pain when compared to healthy controls.

CHAPTER 3 ARTICLES

The third chapter of this thesis includes four articles, two of which have been published, and two that are under review. The first three articles investigate the first aim of the thesis project to "identify psychosocial and psychophysical profiles in a population of pediatric patients with chronic pain." As there are limited studies phenotyping pediatric patients with chronic pain including psychophysical measures, these studies, to our current knowledge, are some of the first to fill an important gap in the literature by including psychosocial and psychophysical measures in our analyses. The first article fills a gap in the literature through the analysis of a large subpopulation of pediatric patients with chronic pain, specifically chronic back pain. The second article describes different clinical phenotypes of central pain mechanisms of youth with chronic pain. The third article builds upon the first two to describe that the combination of self-reported questionnaires, and static and dynamic QST can identify clinically relevant profiles of pediatric patients with chronic musculoskeletal pain and contribute to personalized therapy. The fourth article explored the second aim of the thesis project to "investigate distinct electroencephalographic characteristics underlying acute or chronic pain." The analysis involved a large sample of children and adolescents with chronic musculoskeletal pain who underwent EEG recording combined with sensory testing, therefore, filling a gap in the literature highlighting how those with chronic pain integrate and perceive pain differently than healthy controls.

Manuscript 1 – Psychosocial and psychophysical assessment in pediatric patients and young adults with chronic back pain: a cluster analysis

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3.1.1 Article Identifiers

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3.1.2 Abstract

Background: Identifying subgroups with different clinical profiles may inform tailored management and improve outcomes. The objective of this study was to identify psychosocial and psychophysical profiles of children and adolescents with chronic back pain.

Methods: One hundred and ninety- eight patients with chronic back pain were recruited for the study. Pain assessment was mainly conducted in the form of an interview and with the use of validated pain- related questionnaires assessing their psychosocial factors and disability. All patients underwent mechanical and thermal quantitative sensory tests assessing detection and pain thresholds, and conditioned pain modulation efficacy.

Results: Hierarchal clustering partitioned our patients into three clusters accounting for 34.73% of the total variation of the data. The adaptive cluster represented 45.5% of the patients and was characterized to display high thermal and pressure pain thresholds. The high somatic symptoms cluster, representing 19.2% of patients, was characterized to use more sensory, affective, evaluative and temporal descriptors of pain, more likely to report their pain as neuropathic of nature, report a more functional disability, report symptoms of anxiety and depression and report poor sleep quality. The pain-sensitive cluster, representing 35.4% of the cohort, displayed deep tissue sensitivity and thermal hyperalgesia.

Conclusions: This study identified clinical profiles of children and adolescents experiencing chronic back pain based on specific psychophysical and psychosocial characteristics highlighting

that chronic pain treatment should address underlying nociceptive and non- nociceptive mechanisms.

Significance: To our current knowledge, this study is the first to conduct cluster analysis with youth experiencing chronic back pain and displays clinical profiles based on specific physical and psychosocial characteristics. This study highlights that in a clinical context, chronic pain assessment should include multiple elements contributing to pain which can be assessed in a clinical context and addressed when pathoanatomical symptoms are unidentifiable.

3.1.3 Introduction

Chronic or recurrent back pain in the pediatric population is less prevalent than adults, affecting 14-24% of children and adolescents and is usually associated with post-trauma or known severe pathological conditions [1-5]. However, when pathoanatomical symptoms are unidentifiable, the diagnosis is labelled as non-specific chronic back pain. Patients with chronic back pain experience functional disability, higher rates of missed school, poor sleep quality and mental health problems when compared to age-matched pain-free controls [6-10], and are at risk of experiencing chronic pain throughout adulthood [11-14].

A major limitation in treatment outcomes for chronic back pain is the heterogeneity of the population. Moreover, there are limited pediatric studies, especially randomized control trials, that have documented standardized measures associated with treatment response [15-17]. We have previously shown that different pain processing mechanisms may be involved in adolescents with idiopathic scoliosis and chronic back pain [18]. These results highlight that, despite similar diagnosis, characterizing the psychophysical profile of patients with chronic pain through quantitative sensory tests (QST), may be relevant to consider as a component to guide pain management to become tailored to address underlying etiological mechanisms.

Due to the heterogeneity within chronic pain conditions and that different chronic pain conditions may share similar characteristics [19], researchers and clinicians have turned to identify subgroups with distinct psychophysical profiles in different samples of patients with chronic pain. Subgroups of adult patients with chronic low back pain [20, 21], temporomandibular disorder [22] and other chronic pain conditions [23] have been successfully identified. Rabey et al. (2015) investigated subgroups in a cohort of chronic low back pain based on their QST results. They identified three clusters in which those that displayed increased thermal and pressure pain sensitivity had a greater proportion of females, and higher scores for depression and poor sleep quality [20]. The main limitation for this study was including only the QST results as factors in their cluster analysis. Numerous factors influence quantitative sensory testing, such as age, sex, and psychosocial factors [24-27]. Including these factors within the cluster analysis may give more insight in data interpretation and interventions tailored for these subgroups. Bair et al. (2016) included psychophysical and psychosocial measures in their cluster analysis. However, they used a supervised cluster approach which involves selecting specific variables in their analysis aligning with their objective to identify risk factors for chronic pain in healthy individuals who have a similar psychophysical profile as patients with temporomandibular disorders [22].

Researchers and clinicians have also turned to identify heterogeneous subgroups of pediatric chronic pain patients [28-31]. However, these studies strictly investigated pain and psychosocial characteristics in their cluster analysis and there is limited data evaluating subgroups based on the psychophysical profile of pediatric chronic pain patients. Therefore, the objective of this study was to identify specific psychophysical and psychosocial profiles among a cohort of pediatric patients with chronic back pain. The aim was to conduct an unsupervised statistical clustering approach involving the QST results and psychosocial context of the patients. We hypothesized that

subgroups of patients with chronic back pain can be clustered based on similar psychophysical and psychosocial characteristics.

3.1.4 Methods

3.1.4.1 Study approval

Ethics approval was obtained prior to the beginning of the recruitment from the Research Ethics Board of McGill University (A11- M62- 15B). Participants received written informed consent prior to inclusion in the study and a signature was obtained by the participant or their parent/legal guardian, if the participant was under the age of 14 years old, prior to the beginning of the study. The study was conducted in accordance with the Declaration of Helsinki. All participants were de- identified according to the institutional ethics guidelines.

3.1.4.2 Participants

Patient recruitment occurred between January 2016 and October 2017. Potential participants from the spine and orthopedic outpatient clinics and from the Chronic Pain Services of our institution were identified by a research assistant based on the presence of chronic pain reported in their electronic medical charts or by reference of the patient's physician. At their hospital visit for treatment seeking either for an orthopedic condition or for pain itself, patients were approached by a research assistant to participate in the study and to confirm eligibility criteria prior to receiving signed consent. Inclusion criteria were being aged between 10-21 years old with chronic back pain (persistent or recurrent pain at least once a week for longer than three months) [32]. Patients who did not speak English or French or had a diagnosis of developmental delay that would interfere with completing measures were excluded.

3.1.4.3 Primary outcome measures

3.1.4.3.1 Sociodemographic characteristics and medical history

Patient characteristics such as age, sex, ethnicity and pathology were collected by a research assistant.

3.1.4.3.2 Clinical characteristics

Pain assessment was mainly conducted in the form of a face- to- face interview and with the use of standardized pain- related questionnaires that have been validated in clinical paediatric studies assessing pain [33-36]. Patients were asked about the duration and frequency of their pain. The location of pain was reported using a modified version of the adolescent paediatric pain tool (APPT) [37], in which a diagram of the back was divided into 10 segments to identify specific pain locations [18, 38]. In addition, pain intensity experienced over the last month in each divided back segment of the diagram was reported using an 11-point numerical rating scale (NRS 0–10, 0 = no pain, 10 = the worst pain imaginable). Moreover, the pain experience was assessed using a list of 67 descriptive words in the APPT, assessing the four dimensions of pain (sensory, affective, evaluative and temporal) [39]. The APPT has been shown to have adequate content, construct, and criterion validity, and reliability in clinical and non-clinical groups of children and adolescents between 8 to 17 years old [40].To identify if their pain had a neuropathic component, the Douleur Neuropathique 4 (DN4) questionnaire was completed by patients. By summing all ten questions, scores equal to or greater than 4 indicated that the pain experienced by the patient is likely neuropathic [33, 41]. The DN4 questionnaire has not been validated in children and adolescents. However, despite its very low-level evidence for satisfactory criterion validity and low-level

evidence for satisfactory construct validity and reliability, the DN4 questionnaire has been described to be the most suitable for clinical use [42, 43].

3.1.4.3.3 Anxiety and depressive symptoms

The revised child anxiety and depression scale (RCADS) questionnaire was completed by patients to assess children's self-report of depression and anxiety corresponding to the 4th edition of the diagnostic and statistical manual of mental disorders [44]. Based on the patient's age and grade in school, their total scores are converted into a T-score, in which a T-score between 65 and 69 indicates borderline clinical threshold, and a T-score of 70 or higher indicates above clinical threshold for anxiety and depression. The RCADS has been validated in clinical and non- clinical groups of children and adolescents in grades 3–12 and showed good internal consistency (Cronbach $\alpha = 0.78–0.88$) and item set and factor definitions consistent with DSM-IV anxiety disorders and depression [44, 45].

3.1.4.3.4 Functional disability

The functional disability inventory (FDI) questionnaire was completed by patients, in which the total score is summed to detect different levels of disability [46]. The FDI has been reported to have high internal consistency, moderate to high test- retest reliability, moderate cross-informant (parent-child) reliability and good predictive validity [35, 46]. The FDI is based on four-level classifications system: A score of 0 to 12 inclusively represents no/ minimal disability and patients can function well, despite experiencing pain; a score from 13 to 20 inclusively represents mild disability; a score from 21 to 29 inclusively represents moderate disability; a score of 30 or higher represents severe disability.

3.1.4.3.5 Sleep quality

The Pittsburgh sleep quality index (PSQI) questionnaire was completed by patients to assess sleep quality, in which a global score of 5 or higher indicated poor sleep quality [47]. The PSQI is the most commonly used measure in clinical and research settings showing good internal consistency (Cronbach $\alpha = 0.70– 0.83$) and has been validated in clinical and non- clinical groups of adolescents [48-50].

3.1.4.3.6 Quantitative sensory testing

Each patient underwent a specific protocol of mechanical and thermal quantitative sensory tests (QST) to obtain a comprehensive profile of somatosensory functioning. The protocol was based on an initiative of the Quebec Pain Research Network [51]. All tests were conducted by research assistants who were trained and evaluated by the principal investigator of the study. Mechanical and thermal procedures were performed on the left volar forearm, 2 inches from the left elbow crease as the control area and followed by the most painful anatomical region of the back indicated by the patient as the affected area. A demonstration of every test was explained and performed on the left thenar eminence of the patient. The protocol previously described [18] consisted of four tests assessing six parameters: Mechanical detection threshold, pressure pain threshold, heat pain threshold, heat tolerance threshold, temporal summation of pain and conditioned pain modulation.

3.1.4.3.6.1 Mechanical quantitative sensory testing assessment

Mechanical detection threshold (MDT), using standardized von Frey filaments (Touch-Test™ Sensory Evaluators, USA) with forces ranging between 0.008 and 300 grams, was evaluated to assess tactile sensitivity [18, 25, 52]. The geometric mean of six threshold values was calculated and reported in grams. Pressure pain threshold (PPT), using the JTech Algometer (JTech

Medical, USA) with a 1- cm2 probe, was evaluated to assess deep- tissue sensitivity [18, 25]. The pressure was applied increasing at a rate of ~1 N/s (~10 kPa/s) until the patient reported pain. The mean of three recorded values was calculated and reported in Newtons.

3.1.4.3.6.2 Thermal quantitative sensory testing assessment

Heat pain threshold (HPT) and heat pain tolerance threshold (HTT) was evaluated using a 9- cm2 warm calibrated thermode connected to the Q- sense apparatus (Medoc, Israel). The thermode, initially set at 32.0°C, was placed on the left volar forearm of the patient and increased at a rate of 0.3°C/second to reach the maximum value of 50.0°C as a security cut- off. HPT (when the patient first report pain) and HTT (when the pain was intolerable) were assessed three times and the mean was calculated and reported in degree Celsius.

A conditioned pain modulation (CPM) paradigm was then performed using tonic heat on the right forearm as the test stimulus and the cold pressor task on the left arm as the conditioning stimulus as previously described protocols [18, 53, 54]. First, a thermode was applied to the forearm to reach a pre- determined test temperature to a 5/10 pain intensity. Once the target temperature was reached, it remained constant for 120 seconds. Patients were not told that the temperature of the thermode would remain constant over time to avoid expectation effects. Using a computerized pain scale (CoPS 0–10; 0 = no pain, 10 = the worst pain imaginable), patients were asked to continuously rate their pain to identify if there is temporal summation of pain (TSP) [18, 54]. The presence of temporal summation (i.e. endogenous facilitatory pain response) was defined as a 2/10 increase in pain intensity using the CoPS at the end of the test in comparison to the pain intensity 60 s after the beginning of the test. A change in pain intensity of 2/10 on a NRS was determined as a minimum clinically significant difference [55]. Once the tonic heat test was completed, patients performed a cold pressor task (CPT) involving the immersion of their forearm

in a filled with cold water (12°C) for 2 min to trigger the descending inhibitory pain response. The CPT was immediately followed by a second tonic heat test. The patient's capacity to endogenously inhibit pain was described previously as the diffuse noxious inhibitory control, and here measured as the CPM efficiency was then calculated as the percentage difference between the mean pain intensity of the test stimulus before and after the conditioning stimulus over the mean pain intensity during the test stimulus before the conditioning stimulus. A negative percentage result under −30% indicated an optimal inhibitory pain response, a negative percentage result between −10 and −30% indicated a suboptimal inhibitory pain response, and a negative percentage result above −10% or a positive percentage result indicated an inefficient or facilitatory pain response [18, 54]. A 10%-30% reduction in pain was labelled to be a minimal improvement, whilst a 30% reduction in pain intensity was labelled to be a clinically important difference in pain intensity [55] and is approximately the mean value of inhibitory CPM observed in previous studies [18, 53, 54, 56].

3.1.4.4 Statistical analysis

Descriptive statistics were performed using the R Studio software to summarize the collected data regarding the patients' characteristics, clinical data relative to pain, psychosocial factors and QST results. Sample size requirements for principal component analysis (PCA) are not definitive and are dependent on many factors. Therefore, the sample size was based on population proportion in which minimally 14% of the paediatric population is affected by chronic back pain. Based on this assumption, a sample size of 185 patients is required to achieve 90% statistical power at the 0.05 significance level.

An unsupervised cluster analysis was performed using the FactoMineR package in the R Studio software [57] to subgroup patients into clinical profiles and potentially identify responders to specific therapeutic strategies. To profile the patients based on their psychophysical and

psychosocial characteristics, the cluster analysis involved 17 indicator variables: sensory descriptors, affective descriptors, evaluative descriptors, temporal descriptors, DN4 total score, FDI total score, RCADS total T-score, PQSI global score, mechanical detection threshold in the control and affected area, pressure pain threshold in the control and affected area, heat pain threshold, heat tolerance threshold, the average pain score during the cold pressor task, CPM efficiency score and the pain score during the thermal temporal summation of pain. Other quantitative and qualitative outcome measures were included as supplementary variables as they do not represent underlying mechanisms of pain and instead may represent consequences of chronic back pain: location of recruitment, age, sex, ethnicity, duration of pain, frequency of pain, duration of painful episodes, pathology, most painful location, average pain reported in the back, pain radiating down the legs and test temperature for the CPM assessment. Since all measures had different units, iterative PCA using the FactorMineR package in the R Studio software was first conducted as a data reduction technique standardizing all variables into Z-scores. Principal component analysis was conducted to investigate interrelationships between and within psychophysical and psychosocial variables to determine whether a smaller number of principal components is representative of the total variation in the data. Standardization of all variables was to ensure equal importance of each variable in the PCA. Missing data for a maximum of two variables were observed for eight patients. No differences were observed in these eight patients in comparison to the rest of the sample regarding their demographic characteristics (data not shown). Therefore, these eight patients were kept in the analysis. Missing data were imputed for the indicator variables using the missMDA package which takes into account similarities between the values of the variables of each patient [57, 58]. Principal components (PCs) with eigenvalues >1 were retained [59]. Variable loading on each principal component was considered significant if

>0.3 [59]. Hierarchical clustering with k- means consolidation was conducted on the principal components. The hierarchical clustering was, therefore, performed multiple times to minimize within- cluster variability and maximize between- cluster variability. The best partition of clusters was the one with the highest relative loss of inertia [59]. An analysis of variance (ANOVA) model was conducted along with a Fisher test to determine which principal components best represent each cluster and determine cluster effect. Differences between clusters regarding their characteristics, clinical data relative to pain, psychosocial factors and QST results was conducted using the chi- squared test and Kruskal- Wallis one- way ANOVA followed by Dunn's test depending on whether the variable was qualitative or quantitative, respectively.

3.1.5 Results

Two hundred and four patients were recruited for this cross- sectional study. However, six patients dropped out prior to the quantitative sensory tests. Therefore, the data of 198 patients with chronic back pain were analysed, in which 170 (85.9%) were recruited from the spine and orthopaedic outpatient clinics whilst 28 (14.1%) the chronic pain services of our institution. The mean age was 15.69 ± 2.25 years old and 81.8% of our cohort were females (Table 3-1). The majority of the patients were Caucasian (90.4%), experience pain for more than 12 months (72.2%), experience pain on a daily basis (65.2%) and experience constant painful episodes (55.6%). Moreover, 25.8% of the cohort reported back pain radiating down their legs, whilst 27.8% of our cohort self- report their pain as most likely to be neuropathic. Among the cohort, 71.2% reported their most painful location along their spine. Furthermore, 54.6% of the cohort self-reported mild to severe functional disability, 7.6% self- reported borderline of above clinical threshold symptoms of anxiety and depression and 72.7% self- reported poor sleep quality. Large variability was observed for the QST results in the cohort. The inhibitory pain control assessment

revealed great variability among the cohort. The CPM efficiency was optimal in 51.5%, suboptimal in 22.7% and inefficient in 25.8% of the cohort. Moreover, 13.6% of the cohort displayed temporal summation of pain.

Table 3-1. Demographics, clinical data relative to pain and psychosocial and psychophysical characteristics of cohort

Variable	Total sample (*n* = 198)
Location of recruitment, *n* (%)	
Spine and orthopaedic outpatient clinics	170 (85.9)
Chronic pain services	28 (14.1)
Age, Mean ± SD	15.69 ± 2.25
Sex, *n* (%)	
Female	162 (81.8)
Male	36 (18.2)
Ethnicity, *n* (%)	
Caucasian	179 (90.4)
Black or African American	10 (5.1)
Asian	4 (2.0)
Interracial	5 (2.5)
Duration of pain, *n* (%)	
3–6 months	14 (7.1)
6–12 months	41 (20.7)
> 12 months	143 (72.2)
Frequency of pain, *n* (%)	
Daily	129 (65.2)
Every 2nd day	43 (21.7)
Once a week	26 (13.1)
Duration of painful episodes, *n* (%)	
Few seconds	8 (4.0)
Few minutes	36 (18.2)
One hour	44 (22.2)
Constant	110 (55.6)
Pathology, *n* (%)	
Arthritic	6 (3.0)
Disc protrusion	8 (4.0)
Mechanical back pain	14 (7.1)
Scoliosis	115 (58.1)
Spondylolysis/Spondylolisthesis	13 (6.6)
Tight hamstrings	9 (4.5)
Non-specific back pain	33 (16.7)
Most painful location, *n* (%)	
Neck	3 (1.5)
Left upper back	6 (3.0)
Center upper back	38 (19.2)

Variable	Total sample (*n* = 198)
Right upper back	11 (5.6)
Left middle back	8 (4.0)
Center middle back	37 (18.7)
Right middle back	12 (6.1)
Left lower back	12 (6.1)
Center lower back	63 (31.8)
Right lower back	6 (3.0)
Average pain reported, NRS (0–10), Mean (CI)	
Neck	2.91 (2.50–3.32)
Left upper back	2.73 (2.32–3.14)
Center upper back	3.44 (3.00–3.87)
Right upper back	2.46 (2.05–2.87)
Left middle back	2.80 (2.39–3.21)
Center middle back	4.32 (3.90–4.74)
Right middle back	2.56 (2.16–2.95)
Left lower back	3.07 (2.61–3.53)
Center lower back	4.09 (3.63–4.54)
Right lower back	3.18 (2.73–3.64)
Pain radiating down legs, *n* (%)	
Yes	51 (25.8)
No	140 (70.7)
Descriptors of pain used, Mean (%) ± SD	
Sensory	18.04 ± 11.61
Affective	8.92 ± 12.00
Evaluative	34.13 ± 21.41
Temporal	23.94 ± 13.78
Neuropathic component, *n* (%)	
Mean score of DN4 questionnaire, Mean ± SD	2.46 ± 2.08
Likely neuropathic	55 (27.8)
Not likely neuropathic	143 (72.2)
Functional Disability, *n* (%)	
Mean score of FDI, Mean ± SD	15.43 ± 10.31
None or minimal	89 (44.9)
Mild	50 (25.3)
Moderate	37 (18.7)
Severe	21 (10.6)
Anxiety and Depression Symptoms, *n* (%)	
Mean T-score of RCADS, Mean ± SD	45.34 ± 12.39
Below clinical threshold	183 (92.4)
Borderline	5 (2.5)
Above clinical threshold	10 (5.1)
Sleep Quality, *n* (%)	
Mean global score of PSQI, Mean ± SD	6.98 ± 3.48
Good sleep quality	54 (27.3)
Poor sleep quality	144 (72.7)

Variable	Total sample (*n* = 198)
MDT (g), Mean ± SD	
Control area	0.52 ± 1.65
Affected area	1.47 ± 12.37
PPT (N), Mean ± SD	
Control area	27.62 ± 14.82
Affected area	26.38 ± 17.44
HPT (°C), Mean ± SD	39.24 ± 3.17
HTT (°C), Mean ± SD	45.16 ± 2.41
Test temperature for CPM assessment (°C), Mean ±SD	43.56 ± 2.51
CPT average pain score NRS (0–10), Mean ± SD	6.98 ± 2.32
CPM, *n* (%)	
CPM efficiency (%), Mean ±SD	−29.44 ± 42.87
Inefficient	51 (25.8)
Suboptimal	45 (22.7)
Optimal	102 (51.5)
TSP, *n* (%)	
TSP pain score NRS (0–10), Mean ±SD	0.09 ± 2.07
No presence	171 (86.4)
Presence	27 (13.6)

Abbreviations: CI, 95% confidence interval; CPM, conditioned pain modulation; CPT, cold pressor task; DN4, douleur neuropathique 4 questionnaire; FDI, functional disability index; HPT, heat pain threshold; HTT, heat tolerance threshold; MDT, mechanical detection threshold; PPT, pressure pain threshold; PSQI, Pittsburgh sleep quality index; RCADS, revised children's anxiety and depression scale; SD, standard deviation; TSP, temporal summation of pain.

3.1.5.1 Principal component analysis

Iterative principal component analysis derived five principal components (PC) with eigenvalues >1 accounting for 59.2% of the total variation in the data. Variable loading on each principal component is summarized in Table 3-2. The PCs can be summarized as representing the dimensions of psychosocial factors (PC1), pressure pain and heat tolerance thresholds (PC2), mechanical detection threshold (PC4) and CPM efficiency (PC5). No significant variable loading was observed for PC3. The PC scores were calculated for each patient using the component loadings and were used to replace the indicator variables in the cluster analysis.

Table 3-2 Principal component analysis of psychophysical variables

Variable	Component 1	Component 2	Component 3	Component 4	Component 5
Sensory descriptors	**0.556**	0.115	0.054	0.007	0.003
Affective descriptors	**0.463**	0.053	0.017	0.05	0.008
Evaluative descriptors	**0.445**	0.022	0.103	0.001	0.009
Temporal descriptors	0.188	0.071	0.144	0.012	0.005
DN4 Total score	**0.321**	0.08	0.004	0.074	0.058
FDI Total score	**0.521**	0.058	0.048	0.008	0.005
Anxiety and Depression Total T-score	**0.303**	0.003	0.169	0.075	0.005
PSQI score	0.295	0.054	0.209	0.037	0.02
MDT control	0.005	0.016	0.001	**0.496**	0.008
MDT affected	0.016	0.003	0.069	0.115	**0.377**
PPT control	0.14	**0.401**	0.121	0.036	0.007
PPT affected	0.136	**0.319**	0.202	0.09	0
HPT	0.142	0.289	0.072	0.039	0.007
HTT	0.164	**0.446**	0.116	0.015	0.006
CPT average pain score	0.13	0.259	0.012	0	0.181
CPM efficiency	0.003	0.05	0.002	0.156	**0.451**
TSP pain score	0.002	0.136	0.122	0.008	0.185

Note: Variable loading on each component was considered significant if >0.3 (bolded). Abbreviations: CPM, conditioned pain modulation; CPT, cold pressor task; DN4, douleur neuropathique 4 questionnaire; FDI, functional disability index; HPT, heat pain threshold; HTT, heat tolerance threshold; MDT, mechanical detection threshold; PPT, pressure pain threshold; PSQI, Pittsburgh sleep quality index; TSP, temporal summation of pain

3.1.5.2 Cluster analysis

Hierarchal clustering partitioned our patients into three clusters accounting for 34.73% of the total variation in the data. Eighty- nine patients (44.9%) were grouped in cluster 1, 71 patients (35.9%) and 38 patients (19.2%) were grouped in cluster 2 and cluster 3, respectively. Figure 3-1 displays the three clusters according to principal components 1 and 2. Patients grouped in cluster 1 are characterized by significantly low values for PC1 ($t = 5.77$, $p < 0.001$) and high values for PC2 ($t = 5.43$, $p < 0.001$) and we, therefore, named it the adaptive cluster. In contrast, patients

grouped in cluster 2 are mainly characterized by significantly low values for PC2 ($t = 7.54$, $p < 0.001$) and was, therefore, named the pain-sensitive cluster. Moreover, patients grouped in cluster 3 are mainly characterized by significantly high values for PC1 ($t = 11.54$, $p < 0.001$) and thus named the high somatic symptoms cluster.

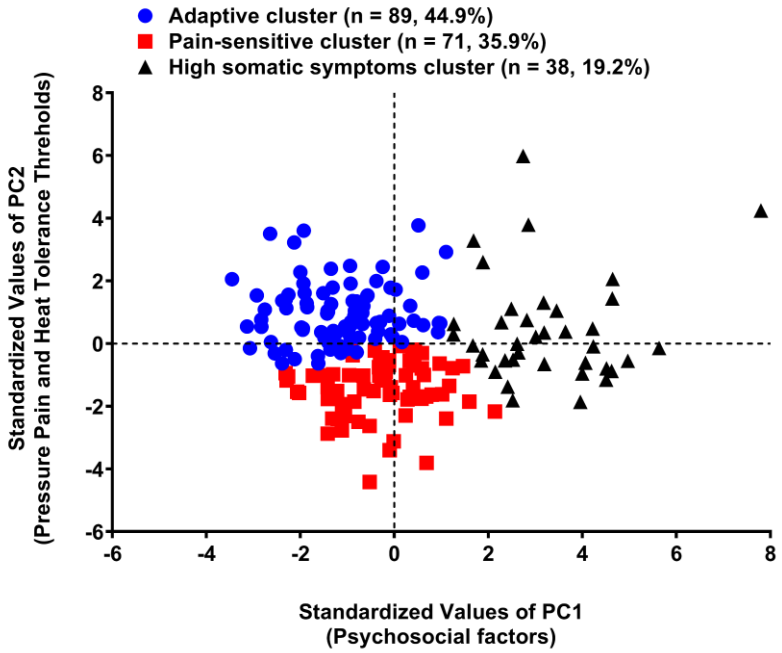

Figure 3-1. Results of the hierarchical clustering analysis displaying three clusters derived from the principal component (PC) scores of PC1 and PC2 representing the dimensions of psychosocial factors, and pressure pain and heat tolerance thresholds, respectively.
The adaptive cluster is characterized by significantly higher values for pressure pain and heat tolerance thresholds. In contrast, the pain- sensitive cluster is mainly characterized by lower values for pressure pain and heat tolerance thresholds. The high somatic symptoms cluster is mainly characterized by having the highest values for the dimension of psychological factors.

3.1.5.3 Profiling of clusters

No significant differences were observed between clusters in regard to their age, sex, ethnicity, duration of pain, duration of painful episodes, pathology or location of pain (Table 3-3). However, a significant association was observed between cluster membership and the location of recruitment in the study ($p < 0.001$) and the reported frequency of pain ($p = 0.008$). A higher proportion of patients grouped in the high symptomatic symptoms cluster were recruited from the

chronic pain services at our institution and all reported pain at least every second day. Moreover, the high somatic symptom cluster reported significantly higher pain intensity in all regions of the back ($p < 0.05$). Furthermore, a higher proportion of patients in the high somatic symptoms clusters reported their back pain radiating down their legs ($p < 0.001$).

Table 3-3. Differences between clusters regarding demographics and clinical data relative to pain

Variable	Adaptive cluster (*n* = 89)	Pain-sensitive cluster (*n* = 71)	High somatic symptoms cluster (*n* = 38)	$\chi 2$ value	*p* - value
Location of recruitment, *n* (%)					
Spine and orthopaedic outpatient clinics	83 (93.3)	62 (87.3)	25 (65.8)	16.75*	**<0.001**
Chronic pain services	6 (6.7)	9 (12.7)	13 (34.2)		
Age, Mean ±SD	15.74 ± 2.15	15.32 ± 2.34	16.26 ± 2.25	2.23†	0.110
Sex, *n* (%)					
Female	69 (77.5)	61 (85.9)	32 (84.2)	2.05*	0.359
Male	20 (22.5)	10 (14.1)	6 (15.8)		
Ethnicity, *n* (%)					
Caucasian	82 (92.1)	60 (84.5)	37 (97.4)	11.00*	0.088
Black or African American	2 (2.2)	8 (11.3)	0 (0.0)		
Asian	3 (3.4)	1 (1.4)	0 (0.0)		
Interracial	2 (2.2)	2 (2.8)	1 (2.6)		
Duration of pain, *n* (%)					
3–6 months	7 (7.9)	6 (8.5)	1 (2.6)	1.91*	0.751
6–12 months	20 (22.5)	14 (19.7)	7 (18.4)		
> 12 months	62 (69.7)	51 (71.8)	30 (78.9)		
Frequency of pain, *n* (%)					
Daily	55 (61.8)	40 (56.3)	34 (89.5)	13.71*	**0.008**
Every 2nd day	20 (22.5)	19 (26.8)	4 (10.5)		
Once a week	14 (15.7)	12 (16.9)	0 (0.0)		
Duration of painful episodes, *n* (%)					
Few seconds	6 (6.7)	2 (2.8)	0 (0.0)	7.78*	0.255
Few minutes	16 (18.0)	16 (22.5)	4 (10.5)		
One hour	20 (22.5)	17 (23.9)	7 (18.4)		
Constant	47 (52.9)	36 (50.7)	27 (71.1)		
Pathology, *n* (%)					
Arthritic	3 (3.4)	1 (1.4)	2 (5.3)	16.48*	0.170
Disc protrusion	4 (4.5)	1 (1.4)	3 (7.9)		
Mechanical back pain	9 (10.1)	3 (4.2)	2 (5.3)		

Variable	Adaptive cluster (*n* = 89)	Pain-sensitive cluster (*n* = 71)	High somatic symptoms cluster (*n* = 38)	$\chi 2$ value	*p* - value
Scoliosis	52 (58.4)	47 (66.2)	16 (42.1)		
Spondylolysis/ Spondylolisthesis	7 (7.9)	5 (7.0)	1 (2.6)		
Tight hamstrings	4 (4.5)	3 (4.3)	2 (5.3)		
Non-specific back pain	10 (11.2)	11 (15.5)	12 (31.6)		
Most painful location, *n* (%)					
Neck	2 (2.2)	0	1 (2.6)	17.10*	0.516
Left upper back	2 (2.2)	1 (1.4)	3 (7.9)		
Center upper back	13 (14.6)	15 (21.1)	10 (26.3)		
Right upper back	5 (5.6)	5 (7.0)	1 (2.6)		
Left middle back	5 (5.6)	3 (4.3)	0		
Center middle back	15 (16.9)	14 (19.7)	8 (21.1)		
Right middle back	6 (6.7)	5 (7.0)	1 (2.6)		
Left lower back	6 (6.7)	6 (8.5)	0		
Center lower back	32 (36.0)	20 (28.2)	11 (28.9)		
Right lower back	3 (3.4)	1 (1.4)	2 (5.3)		
Average pain reported, NRS (0–10), Mean (CI)					
Neck	2.82 (2.22-3.42)[c]	2.28 (1.65-2.90)[c]	4.29 (3.21-5.37)[a,b]	10.84†	**0.004**
Left upper back	2.30 (1.75-2.85)[c]	2.19 (1.58-2.81)[c]	4.75 (3.61-5.89)[a,b]	17.51†	**<0.001**
Center upper back	2.89 (2.29-3.48)[c]	3.32 (2.58-4.07)[c]	4.93 (3.87-6.00)[a,b]	10.63†	**0.005**
Right upper back	2.08 (1.52-2.65)[c]	1.99 (1.37-2.60)[c]	4.22 (3.10-5.35)[a,b]	14.40†	**<0.001**
Left middle back	2.43 (1.86-3.00)[c]	2.56 (1.88-3.24)[c]	4.11 (3.03-5.19)[a,b]	8.58†	**0.014**
Center middle back	3.87 (3.26-4.47)[c]	4.27 (3.55-4.99)	5.47 (4.53-6.42)[a]	7.68†	**0.021**
Right middle back	2.15 (1.57-2.74)[c]	2.49 (1.87-3.11)	3.63 (2.60-4.66)[a]	7.64†	**0.022**
Left lower back	2.65 (1.99-3.31)[c]	2.83 (2.09-3.57)[c]	4.50 (3.33-5.67)[a,b]	10.04†	**0.007**
Center lower back	3.70 (3.06-4.33)[c]	3.65 (2.86-4.44)[c]	5.82 (4.77-6.87)[a,b]	13.54†	**0.001**
Right lower back	2.37 (1.74-3.00)[c]	3.08 (2.36-3.81)[c]	5.28 (4.19-6.37)[a,b]	19.97†	**<0.001**
Pain radiating down legs, *n* (%)					
Yes	18 (20.2)	14 (19.7)	19 (50.0)	18.00*	**<0.001**
No	70 (78.7)	55 (77.5)	15 (39.5)		

Variable	Adaptive cluster (*n* = 89)	Pain-sensitive cluster (*n* = 71)	High somatic symptoms cluster (*n* = 38)	$\chi 2$ value	*p* - value

Note: p- values ≤0.05 are bolded.
Abbreviations: CI, 95% confidence interval; SD, standard deviation.
[a]Significant difference with cluster 1.
[b]Significant difference with cluster 2.
[c]Significant difference with cluster 3.
*Chi- squared test statistic.
†Kruskal- Wallis one- way analysis of variance chi- squared test statistic.

Figure 3-2 displays the Z-scores for the indicator variables for the respective three clusters. Significant between-cluster differences in regard to the raw data of the indicator variables were observed (Table 3-4). The high somatic symptoms cluster was characterized to significantly have the highest scores for all the questionnaires completed ($p < 0.001$). The high somatic symptoms cluster were characterized to group patients who used more sensory, affective, evaluative and temporal descriptors of pain, more likely reported their pain as neuropathic of nature, reported more functional disability, reported symptoms of anxiety and depression, and reported poor sleep quality. The adaptive cluster, in comparison to the pain-sensitive and high somatic symptoms clusters, was characterized to significantly have the highest pressure pain threshold in the control and affected area, highest heat pain and tolerance threshold, and lowest pain intensity reported during the cold pressor task ($p < 0.001$). Interestingly, patients in the adaptive cluster had a higher proportion of patients that display temporal summation pain than the pain-sensitive cluster and the high somatic symptoms cluster ($p = 0.005$). The pain-sensitive cluster, in general, displayed lower pressure pain threshold in the control and affected area, lower heat pain and tolerance threshold, and higher pain intensity reported during the cold pressor task than the adaptive cluster ($p < 0.001$),

but also displayed lower scores for all the questionnaires completed than the high somatic symptoms cluster ($p < 0.001$).

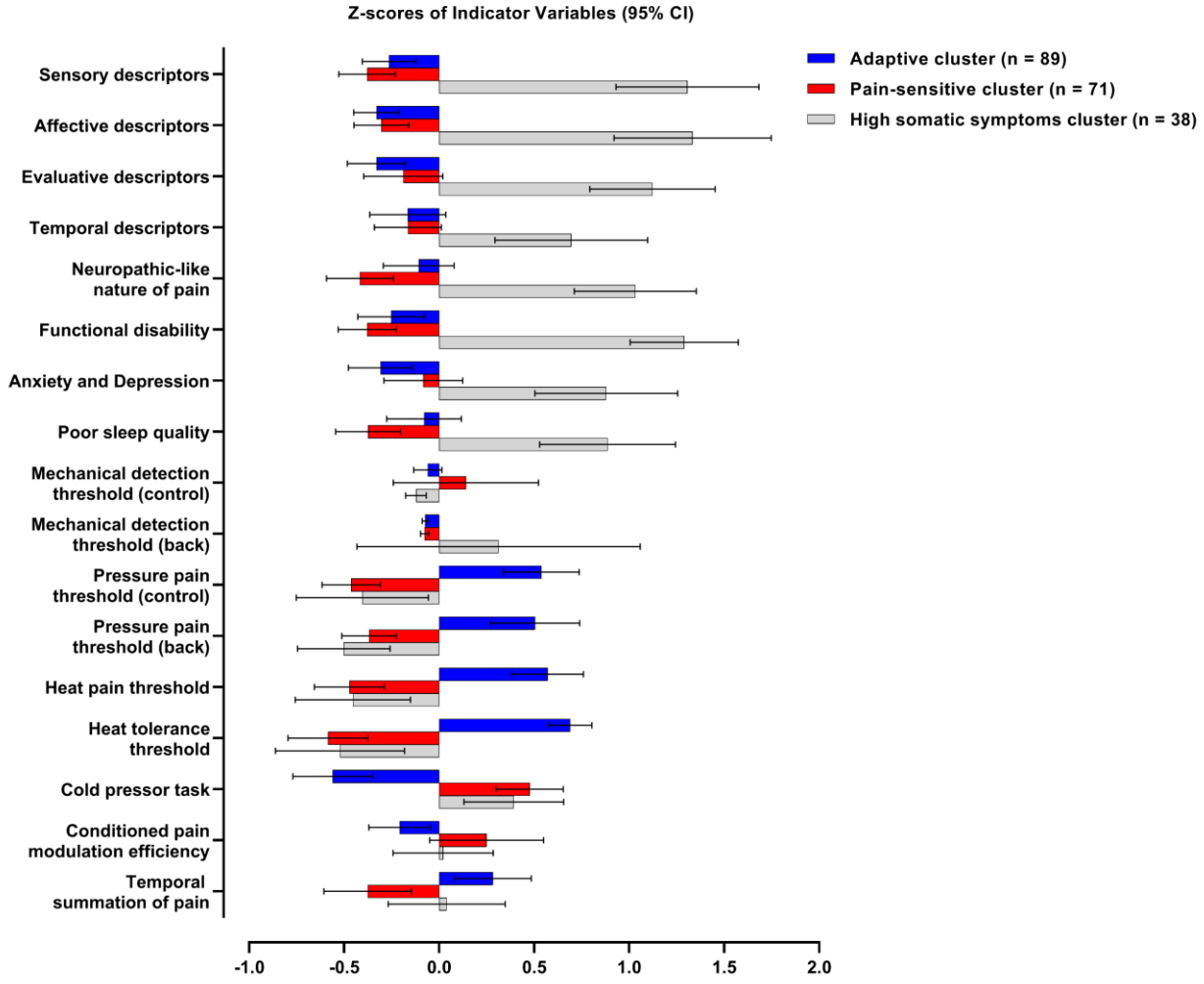

Figure 3-2. Z-scores of the indicator variables.

These plots show the mean values and associated 95% confidence intervals of the indicator variables included in the cluster analysis. Each variable displayed in the figure was normalized to have a mean of 0 and SD 1. Z-scores >0 represent values higher than then the mean of the sample, and z- scores <0 represent values lower than the mean of the sample. DN4, douleur neuropathique 4 questionnaire; FDI, functional disability index; PSQI, Pittsburgh sleep quality index; MDT, mechanical detection threshold; PPT, pressure pain threshold; HPT, heat pain threshold; HTT, heat tolerance threshold; CPT, cold pressor task; CPM, conditioned pain modulation; TSP, temporal summation of pain

Table 3-4. Differences between clusters regarding psychosocial and psychophysical characteristics

Variable	Adaptive cluster (*n* = 89)	Pain-sensitive cluster (*n* = 71)	High somatic symptoms cluster (*n* = 38)	χ2 value	*p* - value
Descriptors of pain used, Mean (%) ± SD					
Sensory	14.98 ± 7.77[c]	13.64 ± 7.18[c]	33.21 ± 13.3[a,b]	63.13[†]	**<0.001**
Affective	4.96 ± 6.79[c]	5.27 ± 7.27[c]	24.92 ± 15.11[a,b]	59.01[†]	**<0.001**
Evaluative	27.06 ± 15.49[c]	30.09 ± 18.70[c]	58.16 ± 21.47[a,b]	49.83[†]	**<0.001**
Temporal	21.66 ± 13.14[c]	21.68 ± 10.27[c]	33.53 ± 16.87[a,b]	19.18[†]	**<0.001**
Neuropathic component, *n* (%)					
Mean score of DN4 questionnaire, Mean ±SD	2.24 ± 1.84[b,c]	1.59 ± 1.55[a,c]	4.61 ± 2.03[a,b]	50.82[†]	**<0.001**
Likely neuropathic	18 (20.2)	10 (14.1)	27 (71.1)	44.64*	**<0.001**
Not likely neuropathic	71 (79.8)	61 (85.9)	11 (28.9)		
Functional Disability, *n* (%)					
Mean score of FDI, Mean ±SD	12.82 ± 8.58[c]	11.52 ± 6.61[c]	28.72 ± 8.91[a,b]	63.06[†]	**<0.001**
None or minimal	48 (53.9)	40 (56.3)	1 (2.6)	94.12*	**<0.001**
Mild	23 (25.8)	21 (29.6)	6 (15.8)		
Moderate	16 (18.0)	9 (12.7)	12 (31.6)		
Severe	2 (2.2)	0	19 (50.0)		
Anxiety and Depression Symptoms, *n* (%)					
Mean T-score of RCADS, Mean ±SD	41.52 ± 9.95[c]	44.30 ± 10.84[c]	56.24 ± 14.17[a,b]	28.36[†]	**<0.001**
Below clinical threshold	88 (98.9)	68 (95.8)	27 (71.1)	32.21*	**<0.001**
Borderline	1 (1.1)	1(1.4)	3 (7.9)		
Above clinical threshold	0	2 (2.8)	8 (21.1)		
Sleep Quality, *n* (%)					
Mean global score of PSQI, Mean ±SD	6.70 ± 3.25[c]	5.68 ± 2.51[c]	10.07 ± 3.79[a,b]	32.50[†]	**<0.001**
Good sleep quality	26 (29.2)	25 (35.2)	3 (7.9)	9.83*	**0.007**
Poor sleep quality	63 (70.8)	46 (64.8)	35 (92.1)		
MDT (g), Mean ± SD					
Control area	0.42 ± 0.58	0.75 ± 2.66	0.31 ± 0.27	0.45[†]	0.800
Affected area	0.56 ± 0.95	0.53 ± 1.14	5.34 ± 28.04	1.38[†]	0.501

Variable	Adaptive cluster (*n* = 89)	Pain-sensitive cluster (*n* = 71)	High somatic symptoms cluster (*n* = 38)	χ2 value	*p* - value
PPT (N), Mean ± SD					
Control area	35.58 ± 14.05[b,c]	20.75 ± 9.53[a]	21.62 ± 15.68[a]	53.12†	**<0.001**
Affected area	35.18 ± 19.41[b,c]	19.94 ± 10.49[a]	17.62 ± 12.92[a]	43.36†	**<0.001**
HPT (°C), Mean ± SD	41.04 ± 2.83[b,c]	37.74 ± 2.47[a]	37.80 ± 2.92[a]	51.18†	**<0.001**
HTT (°C), Mean ± SD	46.82 ± 1.30[b,c]	43.75 ± 2.13[a]	43.9 ± 2.48[a]	94.47†	**<0.001**
CPT average pain score NRS (0–10), Mean ± SD	5.68 ± 2.28[b,c]	8.08 ± 1.73[a]	7.89 ± 1.85[a]	52.13†	**<0.001**
CPM, *n* (%)					
CPM efficiency (%), Mean ±SD	-38.37 ± 33.00	-18.73 ± 54.40	-28.53 ± 34.40	3.80†	0.149
Inefficient	17 (19.1)	23 (32.4)	11 (28.9)	4.14*	0.387
Suboptimal	21 (23.6)	16 (22.5)	8 (21.1)		
Optimal	51 (57.3)	32 (45.1)	19 (50.0)		
TSP, *n* (%)					
TSP pain score NRS (0–10), Mean ±SD	0.68 ± 1.99 [b]	-0.69 ± 2.02[a]	0.17 ± 1.94	15.31†	**<0.001**
No presence	70 (78.7)	66 (93.0)	35 (92.1)	10.43*	**0.005**
Presence	19 (21.3)	5 (7.0)	3 (7.9)		

Note: p- values ≤0.05 are bolded.
Abbreviations: CPM, conditioned pain modulation; CPT, cold pressor task; DN4, douleur neuropathique 4 questionnaire; FDI, functional disability index; HPT, heat pain threshold; HTT, heat tolerance threshold; MDT, mechanical detection threshold; PPT, pressure pain threshold; PSQI, Pittsburgh sleep quality index; RCADS, revised children's anxiety and depression scale; SD, standard deviation; TSP, temporal summation of pain.
[a]Significant difference with cluster 1
[b]Significant difference with cluster 2.
[c]Significant difference with cluster 3.
*Chi- squared test statistic.
†Kruskal- Wallis 1- way analysis of variance chi- squared test statistic.

3.1.6 Discussion

The objective of this study was to identify specific psychophysical and psychosocial profiles among a cohort of paediatric patients with chronic back pain. A cluster analysis of these patients suggested three subgroups and were best described by two principal components

representing the dimensions of psychosocial factors, and pressure pain and heat tolerance thresholds. Cluster membership did not vary significantly by age, sex, ethnicity, duration of pain, duration of painful episodes, pathology or most painful location as observed by Schurman et al. (2008) in a cluster analysis of children with recurrent abdominal pain [29]. Furthermore, no difference in tactile sensitivity or efficiency of their descending inhibitory pain response was observed among the groups. To our knowledge, this is the first cluster analysis performed with youth experiencing chronic back pain. Furthermore, our cluster model included QST results and psychosocial factors, building on prior work by Rabey et al. (2015) and Baron et al. (2017) who included only QST results in their cluster analysis [20, 23], and adult and paediatric studies who based their analysis on pain descriptors and psychological symptoms [28-30, 60]. Moreover, we conducted an unsupervised approach to cluster analysis, unlike Bair et al. (2016) who conducted a supervised cluster analysis to determine risk factors for temporomandibular disorder in healthy individuals. Our unsupervised approach was appropriate for the cross- sectional design of the study to identify clusters of patients with chronic back pain that may benefit from a tailored management based on their psychophysical and psychosocial profiles.

3.1.6.1. Profiling of clusters

The adaptive cluster represented 44.9% of the patients and was characterized by a higher thermal and pressure pain threshold. Subgroups of adult patients with chronic back pain presenting with similar psychophysical characteristics have been identified [20, 21]. However, the meaning of the low pressure and heat sensitivity in our cohort remains unclear. The results of sensory testing of the patients in this cluster are visually similar to reference values established in the hand and foot in the paediatric population [25]. This is unlike other paediatric population-based studies that show lower pressure pain thresholds in adolescents with chronic pain [61]. However, Tham et al.

(2016) has shown in a large cohort of adolescents that the heat pain threshold and cold pressor data were not significantly different between those with and without chronic pain [61]. Contrarily to Tham et al., Sethna et al. (2007) observed in paediatric patients with complex regional pain syndromes, an overall significant difference with healthy controls for cold and heat pain thresholds. However, a large percentage of patients were within normal reference intervals [62]. Our results highlight that despite the presence of chronic back pain, there is a subgroup of patients that do not display deep tissue sensitivity or thermal hyperalgesia in either the affected or control area of the body.

A larger proportion of patients that displayed the presence of thermal temporal summation of pain were found in the adaptive cluster. In a systematic review in children with chronic pain conducted by Pas et al. (2018), central hyperexcitability was shown to be present in several paediatric chronic pain conditions [63]. Therefore, the sensitization to a tonic noxious heat stimulation in a region of the body remote from the primary area of pain may suggest that the chronic pain of the patients in the adaptive cluster arise or persist from central processes [64]. In a systematic review on adult patients conducted by Hubscher et al. (2013), a fair association between spinal pain intensity and thermal temporal summation was observed [65]. Although we did not conduct this analysis in our cohort, altogether, our results may suggest that the persistent back pain in the adaptive cluster may arise from central facilitation.

The pain-sensitive cluster, representing 35.9% of the cohort was characterized to have lower thermal and pressure pain thresholds in comparison to the adaptive cluster. Lower pain thresholds in the affected region of the body have been observed in other chronic pain conditions in paediatrics [26, 61]. We recently observed (Teles et al., 2019) in a subset of the cohort with idiopathic scoliosis with chronic back pain that the severity of their curve was significantly

associated with deep tissue sensitivity in the back [18]. Therefore, the diagnosis that may underlie that chronic back pain should not be ignored in this subgroup. Studies investigating strictly psychophysical profiles of adult chronic pain patients observe minimally a three-group solution [20, 66], unlike our results revealing two psychophysical profiles. However, our results highlight that, in contrast to the adaptive cluster, there is a subgroup of patients that display maladaptive pain mechanisms suggesting possible involvement of central and peripheral pain mechanisms that can be targeted.

The adaptive cluster and the pain-sensitive cluster were characterized to have lower scores for all questionnaires (i.e. use less descriptors of pain, not likely to report their pain as neuropathic in nature, none to mild functional disability, report less anxiety and depression symptoms below the clinical threshold and report better sleep quality). Similarly, to other studies conducting cluster analysis of psychological profiles among children with chronic pain, at least two subgroups can be observed [28, 29]. Scharff et al. (2005) observed in a subgroup of children with chronic pain (52.1%) whose questionnaire scores fell within established population norms and was distinguished by low levels of disability [28]. Schurman et al. (2008) conducted a similar cluster analysis and also observed more than half of their sample with better psychological functioning [29]. Therefore, our results are consistent with the chronic pain model where inter- individual variability in the relative contributions of multiple elements of pain would be expected.

Despite their low thermal and pressure pain threshold similar to the pain- sensitive cluster, the high somatic symptoms cluster, representing 19.2% of patients, displayed higher self- report of pain intensity in the back, functional disability, anxiety and depression symptoms, and poor sleep quality. This is as observed by other research groups investigating variations in psychosocial profiles in children and adolescents with chronic pain [28, 29]. Functional disability, mental

distress and sleep problems have been shown to be associated with pain in the paediatric population [7, 67-69]. However, the cause- and effect relationship between pain and these outcomes is unclear. Furthermore, studies investigating strictly psychosocial subgroups of paediatric chronic pain patients observe minimally a three-group solution [28-30], unlike our results revealing two psychosocial profiles. Therefore, future directions may include separate cluster analyses on psychophysical and psychosocial profiles to reveal more subgroups masked by our current cluster approach.

A higher proportion of patients in the high somatic symptoms cluster reported their back pain radiating down their leg and reported their back pain to display neuropathic-like characteristics. Neuropathic pain, usually viewed only as to be a result of lesions affecting the somatosensory system, has also been shown to be triggered in parallel by psychological factors. In 2015, Dimova et al. demonstrated that healthy adults who displayed a pessimistic life attitude also displayed neuropathic-like pain patterns after topical capsaicin application [70]. Therefore, it is hypothesized that the high proportion of patients reporting a neuropathic-like component for their back pain in the high somatic symptoms cluster may be explained by a high tendency of the patients to focus on their pain-related bodily sensations. However, along with reporting neuropathic-like characteristics, patients in the high somatic symptoms cluster displayed similar thermal and pressure pain thresholds to the pain-sensitive cluster, suggesting possible involvement of central and peripheral pain mechanisms. Without the presence of a lesion in the somatosensory system, it may be hypothesized that nociplastic pain may act as the dominant pain mechanism in this cluster of patients such that nociceptive and neuropathic pain are not entirely responsible for the pain [71]. Nociplastic pain is defined as “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" [72]. Recently, clinically useful criteria for nociplastic pain were established such that chronic nociplastic pain was defined as: (1) pain duration >3 months, (2) a regional rather than discrete distribution, (3) not entirely explained by nociceptive or neuropathic pain mechanisms and (4) displaying clinical signs of pain hypersensitivity in the region of pain. The presence of a history of pain hypersensitivity in the region of pain and defined co- morbidities (e.g. sleep disturbance and cognitive problems) strengthen the probability of nociplastic pain [71]. Some patients in the high somatic symptoms cluster meet the requirements of chronic nociplastic pain such that they may report regional pain distribution (i.e. variable pain intensity across the back), report pain that cannot entirely be explained by nociceptive or neuropathic mechanisms, show clinical signs of pain hypersensitivity (i.e. low thermal and pressure thresholds) and psychosocial co- morbidities [73].

3.1.6.2 Clinical implications

The management and treatment of chronic back pain may remain a challenge. Current back pain guidelines highlight multidisciplinary management using a biopsychosocial model as the standard of care. A comprehensive use of exercises, physical therapy, cognitive behavioural therapy, and medical treatments with a active commitment of the patients and parents are associated with positive clinical outcomes [15, 16]. Studies investigating quantitative sensory testing and psychosocial factors in relation to musculoskeletal pain have shown the importance of a multidimensional assessment [18, 61, 74-76]. Georgopoulos et al. (2019) highlight that the baseline assessment with quantitative sensory testing was a valuable instrument to predict clinical outcomes including disability in patients with musculoskeletal pain. Improving the diagnostic process by identifying 'clusters' of patients with chronic back pain based on results of quantitative

sensory testing, pain- related outcomes and psychosocial factors may help clinicians provide an improved individualized care to patients [77].

Exercises, physical therapy and psychological therapies are aimed to focus on helping patients return to their desired level of functioning through progressive engagement in previously avoided activities and a self- management approach to pain [16, 77]. Studies targeting the central pain processes have used physical activity to reduce the presence of temporal summation pain [78, 79]. Therefore, the patients belonging to an adaptive cluster who display temporal summation of pain, possibly arising from central facilitation, may benefit from a multidimensional programme centred on physical activity [80].

Psychological therapies, delivered individually or in groups in the paediatric chronic pain population, have been shown to reduce pain symptoms, disability and negative affect, but also modify social environmental factors to enhance functional status [81]. Hence, a multicomponent approach focused on psychological therapeutic interventions addressing anxiety, depression and poor sleep quality and on the probable pain hypersensitivity may be more beneficial for patients that are grouped in the high somatic symptoms cluster who display more functional disability, mental distress and sleeps problems.

Pharmacological treatments and interventional procedures are mainly supported through studies conducted in adults. Clinical trials in adults suggested that sodium channel modulators such as local anaesthetics could be useful to treat pain conditions associated with peripheral sensitization [82, 83]. Moreover, patients with potential involvement of central pain processes could benefit more from gabapentinoids, inhibiting central neuronal sensitization [84]. Therefore, patients belonging to the pain-sensitive cluster with possible involvement of central and peripheral

pain mechanisms may benefit from a multidimensional program centred on pharmacological or interventional strategies.

3.1.6.3 Limitations and conclusions

There are certain limitations to this study that should be explicit. First, healthy controls were not tested so it is unknown if all pain- free children would fall into one cluster, a new cluster or have a variety of pain profiles as highlighted by Bair et al. (2016). Furthermore, the exclusion of healthy controls limits the extent of the involvement of the underlying nociceptive mechanisms in chronic musculoskeletal pain being clinically relevant. However, the objective of the study was to identify and describe profiles of patients to identify potential treatment responders and ultimately lead to personalized treatment. The second limitation was the cross- sectional nature of the study such that the long- term stability over weeks or months was not studied in this cohort. Therefore, it is unknown whether patients shift from one cluster to another depending on if a therapeutic intervention was given. Future work, conducting a prospective study that includes healthy controls to determine which psychophysical profile is a risk factor to chronic back pain and/or to determine whether a tailored treatment approach based on the clinical profile of the patient is beneficial, is warranted.

In conclusion, despite different pathologies, this study identified clusters of children and adolescents experiencing chronic back pain based on physical and psychosocial profiles. The assessment of chronic back pain should be comprehensive to assess multiple elements contributing to pain, including pathophysiology, somatosensory functioning, and psychosocial factors to improve multidisciplinary pain management.

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3.1.8 Conflict of interest

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3.1.9 Author contribution

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

3.1.10 Data availability statement

The data and code used to support the findings of this study are available from the corresponding author upon request.

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Manuscript 2 – Clusters of facilitatory and inhibitory conditioned pain modulation responses in a large sample of children, adolescents and young adults with chronic pain

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3.2.1 Summary

Findings from the current study add to the literature by describing different clinical phenotypes of central pain mechanisms of youth with chronic pain.

3.2.2 Abstract

Introduction: When investigating the role of facilitatory and inhibitory pain mechanisms such as conditioned pain modulation (CPM) and temporal summation of pain (TSP), it is important to take both into consideration in a single experimental model to provide the most information on subgroups of patients. Therefore, the objective of this study was to identify subgroups in a large population of pediatric patients with chronic pain based on their facilitatory and inhibitory pain mechanisms and compare them with controls.

Methods: 521 females and 147 males between 8 and 21 years old underwent a CPM assessment using a 2-minute tonic noxious heat stimulation as the test stimulus and a 2-minute cold pressor task (CPT) (12°C) as the conditioning stimulus.

Results: The best partition of clusters of patients was three clusters accounting for 27.15% of the total variation in the data. Cluster 1 (n=271) was best characterized by high pain intensity during the CPT, lack of TSP during the test stimuli, and efficient inhibitory CPM. Cluster 2 (n=186) was best characterized by low pain intensity during the CPT, lack of TSP during the test stimuli, and efficient inhibitory CPM. Cluster 3 (n=151) was best characterized by high pain intensity during the CPT, presence of TSP during the test stimuli, and inefficient inhibitory CPM.

Discussion: A single thermal CPM experimental design can identify combinations of facilitatory and inhibitory pain modulation responses. Findings from the current study add to the literature by describing different clinical phenotypes of central pain mechanisms of youth with chronic pain.

Keywords: cluster, pediatric, conditioned pain modulation, chronic pain, control.

3.2.3 Introduction

Chronic pain affects about 11-38% of youth [1]. Using psychophysical procedures, pediatric studies have shown that chronic pain is associated with altered excitatory and inhibitory endogenous pain modulation systems [2-11]. The endogenous inhibitory pathways of pain modulation can be indirectly assessed using a conditioned pain modulation (CPM) paradigm using the concept of "pain inhibits pain", in which one painful stimulus, the conditioning stimulus, modulates another pain-inducing stimulus, the test stimulus [2, 12]. Studies have observed a lower capacity to inhibit the post-conditioned painful test stimulus in patients with chronic pain conditions when compared to age-matched controls [3, 4, 7, 13, 14]. The endogenous facilitatory pain modulation mainly assessed using a temporal summation paradigm have been shown to be involved in some chronic pain conditions [8-11, 15, 16]. Temporal summation of pain (TSP) is referred to as an amplification of pain perception in response to repeated or continuous painful stimulation, at a constant intensity, which indirectly reflect an increased excitability at the spinal level and receptive fields of the nociceptive spinal cord neurons [17]. Evaluating temporal summation will help understand the endogenous facilitatory pain mechanisms (e.g., central sensitization) in youth and its role in chronic pain conditions.

Considering the role of endogenous facilitatory and inhibitory pain responses such as CPM and TSP, and the heterogeneity within the different populations, it is important to take both into consideration in a single experimental model to give as much information as possible on subgroups of patients that may benefit from a specific therapeutic treatment [18]. Researchers and clinicians have turned to identify distinct subgroups of pediatric chronic pain patients that may be relevant for treatment, as individuals respond differently to standardized treatments [11, 19-21]. However, these studies strictly investigated pain and psychosocial characteristics in their analysis and there

is limited data evaluating subgroups based on the endogenous pain mechanisms of pediatric chronic pain patients. Our group has shown the heterogeneity of CPM efficiency and temporal summation in samples of patients with chronic musculoskeletal pain [7, 22-24]. However, the pain modulation responses were considered separately and no association between facilitatory and inhibitory pain modulation responses were investigated or observed.

Therefore, the objective of this study was to identify subgroups in a large population of pediatric patients with chronic pain based on their endogenous facilitatory and inhibitory pain modulation responses. We conducted an exploratory analysis investigating interrelationships between individuals regarding their CPM efficiency and TSP from one CPM experimental design.

3.2.4 Methods

3.2.4.1 Participants

This study regrouped multiple studies whose ethics approval were all obtained prior to the beginning of the recruitment from the McGill University and McGill University Health Centre Research Ethics Boards (A08-M71-14B, A11-M62-15B, A09-M17-17B, 2019-4887). This has facilitated analysis of a large and novel cohort for investigation unlike our previously published work [7, 22-24]. Between 2015 and 2021, patients were recruited in the spine or orthopedic outpatient clinics of the Shriners Hospitals for Children – Canada, or by referral from the Chronic Pain Clinic from the Montreal Children's Hospital. Aged-matched controls with no chronic pain were recruited between 2018 and 2021 through word of mouth, advertisements, and a collaborative high school nearby. Signed informed consent was obtained from participants over 14 years old and parents of participants 13 years old and under. To ensure appropriate comparison across the different studies, appropriate inclusion/exclusion criteria for the patients included in the analysis

were established. Inclusion criteria for patients were male or female between 8 and 21 years old, reporting chronic pain (at least once a week for more than three months). Participants who did not speak English or French, or had developmental delay or substantial functional limitations that would interfere with completing measures were excluded from the study.

3.2.4.2 Conditioned Pain Modulation Assessment

3.2.4.2.1 Pain perception

Pain prior to the assessment was measured verbally using a numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain imaginable). Pain perception during the heat pain procedure was assessed using a computerized visual analogue scale (CoVAS), ranging from 0 (no pain) to 100 (worst pain imaginable), linked to a 9 cm2 warm calibrated thermode connected to a Q-sense apparatus (Medoc, Israel). Pain perception during the cold pain procedure was assessed verbally using a NRS 0-10.

3.2.4.2.2 Pre-test

CPM assessment was conducted using a protocol as previously described by our group [7, 22-24]. Tests were conducted by research assistants, who were trained and evaluated by the principal investigator of the study, following rigorous standards of procedure to decrease between-tester variability. The thermode with a baseline of 32°C and a 0.3°C/second upslope was applied three times. Participants were given the CoVAS and advised to move the cursor towards the "100" mark when they first report pain (pain threshold) and that the cursor had to be at the "100" mark when the pain was intolerable. The mean temperature at which they rated their pain intensity at 50/100 with the CoVAS was calculated.

3.2.4.2.3 Test stimulus (TS)

The thermode was applied to the right forearm to reach a pre-determined test temperature to a pain intensity 50/100 (T50) and it remained constant for 120 seconds. Participants were told to evaluate their pain with the COVAS throughout the test. The average pain intensity during the 120 seconds was calculated.

3.2.4.2.4 Conditioning stimulus (CS)

A cold pressor task (CPT) was used as the conditioning stimulus involving the immersion of their left forearm in a bath filled with cold water (12°C) for 120 seconds. Every 15 seconds, the participants verbally reported their pain intensity using the NRS 0-10. The average pain intensity during the CS was then calculated. If a participant removed their arm before the end of the 120 seconds, an average pain intensity score of 10/10 was given.

3.2.4.2.5 Assessment of inhibitory pain response

To evaluate the endogenous inhibitory pain response (CPM efficiency), the CPT was immediately followed by a second tonic heat TS with the same pre-determined test temperature. Pain modulation was measured as the percentage difference in average pain intensity of the test stimuli [25]: $100\%x(CoVAS_{after}-CoVAS_{before})/CoVAS_{before}$. A CPM efficiency between -100% and -30% was considered optimal, between -30% and -10%, suboptimal, and between -10% and +100%, inefficient. A 30% reduction in pain intensity was labelled to be a clinically important difference [26], and is approximately the mean value of inhibitory CPM observed in previous studies [7, 22, 27, 28].

3.2.4.2.6 Assessment of facilitatory pain response

Facilitatory pain responses (TSP) was assessed as the absolute difference in pain intensity during the last 60 seconds of each TS (temporal summation phase) [27]. An increase or decrease in pain intensity was determined clinically significant if the change was equal or larger than 20/100 during the temporal summation phase [26, 29].

3.2.4.3 Statistical analysis

Statistical analyses were performed using the R Studio software. Data were assessed for normality and descriptive statistics were conducted to describe the sample and presented as mean ± standard deviation, unless indicated otherwise. One-way analysis of variance (ANOVA) was conducted to determine differences in CPM assessment outcomes between gender, duration of chronic pain, presence of more than one pain site, and presence of pain prior to CPM assessment. Spearman correlation was conducted to determine whether age, pain prior to the assessment and T50 were associated with the CPM assessment outcomes. Differences between patients and controls was conducted using the chi-squared test and one-way ANOVA controlling for gender, due to gender differences observed in heat pain threshold (Supplementary Table 1), followed by the Scheffé's test. The effect size (ω^2) for significant ANOVA models was also calculated (small=0.01; medium=0.06; large=0.14). Clusters within the chronic pain sample were identified using an unsupervised clustering method performed using the FactoMineR package [30]. To investigate the facilitatory and inhibitory pain modulation responses, the cluster analysis involved four quantitative indicator variables: 1) the absolute change in pain intensity during the last sixty seconds of the first TS (TS1); 2) the average pain intensity during the CS; 3) the absolute change in pain intensity during the last sixty seconds of the second TS (TS2); and 4) the CPM efficiency. Due to the different scales and units for each variable, hierarchical clustering with k-means

consolidation was conducted on the four variables standardized into z-scores to ensure that all variables were considered equally. The best partition of clusters was the one with the highest relative loss of inertia [31] and based on parsimony.

To determine cluster effect of the indicator variables, an ANOVA model was conducted along with a Fisher test. Differences between clusters and controls was conducted using the chi-squared test and one-way ANOVA controlling for gender followed by Scheffé's test.

3.2.5 Results

639 patients and 60 controls were consented. However, only 608 patients were included in the analysis (n=31 did not complete the CPM assessment or had missing information from the CPM assessment). The mean age for patients was 15.18±2.14 years old (range=8.2 21.4) and 80.92% were females. The mean age for controls was 15.06±2.23 years old (range=10.0-18.9) and 48.33% were females. Most of the patients experienced pain for more than 6 months (n=568) and primarily in their back (n=410). The primary location of pain of the other patients included the head/neck (n=31), the abdomen (n=24), the groin area (n=1), the thorax (n=14), the upper extremities (n=18) and the lower extremities (n=109). Moreover, 50.99% of the patients reported more than one pain site. Prior to the assessment, 70.23% of the patients reported pain with a mean pain intensity of 4.16±2.16. Overall, patients reported a mean pain intensity of 2.95±2.62 (range=0-10) with patients recruited from the pain clinic reporting significantly higher pain intensity prior to the CPM assessment (3.51±2.61) than patients from the outpatient clinics (2.54±2.56, $t=4.57$, $p<0.001$). Only one control reported mild pain prior to the CPM assessment.

The average heat pain threshold was 38.95±3.13°C and 38.71±2.63°C for patients and controls respectively ($F=1.17$, $p=0.280$). The average test temperature was 43.41±2.38°C and 42.84±2.38°C for patients and controls respectively ($F=4.33$, $p=0.038$, $\omega^2<0.01$). Heterogeneity

within our patient sample was observed regarding the CPM efficiency (Figure 3-3). The mean CPM efficiency for patients was -26.13%±43.20%. The mean CPM efficiency for controls was 32.47%±35.47% and was not significantly different from patients (F=2.21, p=0.137).

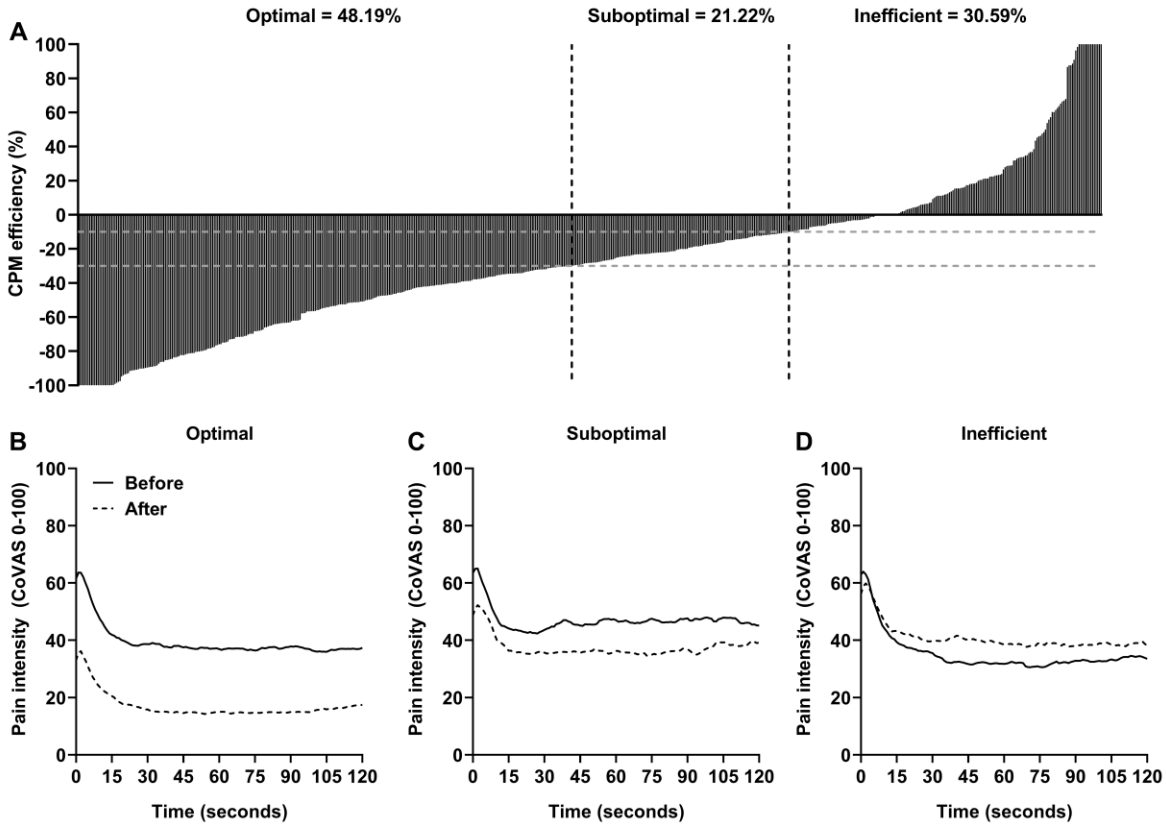

Figure 3-3. Distribution of conditioned pain modulation efficiency of the patient sample
A. Distribution of conditioned pain modulation (CPM) efficiency of the patient sample in which each bar represents one patient (n = 608). A negative value represents pain inhibition while a positive value represents pain facilitation. The grey dotted lines mark the cutoffs for optimal (n = 293), suboptimal (n = 129) and inefficient (n = 186) CPM efficiency. **B-D.** Mean pain intensity during the tonic thermal heat stimulations of the patients based on the different patterns of the CPM score: (B) optimal, (C) suboptimal and (D) inefficient. A greater percentage difference in pain intensity during the tonic thermal heat stimulations demonstrates a greater CPM efficiency. CoVAS: computerized visual analog scale.

Heterogeneity within patients was also observed regarding the change in pain intensity during the last sixty seconds of TS1 (Figure 3-4) and TS2 (Figure 3-5). The mean reported change

in pain intensity during the last sixty seconds of TS1 was 0.45 ± 21.70 in our patients and was significantly different from controls, whose mean reported change in pain intensity was 6.46±19.05 (F=4.92, p=0.027, ω^2=0.01). The mean reported change in pain intensity during the last sixty seconds of TS2 was 1.84±19.05 in our patients, but was not significantly different from controls, whose mean reported change in pain intensity was 5.16±14.49 (F=1.63, p=0.202).

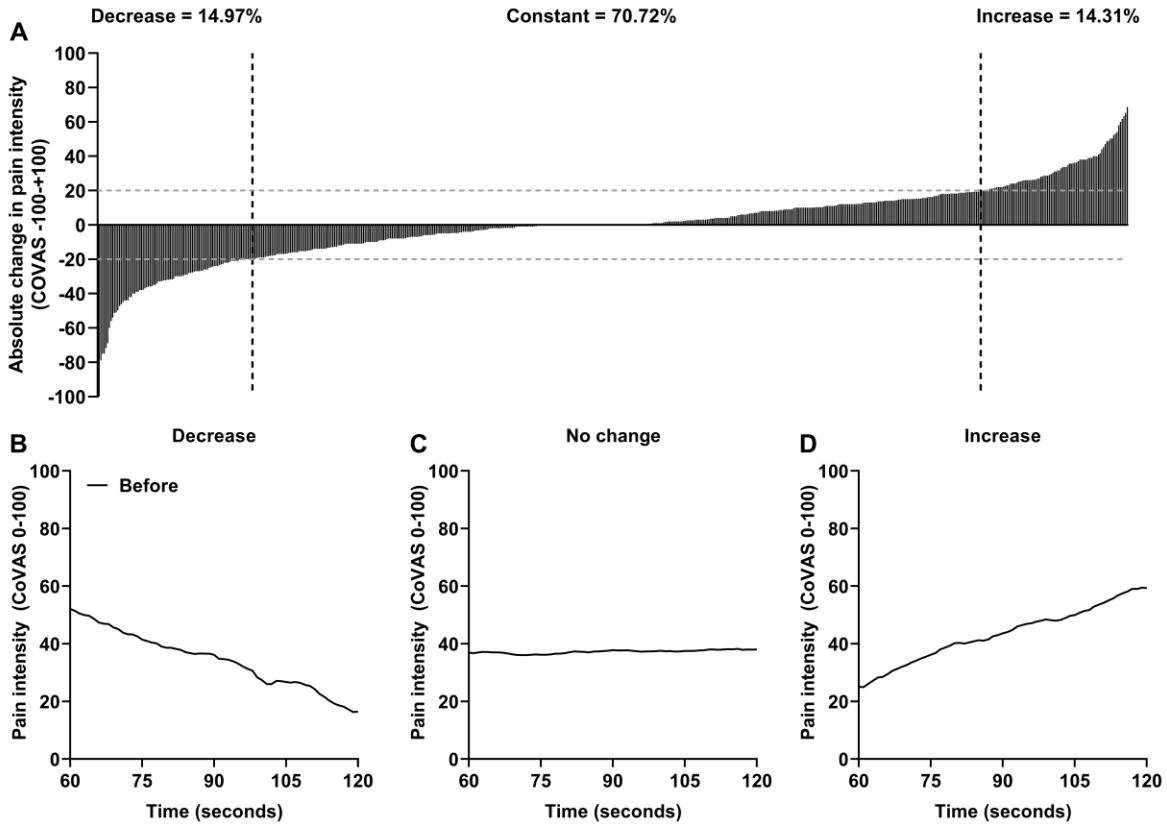

Figure 3-4. Distribution of the change in pain intensity during the tonic thermal heat stimulation before the conditioning stimulus of the patient sample

A. Distribution of the change in pain intensity during the tonic thermal heat stimulation before the conditioning stimulus (TS1) of the patient sample in which each bar represents one patient (n = 608). The grey dotted line marks the cutoffs for a significant decrease of -20/100 (n = 91), no change (n = 430) and a significant increase of 20/100 (n = 87) in pain intensity. **B-D.** Mean pain intensity during the last sixty seconds of the tonic thermal heat stimulation before the conditioning stimulus of the patients based on the different patterns of change in pain intensity: (B) a decrease, (C) no change, or (D) an increase in pain intensity. CoVAS: computerized visual analog scale.

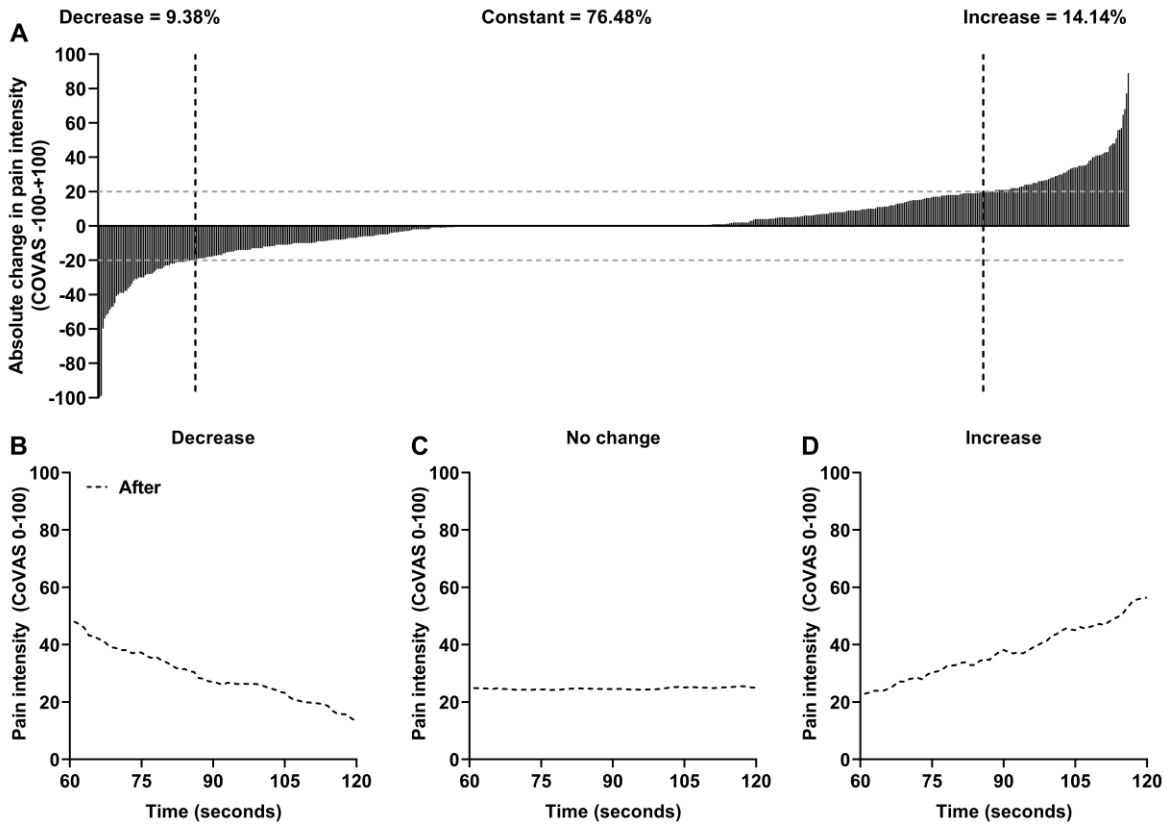

Figure 3-5. Distribution of the change in pain intensity during the tonic thermal heat stimulation after the conditioning stimulus of the patient sample

A. Distribution of the change in pain intensity during the tonic thermal heat stimulation after the conditioning stimulus (TS2) of the patient sample in which each bar represents one patient (n = 608). The grey dotted line marks the cutoffs for a significant decrease of -20/100 (n = 57), no change (n = 465) and a significant increase of 20/100 (n = 86) in pain intensity. **B-D.** Mean pain intensity during the last sixty seconds of the tonic thermal heat stimulation after the conditioning stimulus of the patients based on the different patterns of change in pain intensity: (B) a decrease, (C) no change, or (D) an increase in pain intensity. CoVAS: computerized visual analog scale.

The mean reported pain intensity during the CS was 6.92±2.44 and 6.31±2.41 for patients and controls respectively ($F=4.03$, $p=0.027$, $\omega^2<0.01$). Fifty-one patients and six controls removed their arm before the end of the 120 seconds. However, no difference in CPM efficiency was observed between the participants that completed the CPT and those that did not (data not shown).

A significant positive association was observed between the age of participants and their T50 (rho=0.137, 95%CI=0.059-0.212, p<0.001) and their mean pain intensity during the CPT (rho=-0.086, 95%CI=-0.163--0.008, p=0.027). Furthermore, a significant positive association was observed between the participants' T50 and the change in pain intensity during the temporal summation phase of the TS before (rho=0.205, 95%CI=0.129-0.279, p<0.001) and after (rho=0.218, 95%CI=0.142-0.291, p<0.001) the CPT. Other within-cohort differences or associations can be found in Supplementary Table 1.

3.2.5.1 Cluster analysis

The best partition of clusters of the patient sample was three clusters accounting for 27.15% of the total variation in the data (Figure 3-6). 271 patients (44.57%) were grouped in cluster 1, 186 (30.59%) in cluster 2, and 151 (24.84%) in cluster 3.

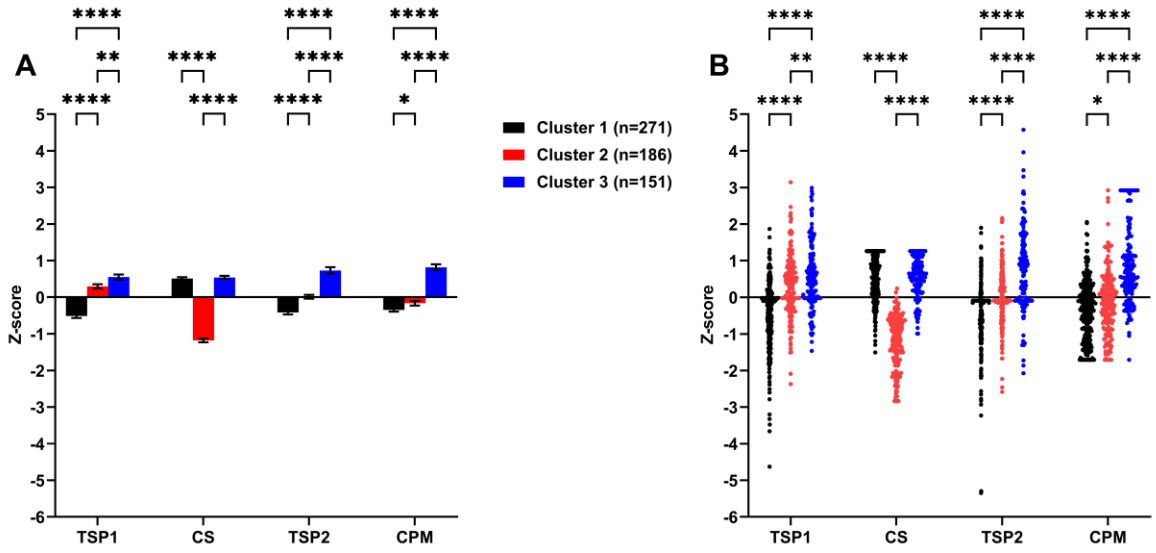

Figure 3-6. Plot of the indicator variables respective of the three clusters
(A) Bar and (B) scatter plot of the indicator variables respective of the three clusters derived from the hierarchical cluster analysis with k-means. A score of zero is aligned with the mean of the sample. The Fisher pairwise comparisons' p values are shown. *p<0.05; **p<0.01; ***p<0.05;

****p<0.01. Bars = mean ± SEM. Points = individual patients. TSP1, change in pain intensity during last 60 seconds of the first test stimulus; CS, conditioning stimulus; TSP2, change in pain intensity during last 60 seconds of the second test stimulus; CPM; conditioned pain modulation efficiency. Patients grouped in cluster 1 are characterized by significantly lower values for TSP1, TSP2 and CPM efficiency compared to cluster 2 and 3. Patients grouped in cluster 3 are characterized by significantly higher values for TSP1, TSP2 and CPM efficiency compared to cluster 2 and 3 compared to cluster 1 and 2. Patients in cluster 2 are characterized to have significantly lower values for CS compared to cluster 1 and 3.

No significant between-cluster difference was observed regarding their demographic characteristics (Table 3-5). However, significant differences were observed between clusters and controls regarding all CPM-related outcomes (ω^2 ranging from 0.05-0.56) (Table 3-6).

Table 3-5 Demographic characteristics of each cluster

Variable	Cluster 1 n = 271)	Cluster 2 (n = 186)	Cluster 3 (n = 151)	Test statistic	p-value
Location of recruitment, n (%)				3.01*	0.222
Chronic pain clinic	106 (39.11)	81 (43.55)	72 (47.68)		
Orthopedic outpatient clinic	165 (60.89)	105 (56.45)	79 (52.32)		
Age, Mean ± SD (Range)	15.15 ± 2.12 (8.2-21.4)	15.26 ± 1.86 (9.0-19.3)	15.15 ± 2.49 (8.3-21.0)	0.21†	0.810
Gender, n (%)				1.84*	0.398
Female	218 (80.44)	156 (83.87)	118 (78.15)		
Male	53 (19.56)	30 (16.13)	33 (21.85)		
Duration of chronic pain, n (%)				1.93*	0.381
3-6 months	18 (6.64)	9 (4.84)	13 (8.61)		
More than 6 months	253 (93.36)	177 (95.16)	138 (91.39)		
Primary location of pain, n (%)				19.00*	0.165
Head/Neck	14 (5.17)	13 (6.99)	4 (2.65)		
Upper limbs	4 (1.48)	10 (5.38)	4 (2.65)		
Thorax	6 (2.21)	6 (3.23)	2 (1.32)		
Abdomen	12 (4.43)	9 (4.84)	3 (1.99)		
Back	192 (70.85)	113 (60.75)	105 (69.53)		
Groin	1 (0.37)	0	0		
Lower limbs	41 (15.13)	35 (18.82)	33 (21.85)		
Presence of secondary pain sites, n (%)				2.89*	0.236
No	139 (51.29)	94 (50.54)	65 (43.04)		
Yes	132 (48.71)	92 (49.46)	86 (56.96)		
Presence of pain prior to CPM assessment, n (%)				1.32*	0.516
No	79 (27.15)	49 (26.34)	48 (31.79)		
Yes	188 (69.38)	137 (73.66)	102 (67.55)		

Average pain intensity, mean ± SD (Range)	3.08 ± 2.78 (0-10)	2.94 ± 2.50 (0-10)	2.73 ± 2.48 (0-8.5)	0.81†	0.444

*Chi squared test statistic. †One-way ANOVA test statistic controlled for gender.
a - c: significant difference through Scheffé's post hoc test ($p<0.05$) from cluster 1 to cluster 3 respectively

Patients in cluster 1 significantly displayed the lowest test temperature used for the TS, and a higher proportion displayed a significant decrease in pain intensity (i.e., -20/100) during the temporal summation phase of TS1 and TS2 (Figure 3-7A). Patients in cluster 2 significantly displayed the highest test temperature used for the TS, and the lowest average pain intensity reported during the CS. Interestingly, despite a large proportion of this cluster displaying optimal CPM efficiency similar to cluster 1, a larger proportion displayed a significant increase in pain intensity (i.e., +20/100) during the temporal summation phase of TS1 and TS2 than cluster 1 (Figure 3-7B). In contrast to cluster 1, patients grouped in cluster 3 significantly displayed a higher test temperature used for the TS, but lower than cluster 2, and a higher proportion displayed a significant increase in pain intensity during the temporal summation phase of TS1 and TS2 (Figure 3-7C). Moreover, a larger proportion of cluster 3 displayed an inefficient CPM.

Table 3-6 Facilitatory and inhibitory pain responses of each cluster and controls

Variable	Cluster 1 (n = 271)	Cluster 2 (n = 186)	Cluster 3 (n = 151)	Controls (n = 60)	Test statistic	p-value	ω^2-value
Heat pain threshold (°C), Mean ± SD	38.23 ± 2.90[b]	39.98 ± 3.33[a,c]	38.96 ± 2.92[b]	38.71 ± 2.63[b]	**13.39†**	**<0.001**	0.05
Test temperature (°C), Mean ± SD	42.70 ± 2.45[b,c]	44.39 ± 1.98[a,c]	43.49 ± 2.27[a,b]	42.84 ± 2.38[b]	**22.04†**	**<0.001**	0.09
Change in pain intensity during last 60 seconds of TS1 (NRS -100 - +100), Mean ± SD	-10.62 ± 20.17[b,c]	6.89 ± 17.72[a]	12.39 ± 19.23[a]	6.46 ± 19.05[a]	**58.54†**	**<0.001**	0.21
Decrease, n (%)	73 (26.94)	12 (6.45)	6 (3.31)	5 (8.33)	**97.73***	**<0.001**	
Constant, n (%)	189 (69.74)	139 (74.73)	102 (67.55)	43 (71.67)			
Increase, n (%)	9 (3.32)	35 (18.82)	43 (28.48)	12 (20.00)			
Average pain intensity during CS (NRS 0 - 10), Mean ± SD	8.16 ± 1.47[b]	4.04 ± 1.70[a,c]	8.24 ± 1.32[b]	6.31 ± 2.41[a,b,c]	**287.23†**	**<0.001**	0.56
Change in pain intensity during last 60 seconds of TS2 (NRS -100 - +100), Mean ± SD	-6.11 ± 16.42[b,c]	2.10 ± 14.11[a,c]	15.78 ± 20.66[a,b]	5.16 ± 14.49[a,c]	**55.90†**	**<0.001**	0.2
Decrease, n (%)	39 (14.39)	11 (5.91)	7 (4.64)	4 (6.67)	**110.15***	**<0.001**	
Constant, n (%)	222 (81.92)	157 (84.41)	86 (56.95)	47 (78.33)			
Increase, n (%)	10 (3.69)	18 (9.68)	58 (38.41)	9 (15.00)			
CPM efficiency (%), Mean ± SD	-41.06 ± 34.19[c]	-33.10 ± 37.84[c]	9.25 ± 44.27[a,b]	-32.67 ± 35.47[c]	**60.87†**	**<0.001**	0.21
Inefficient, n (%)	45 (16.61)	44 (23.66)	97 (64.24)	14 (23.33)	**116.79***	**<0.001**	
Suboptimal, n (%)	61 (22.51)	44 (23.66)	24 (15.89)	12 (20.00)			
Optimal, n (%)	165 (60.89)	98 (52.69)	30 (19.87)	34 (56.67)			

*Chi squared test statistic. †One-way ANOVA test statistic controlled for gender.
a - c: significant difference through Scheffé's post hoc test ($p<0.05$) from cluster 1 to cluster 3 respectively
ω^2-value: 0.01 (small), 0.06 (medium), 0.14 (large)
TS1, tonic thermal heat stimulation before the conditioning stimulus CS, conditioning stimulus; TS2, tonic thermal heat stimulation after the conditioning stimulus, CPM, conditioned pain modulation

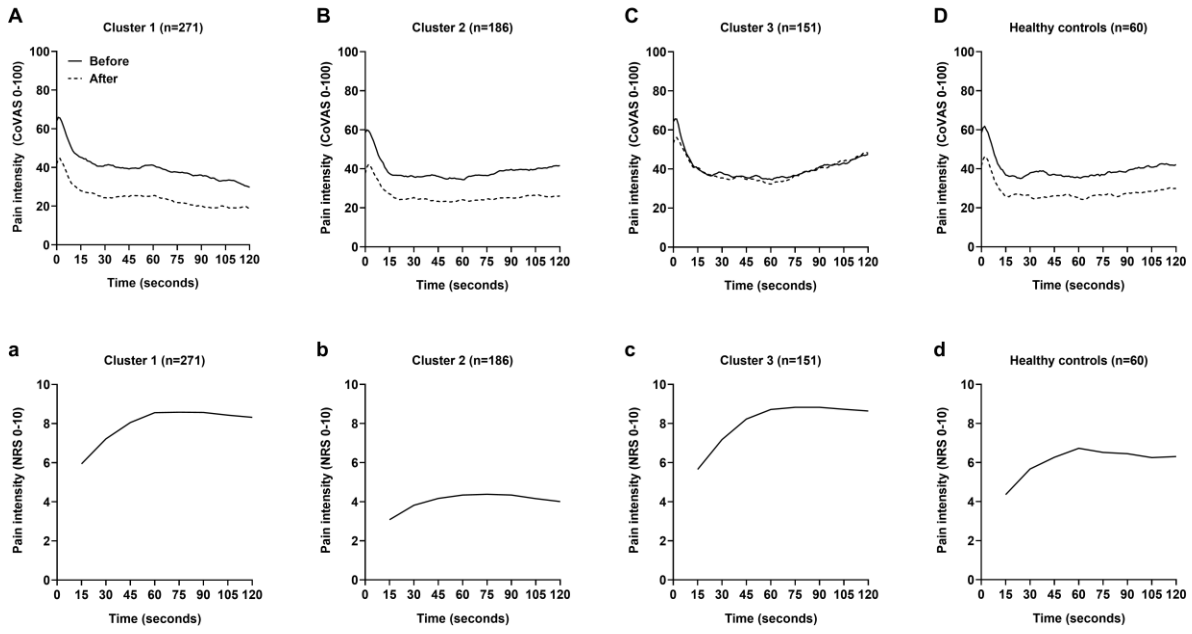

Figure 3-7. Mean pain intensity during the tonic thermal heat stimulations and cold pressor task for each patient cluster and healthy controls
Mean pain intensity during the tonic thermal heat stimulations (**A-D**) and cold pressor task (**a-d**) for each patient cluster and healthy controls. CoVAS: computerized visual analog scale; NRS, numerical rating scale.

When the clusters were compared to the controls, a significant difference in heat pain threshold ($p=0.025$) and T50 ($p<0.001$) was observed between cluster 2 and the controls. The heat pain threshold and T50 of controls were significantly lower than patients in cluster 2. A higher proportion of controls displayed a significant increase in pain intensity during the last sixty seconds of TS1 and TS2 than patients in cluster 1 ($p<0.001$). However, a smaller proportion of controls displayed a significant increase in pain intensity during the last sixty seconds of TS2 than patients

in cluster 3 (p=0.002). The average pain intensity of controls during the CPT was significantly different to all clusters. When controlling for gender, the average pain during the CPT of patients in cluster 2 was significantly lower than controls (p<0.001), while the average pain during the CPT of patients in cluster 1 (p<0.001) and 3 (p<0.001) were significantly higher than controls (Figure 3-7D). The mean CPM efficiency of controls was optimal and significantly different (p<0.001) from patients in cluster 3 which was inefficient.

3.2.6 Discussion

The objective of this study was to identify subgroups of patients with chronic pain based on their endogenous pain mechanisms. This analysis revealed heterogeneity in our patients regarding their facilitatory and inhibitory pain responses from one experimental design. We observed a significant association between the T50 and the age of the participants, and the change in pain intensity during the temporal summation phase of the TS. Furthermore, based on the CPM assessment outcomes of the patients, three subgroups were identified to best describe the patients. Cluster 1 was best characterized by high pain intensity during the CPT, lack of TSP, and efficient inhibitory CPM. Cluster 2 was best characterized by low pain intensity during the CPT, lack of TSP, and efficient inhibitory CPM. Cluster 3 was best characterized by high pain intensity during the CPT, presence of TSP, and inefficient inhibitory CPM.

A weak positive correlation was observed between the test temperature of the test stimuli of the participants and their age. Research in small samples of healthy children and adolescents or with Type 1 diabetes mellitus have observed no correlation between age and heat-induced pain threshold [32, 33]. However, Blankenburg et al. [34] observed a strong effect of age on heat pain threshold in a large population of healthy children and adolescents. Our findings extend their observation by demonstrating in a large population of pediatric sample with or without chronic

pain, that younger children are more sensitive to heat-induced pain. Age and sex have been shown to impact CPM in adult populations, such that males have a greater CPM efficiency than females, and older adults show less CPM [35]. Only the effect of age has been observed in healthy youth, such that older children (12–17 years) showed greater CPM efficiency compared to younger (8–11 years) children [36]. In the current study, no association was observed between age or sex and CPM efficiency, and no age/sex differences were observed between clusters. Although it has been hypothesized that pain inhibitory mechanisms may develop throughout childhood, and become stronger during adolescence, other predetermining factors may moderate the effect of age on CPM efficiency.

A significant difference in the average pain intensity reported during the CPT was observed between the patients and controls. The literature has shown conflicting results regarding pain responsivity in children with chronic pain during the CPT compared with controls [37-40]. Due to individual variability in pain perception, a group difference in pain perception in previous studies with smaller sample sizes may be difficult to detect. Our large sample found a significant effect between groups that is small in magnitude but was more evident after cluster analysis, where patients grouped in cluster 1 and 3 reported significantly higher pain intensity during the CPT. Several aspects of the CPT methodology may also explain the conflicting results in the literature, such as CPT preparation, water temperature, immersion time, audience effects, arm removal, and measurement of pain outcomes [41]. An advantage of the CPT is the opportunity to observe or explore the influence of psychosocial and cognitive factors on pain and to test new psychological interventions for pain [42, 43]. Holley et al. (2017) observed that higher state pain catastrophizing in youth with new onset pain significantly predicted higher cold pressor pain, but trait pain catastrophizing had an inverse relationship [39]. This suggests that state and trait characteristics in

our population of pediatric patients may have different patterns of relevance in their chronic and acute pain experiences and may explain why patients in cluster 1 and 3 displayed higher pain intensity during the cold pressor task.

Patients grouped in cluster 3 displayed significant manifestation of impairment in central pain modulation, as observed in the presence of increased TSP during the test stimuli, and the large proportion of patients that displayed inefficient descending inhibitory pain control in this cluster, especially in comparison to controls. Studies in children and adolescents with chronic pain have observed overall lower inhibitory CPM response and facilitated temporal summation in comparison to controls [2]. Walker et al. (2012) observed that a subgroup of pediatric patients with functional abdominal pain and met the criteria for functional gastrointestinal disorders at their follow-up appointment, presented significantly greater thermal pain wind-up at their follow-up appointment, suggesting the involvement of central pain modulation in this transition [11]. In our large population of patients, we observed a small proportion of patients (24.84%) displayed amplification in facilitatory pain mechanisms with impairment in inhibitory conditioned pain modulation responses. With such manifestation of impairment in central pain modulation, these patients are suggested to be at high propensity for widespread pain and co-morbidities in the future [18, 44]. However, this was not investigated due the cross-sectional nature of the analysis such that the long-term stability over weeks or months was not studied in this population. Neuronal plasticity occurs in children throughout development which can shape the functional integrity of the descending inhibitory systems. A previous study in young children observed that prematurity and exposure to numerous painful interventions after birth lead to alterations in the endogenous pain modulatory mechanisms [45]. Therefore, it is unknown whether patients shift from one cluster

to another depending on multiple factors such as developmental neuroplasticity or if a therapeutic intervention was given [46, 47].

Unexpectedly, a significant difference was observed between patients and controls regarding the test temperature of the test stimuli, in which patients required higher temperature to induce pain intensity of 50/100. However, the effect size was very small, but this effect emerged nevertheless as being significantly different probably due to the large sample size that was recruited in the current study. The effect size became medium after cluster analysis was conducted, such that a significant difference in heat pain threshold and T50 was observed only between cluster 2 and controls. Studies using thermal modalities during CPM assessment in pediatrics display conflicting results between patients and controls regarding their heat pain threshold or test temperature [3, 14, 39, 48]. Thermal experimental heat pain through a thermode allows for predictable stimulations of pain with a sharp and piercing sensation with various durations [49]. As thermal pain threshold and the T50 reflect the perception of acute pain, the fact we did not observe hyperalgesic responses in the pediatric chronic pain patients using these measures may not be fully surprising, as they probably do not target mechanisms relevant to chronic pain. There is indeed evidence in the adult literature indicating that tonic noxious stimuli correlate better with clinical pain than acute stimuli, because clinically relevant pain rarely lasts only for a few seconds [50-52]. Pain normally lasts for minutes to hours, or longer. It has been proposed that tonic stimulation paradigms seem better to investigate pain in more real-world circumstances by the fact that tonic noxious stimuli recruit endogenous pain modulation mechanisms [50-52].

A significant difference was observed in the change in pain intensity during the temporal summation phase of the TS before the CS between our patients and controls. Unexpectedly, the change in pain intensity during the temporal summation phase of TS1 of controls was significantly

higher than patients. However, the effect size was small. This statistical significance between cohorts was probably due to the large patient sample size. Moderate effects were only observed after cluster analysis was conducted. A study conducted by Potvin et al. observed lower temporal summation of pain in a large proportion of adult patients with fibromyalgia when compared to controls [53]. However, the test temperature was significantly lower in patients with fibromyalgia suggesting that hypersensitivity may have been present prior to the CPM assessment, which was not the case in our sample. Studies in children have shown conflicting results regarding the presence or absence of TSP in patients with chronic pain [48, 54]. However, these studies had a small sample size, meaning that the observed lack of significant differences may be due to a lack of statistical power (e.g. type-II error). Therefore, our results highlight that in a large sample of pediatric patients with chronic pain, there is only a subgroup of patients that display hyperexcitability of the central nervous system through TSP.

The generalizability of our findings to children, adolescents and young adults with chronic pain should be interpreted considering certain limitations. Chronic pain is a dynamic and complex phenomenon influenced by many variables such as individual predisposition, pathology, psychological factors and environmental factors [37, 45, 55, 56]. Most of the patients reported pain in their back due to the patients primarily being recruited from the spine outpatient clinics of our institution, and two of the four studies including only patients with spinal pathologies. Therefore, despite no between-cluster difference based on location of pain or other demographic and clinical variables, replication studies using a similar simple clustering method investigating facilitatory pain responses and inhibitory conditioned pain modulation responses alongside the medical history of patients, their psychosocial variables, and their physical functioning is warranted. Another limitation is the small sample of controls in our analysis. It is unknown if similar differences would

have been observed if the control group would have been larger. Furthermore, another limitation was the use of a single experimental model for CPM and TSP. Different paradigms for CPM have been conducted in the pediatric population [2]. Temporal summation can also be assessed by applying a series of heat-pain stimuli of the same temperature (e.g., 47°C) [11]. It is unknown whether the use of another experimental pain procedure would have produced different results. Although the main strength of the current experimental procedure allows to elicit and measure multiple pain modulation responses, adding another CPM paradigm and TSP paradigm may further the strengthen our findings.

In conclusion, this study highlights the heterogeneity in facilitatory and inhibitory pain modulation responses in a large sample of pediatric patients with chronic pain. Furthermore, chronic pediatric pain was found to be associated with cold hyperalgesia, and a subgroup of patients was identified to display increased TSP and reduced inhibitory CPM efficacy. Future studies with a longitudinal design are required to replicate the clusters identified and to determine is these clusters predict the development of diffuse widespread pain. Moreover, such studies will need to pay attention to the methodological characteristics of the experimental paradigms conducted.

3.2.7 Acknowledgements

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3.2.9 Supplementary material

Supplementary Table 1. Within cohort differences and correlations

Variable	HPT	T50	TSP1	CS	TSP2	CPM
***Age**	0.038 (0.329)	0.137 (<0.001)	-0.010 (0.791)	-0.086 (0.027)	-0.028 (0.476)	0.038 (0.333)
†**Gender**	4.571 (0.033)	1.089 (0.297)	0.178 (0.673)	0.254 (0.615)	0.087 (0.768)	1.941 (0.164)
***Pain prior to CPM assessment**	-0.078 (0.045)	-0.004 (0.911)	-0.022 (0.572)	0.036 (0.355)	-0.071 (0.068)	0.037 (0.336)
***Test temperature**			0.172 (<0.001)		0.157 (<0.001)	-0.031 (0.421)

Data is presented as rho-value (p-value), except for gender which is presented as F-value (p-value)
*Spearman correlation. †One-way ANOVA test.

Manuscript 3 – Phenotyping chronic musculoskeletal pain in male and female adolescents: psychosocial profiles, somatosensory profiles and pain modulatory profiles

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3.3.2 Abstract

Purpose: A major limitation in treatment outcomes for chronic pain is the heterogeneity of the population. Therefore, a personalized approach to the assessment and treatment of children and adolescents with chronic pain conditions is needed. The objective of the study was to subgroup pediatric patients with chronic MSK pain that will be phenotypically different from each other based on their psychosocial profile, somatosensory function, and pain modulation.

Patients and Methods: This observational cohort study recruited 302 adolescents (10–18 years) with chronic musculoskeletal pain and 80 age-matched controls. After validated self-report questionnaires on psychosocial factors were completed, quantitative sensory tests (QST) and conditioned pain modulation (CPM) were performed.

Results: Three psychosocial subgroups were identified: adaptive pain (n=125), high pain dysfunctional (n=115), high somatic symptoms (n=62). Based on QST, four somatosensory profiles were observed: normal QST (n=155), thermal hyperalgesia (n=98), mechanical hyperalgesia (n=34) and sensory loss (n=15). Based on CPM and temporal summation of pain

(TSP), four distinct groups were formed, dysfunctional central processing group (n=27) had suboptimal CPM and present TSP, dysfunctional inhibition group (n=136) had suboptimal CPM and absent TSP, facilitation group (n=18) had optimal CPM and present TSP, and functional central processing (n=112) had optimal CPM and absent TSP. A significant association between the psychosocial and somatosensory profiles. However, no association was observed between the psychosocial or somatosensory profiles and pain modulatory profiles.

Conclusion: Our results provide evidence that adolescents with chronic musculoskeletal pain are a heterogenous population comprising subgroups that may reflect distinct mechanisms and may benefit from different treatment approaches. The combination of screening self-reported questionnaires, QST, and CPM facilitate subgrouping of adolescents with chronic MSK pain in the clinical context and may ultimately contribute to personalized therapy.

Keywords: adolescents, chronic pain, musculoskeletal pain, quantitative sensory testing, conditioned pain modulation, temporal summation of pain

3.3.3 Introduction

Chronic pain is common affecting 11–38% of the children and adolescents with musculoskeletal pain being one of the most common types of pain [1,2]. Pain may have an idiopathic origin, may arise from a disease process, from treatments such as surgery, from trauma or injury, and may even involve pathological changes in central pain processing [3]. Patients with chronic pain also may experience functional disability, higher rates of missed school, poor sleep quality and mental health problems [4–6]. Understanding chronic pain in children and adolescents is crucial because about 20% of the children and adolescents living with chronic pain, have persistent pain in adulthood [7–10].

A major limitation in treatment outcomes for chronic pain is the heterogeneity of the population. Moreover, there is lack of strong evidence on the efficacy or risk supporting the use pharmacological treatments in pediatric chronic pain [11]. Therefore, a personalized approach to the assessment and treatment of children and adolescents with chronic pain conditions is needed. Researchers and clinicians have turned to identify heterogeneous subgroups of pediatric chronic pain patients [12–15]. However, these studies strictly investigated pain and psychosocial characteristics in their cluster analysis. Moreover, there are limited data evaluating subgroups based on the changes in somatosensory function and pain modulation of pediatric patients with chronic pain conditions [16]. Detailed phenotyping using recommended core outcomes [17], and tests such as quantitative sensory testing (QST) and conditioned pain modulation (CPM) may provide valuable information for individualized therapy.

The biopsychosocial approach to pain recognizes pain as a complex multidimensional experience that is the result of the interaction of biological, psychological and social factors. Each individual applies the term "pain" to a specific experience usually related to injury in their life, leading to different perception and expectation of pain [18]. Therefore, recommended core outcomes for pain trials encompass measures of psychosocial factors (e.g., pain catastrophizing, anxiety, depression, etc.), pain variability and pain qualities, and sleep and fatigue [19]. These domains can be assessed through standardized interviews or a diversity of self-reported questionnaires. Pain can be clinically divided into three categories reflecting an individual's somatosensory functioning: nociceptive, neuropathic and nociplastic [20]. Many sophisticated quantitative sensory tests provide information on the nociceptive transduction and/or modulation from all aspects of the somatosensory system, leading to mechanism-based pain management. QST is a set of non-invasive tests that examines the somatosensory function in children and adolescents

[21–23]. Studies using static QST (i.e., focusing on the determination of sensory threshold, or the rating of a single stimulus, and the corresponding magnitude of pain) have highlighted that in response to an objective sensory stimulus, either thermal or mechanical, an individual's perception and expectation of pain can be measured in a semi-objective manner [21,24–28]. Studies in the pediatric population using dynamic QST (i.e., focusing on the evaluation of pain modulation) have shown that chronic pain conditions are associated with altered excitatory and inhibitory endogenous pain modulation systems [10,15,29–36]. The endogenous inhibitory pathways of pain modulation can be indirectly assessed using the CPM paradigm [29,37]. Assessing CPM in a clinical setting may be a valuable tool to assess any deficits in the descending inhibitory pain response found in some chronic pain conditions such as abdominal pain and chronic musculoskeletal pain in youth when compared to healthy controls [10,30,33,38,39]. The endogenous facilitatory phenomenon of pain modulation such as temporal summation has been shown to be involved in the development of some chronic pain conditions such as sickle cell disease, fibromyalgia, migraines, and functional abdominal pain [15,34–36,40,41]. Evaluating temporal summation through repeated or continuous painful stimulation, at a constant intensity, may help understand the mechanisms of central sensitization in children and adolescents and its role in the genesis and maintenance of some chronic pain conditions [15,34–36,40,41].

The objective of the study was to subgroup pediatric patients with chronic MSK pain that will be phenotypically different from each other based on their psychosocial profile, somatosensory function, and pain modulation. We hypothesized that, through patient-reported outcomes extracted from questionnaires, and static and dynamic QST, distinct psychosocial profiles, somatosensory phenotypes and pain modulatory phenotypes would be identified in adolescents with chronic MSK pain.

3.3.4 Materials and methods

Ethics approval was obtained prior to the beginning of the recruitment from the Research Ethics Board of McGill University (A09-M17-17B). The study was conducted in accordance with the Declaration of Helsinki. Participants received a written informed consent prior to inclusion in the study, and a signature was obtained by the participant (14 years old and older) or their parent/legal guardian prior to the beginning of the study (13 years old and younger). Reporting is in accordance with the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines for cohort studies [42]. Throughout the article, we use the World Health Organization definition of adolescents (persons aged between 10 and 19 years) [43].

3.3.4.1 Participants

Participant recruitment occurred between January 2018 and June 2021. Potential patients between 10 and 18 years old were identified by a research assistant at the orthopedic outpatient clinics of the Shriner's Hospital Canada and from the Edwards Family Interdisciplinary Center for Complex Pain of the Montreal Children's Hospital. Potential candidates for the study included patients reporting chronic primary or secondary musculoskeletal pain (persistent or recurrent pain at least once a week for longer than 3 months) [44] in their electronic medical charts or by reference of the patient's physician. At their hospital visit for treatment seeking either for an orthopedic condition or for pain itself, patients were approached by a research assistant to participate in the study and to confirm eligibility prior to receiving signed consent. Potential aged-matched controls between 10 and 18 years old were recruited through word of mouth, recruitment advertisements in local magazines and social media, and a collaborative high school near our institutions. As recommended [45], a screening checklist for control recruitment was completed by a research assistant to ensure eligibility of "healthy" participants. The exclusion criteria for age matched

controls included 1) pain in the last 14 days, 2) pain lasting more than 24 hours on more than 3 days in the past 3 months, 3) taking more than 10 tablets of medication per month in the last 3 months, 4) suffering from diseases accompanied by long-lasting pain for longer than 3 months, 5) had psychological or psychiatric treatment for a long period in the past 5 years, 6) smoking more than 39 cigarettes per day, 7) drinking a lot of alcohol regularly, 8) consuming illegal drugs, including cannabis in the past month, 9) taking psychostimulants or other medication for therapeutic purposes regularly, and 10) having health issues, disorders or chronic dermal diseases in the tested areas [45]. Participants who did not speak English or French or had a diagnosis of developmental delay that would interfere with completing measures were also excluded.

3.3.4.2 Participant-reported outcome measures

3.3.4.2.1 Sociodemographic characteristics and medical history

Participant characteristics such as age, self-reported gender, ethnicity, past hospitalizations, and past surgeries were collected by a research assistant through face-to-face interviews.

3.3.4.2.2 Pain assessment

Pain assessment was mainly conducted in the form of a face-to-face interview and with the use of standardized pain-related questionnaires that have been validated in clinical pediatric studies assessing pain [46–49]. Patients were asked about the location of their primary site of pain using a body chart from the Adolescent Pediatric Pain Tool (APPT) [50] which was divided into 67 sections, and the duration and frequency of their pain. The current pain intensity and average, worst and best pain intensity over the last month was reported using the numerical rating scale (NRS) ranging from 0 (no pain at all) to 10 (worst pain imaginable). Moreover, the pain experience

was assessed using a list of 67 descriptive words in the APPT, assessing the four dimensions of pain (37 sensory, 11 affective, 8 evaluative and 11 temporal descriptive words) [50]. The APPT has been shown to have adequate content, construct, and criterion validity, and reliability in clinical and nonclinical groups of children and adolescents between 8 and 17 years old [51]. To identify if their pain had a neuropathic component, the Douleur Neuropathique 4 (DN4) questionnaire was completed by patients and the physicians. By summing all 10 questions, scores of equal to or greater than 4 indicated that the pain experienced by the patient is likely neuropathic [46,52]. The DN4 questionnaire has not been validated in children and adolescents. However, despite its very low-level evidence for satisfactory criterion validity and low-level evidence for satisfactory construct validity and reliability, the DN4 questionnaire has been described to be the most suitable for clinical use [53,54]. The Functional Disability Inventory (FDI) questionnaire was completed by patients, in which the total score is summed to detect different levels of disability [55]. The FDI has been reported to have high internal consistency, moderate-to-high test–retest reliability, moderate cross-informant (parent–child) reliability, and good predictive validity [48,55]. The FDI is 15-item scale using a Likert-type rating scale, ranging from 0 (no trouble) to 4 (impossible) for a maximum score of 60 (0–12 no/minimal, 13–20 mild, 21–29 moderate, and ≥30 severe disability).

3.3.4.2.3 Pain catastrophizing

The Pain Catastrophizing Scale for Children (PCS-C) was completed by patients and controls to assess the degree to which they experienced negative thoughts or feelings while experiencing pain [56]. The PCS-C is a 13-item scale and can be divided into three subscales: rumination, magnification and helplessness. Responses for each statement are done using a Likert-type rating scale, ranging from 0 (not at all) to 4 (extremely) for a maximum score of 52 (0–14

low, 15–25 moderate and ≥26 high catastrophizing) [57]. The PCS-C has been shown to have good internal consistency [58] as well as sufficient test–retest stability [59], and good construct and predictive validity [56]. The cut-offs have been established to identify significant differences in child functioning across catastrophizing levels in children and adolescents with chronic pain [57].

3.3.4.2.4 Anxiety and depressive symptoms

The Revised Child Anxiety and Depression Scale (RCADS) questionnaire was completed by patients and controls to assess children's self-report of depression and anxiety [60]. Based on the participant's age and grade in school, their total scores are converted into a *T*-score (≤64 below, 65–69 borderline, and ≥70 above clinical threshold). The RCADS has been validated in clinical and nonclinical groups of children and adolescents in grades 3–12, and showed good internal consistency (Cronbach α=0.78–0.88) and item set and factor definitions consistent with DSM-IV anxiety disorders and depression [60,61].

3.3.4.2.5 Sleep quality

The Pittsburgh Sleep Quality Index (PSQI) questionnaire was completed by patients and controls to assess sleep quality, in which a global score of 5 or higher indicated poor sleep quality [62]. The PSQI is the most commonly used measure in clinical and research settings showing good internal consistency (Cronbach α=0.70–0.83) and has been validated in clinical and nonclinical groups of adolescents [63–65].

3.3.4.3 Quantitative sensory testing

Each participant underwent a specific protocol of mechanical and thermal QST, lasting 37.0±11.5 minutes in a 22.7±0.7°C private room, to obtain a comprehensive profile of somatosensory functioning adapted from previous studies to reduce complexity and time, and fit

within the time constraints of clinical routines [28,66,67]. For patient participants, mechanical QST was performed on the left volar forearm as the control area and followed by their most painful anatomical region indicated by the patient as the affected area. For "healthy" participants, mechanical QST was performed on the left volar forearm. For all participants, thermal QST was performed on the left volar forearm. Eight sensory parameters were tested in the same sequence and included:

1. Mechanical detection threshold (MDT). Calibrated von Frey filaments ranging between 0.008 and 300 grams were applied sequentially in an up-down method, and the threshold was measured as the geometrical mean of the three last detected and three first detected filaments.
2. Dynamic mechanical allodynia (DMA). A standardized brush exerting light touch at a single stroke for 2 cm in length was applied five times. The pain intensity (NRS 0–10) was reported after each stroke, and the average was calculated.
3. Vibration detection threshold (VDT). A tuning fork was applied to a joint or bony prominence of the tested area three times, and the threshold was measured as the average score at which the participants no longer detected the vibration (x/8).
4. Mechanical pain summation (MPS). One and 10 stimulations from a calibrated pinprick were applied, and the participants reported their pain immediately at the end of the stimulation(s) and every 15 seconds post-stimuli during a 60-second period. The whole sequence was conducted three times. The wind-up ratio (WUR) was measured as the ratio of the average pain intensity immediately reported after the train of 10 stimuli over the average pain intensity immediately reported after one stimulus. The presence of painful after-sensations (ie, pain intensity >0 using the NRS 0–10) at the end of the 60-second period after 1 and 10 stimuli were also noted.

5. Pressure pain threshold (PPT). A handheld algometer was applied perpendicular to the body surface under underlying bone or muscle, and the threshold was measured as the mean of three trials.
6. Warm detection threshold (WDT), and heat pain threshold (HPT). A 9-cm2 warm calibrated thermode connected to a Q-sense apparatus (Medoc, Israel) with a baseline 32°C, 0.3°C/second upslope, and a limit of 50°C was applied three times. The thresholds were calculated from the mean of the 3 three trials for each modality (when they first sensed heat, and when they first reported pain).

3.3.4.4 Conditioned Pain Modulation

CPM assessment, lasting 22.3±4.1 minutes, was conducted using tonic heat on the right forearm as the test stimulus and the cold pressor task on the left arm as the conditioning stimulus as previously described protocols [29,33,68–71]. For the test stimulus, a thermode was applied to the right volar forearm to reach a predetermined test temperature to a pain intensity 50/100 (T50). The maximum value of 46.9°C was used as a security cut-off. Once the target temperature was reached, it remained constant for 120 seconds. To avoid expectation effects, participants were told that the temperature of the thermode could increase, remain stable or decrease and that they would have to evaluate their pain with a computerized visual analogue scale (CoVAS) throughout the test. This scale ranged from 0 (no pain) to 100 (worst pain imaginable). At the end of the 120 seconds of the test-stimulus, the average pain intensity during the 120 seconds was calculated. A cold pressor task (CPT) was used as the conditioning stimulus involving the immersion of their left forearm in a bath filled with cold water (12°C) for 120 seconds to trigger the descending inhibitory pain response. Every 15 seconds, the participants were asked to report their pain intensity using the NRS 0–10. The average pain intensity during the conditioning stimulus was

then calculated. If a participant removed their arm before the end of the 120 seconds, an average pain intensity score of 10/10 was given. In order to evaluate the endogenous inhibitory pathways of pain modulation, and here measured as the CPM efficiency, the CPT was immediately followed by a second tonic heat test stimulus. The same pre-determined test temperature for each participant was used for the second tonic heat test stimulus. In addition, the thermode was not placed on the exact same area in the right volar forearm to avoid peripheral sensitization. CPM efficiency was measured as the percentage difference in average pain intensity of the test stimuli reported with the CoVAS such that a negative value for CPM response represents pain reduction with a more efficient CPM response [$100\% \times (CoVAS_{after} - CoVAS_{before})/CoVAS_{before}$] [72]. A CPM efficiency between −100% and −30% was considered as optimal, between −30% and −10%, suboptimal, and between −10% and +100%, inefficient. These cut-offs were determined based on a clinical important change in pain intensity measured on an 11-point numerical pain rating scale. A 10–30% reduction in pain was labeled to be a minimal improvement, while a 30% reduction in pain intensity was labelled to be a clinically important difference in pain intensity, and is approximately the mean value of inhibitory conditioned pain modulation observed in previous studies [33,69–71]. Endogenous facilitatory pain mechanisms, and here measured as temporal summation of pain (TSP), was assessed as the absolute difference in pain intensity during the last 60 seconds of the first test-stimuli (temporal summation phase) [69]. Based on previous studies, an increase in pain intensity was determined to be minimally clinically significant if the change was equal or larger than 2/10 during the test stimuli [73,74].

3.3.4.5 Statistical Analysis

Data were analyzed using R Studio and plotted using Prism Version 9. QST parameters were analyzed in accordance with previous studies in adolescents [16,28]. Analyses were based on

available data, with no imputation for missing data. Descriptive statistics are presented as mean and standard deviation, unless otherwise specified. Differences between patients and healthy controls were compared with the Student *t*-test. Differences within patients and controls in regards to age, gender and race for the psychosocial, QST and CPM assessment outcomes were compared with using a three-way analysis of variance (ANOVA). Comparisons with the affected area thresholds in patients were based on within-cohort control measures at the control area. This gives sensitive within-participant comparisons for clinical testing. Comparisons with the control area thresholds in patients were based on between-cohort control measures at the control area. To compare QST parameters independently of their physical dimension, *z*-scores were calculated (e.g., *z*-score = affected $site_{patient}$ – control $site_{patient}$ cohort mean/control $site_{patient}$ cohort SD). An average *z*-score for all QST parameters of the control and affected area was then calculated for each patient. Gain of function (hyperalgesia) is indicated as a positive *z*-score and a loss of function (sensory loss) as a negative score.

Psychosocial profiles within the pediatric chronic pain sample were identified using an unsupervised clustering method performed using the FactoMineR package in the R Studio software [75]. The cluster analysis involved nine quantitative indicator variables (pain catastrophizing, self-reported neuropathic component of pain, functional disability, sensory, affective, evaluative and temporal descriptors of pain, anxiety and depression symptoms, and sleep quality). Due to the different scales for each variable, the nine variables were standardized into *z*-scores to ensure that all variables are considered equally. Hierarchical clustering with k-means consolidation using the FactorMineR package in the R Studio software was conducted on the standardized indicator variables. The hierarchical clustering was therefore performed multiple times to minimize within-cluster variability and maximize between-cluster variability. The best

partition of clusters was the one with the highest relative loss of inertia [76] and based on parsimony. To determine cluster effect of the indicator variables, an ANOVA model was conducted along with a Scheffe test.

We used a deterministic approach to phenotype our patient cohort using the patient's somatosensory profile (sensory loss, mechanical hyperalgesia, thermal hyperalgesia or healthy) [16,77,78]. An ANOVA model was then conducted along with a Scheffe test to evaluate the main effect of the patients' somatosensory profiles using their QST values.

We used the pre-determined cut-offs mentioned above to subgroup our patient cohort based on their facilitatory and inhibitory pain modulation responses [79]. Patients who displayed suboptimal or inefficient CPM and temporal summation of pain were included in the "dysfunctional central processing" subgroup. Patients who displayed optimal CPM and temporal summation of pain were grouped under the "facilitation" subgroup. Patients who displayed suboptimal or inefficient CPM and absence of temporal summation of pain were grouped under the "dysfunctional inhibition" subgroup. Patients who displayed optimal CPM and absence of temporal summation of pain were grouped under the "functional central processing" subgroup. An ANOVA model along with a Scheffe test was then conducted to evaluate the main effect of the CPM profiles of the patients on their CPM outcomes.

To investigate associations between psychosocial profiles, somatosensory profiles and pain modulatory profiles, a chi-square test was conducted. One-way ANOVAs were conducted for the distinct profiles to identify differences with regard to all outcome measures.

3.3.5 Results

3.3.5.1 Patients clinical characteristics and pain assessment

Three hundred and six patients with chronic musculoskeletal pain were recruited from January 2018 to June 2021 (Figure 3-8). Four patients were excluded after subsequent evaluation revealed they did not experience pain at least once a week (n=3) or they had difficulty understanding and answering the interview questions (n=1). Therefore, the data of 302 patients are presented (Table 3-7), but only 293 patients completed the CPM assessment (Figure 3-9). Eighty age-matched controls were also recruited from January 2018 to June 2021. Age-matched controls were recruited through word of mouth (n=22), our institution's staff children (n=16), our institution's patients relatives (n=6), pamphlets and social media (n=9), and a collaborative high school near our institution (n=27).

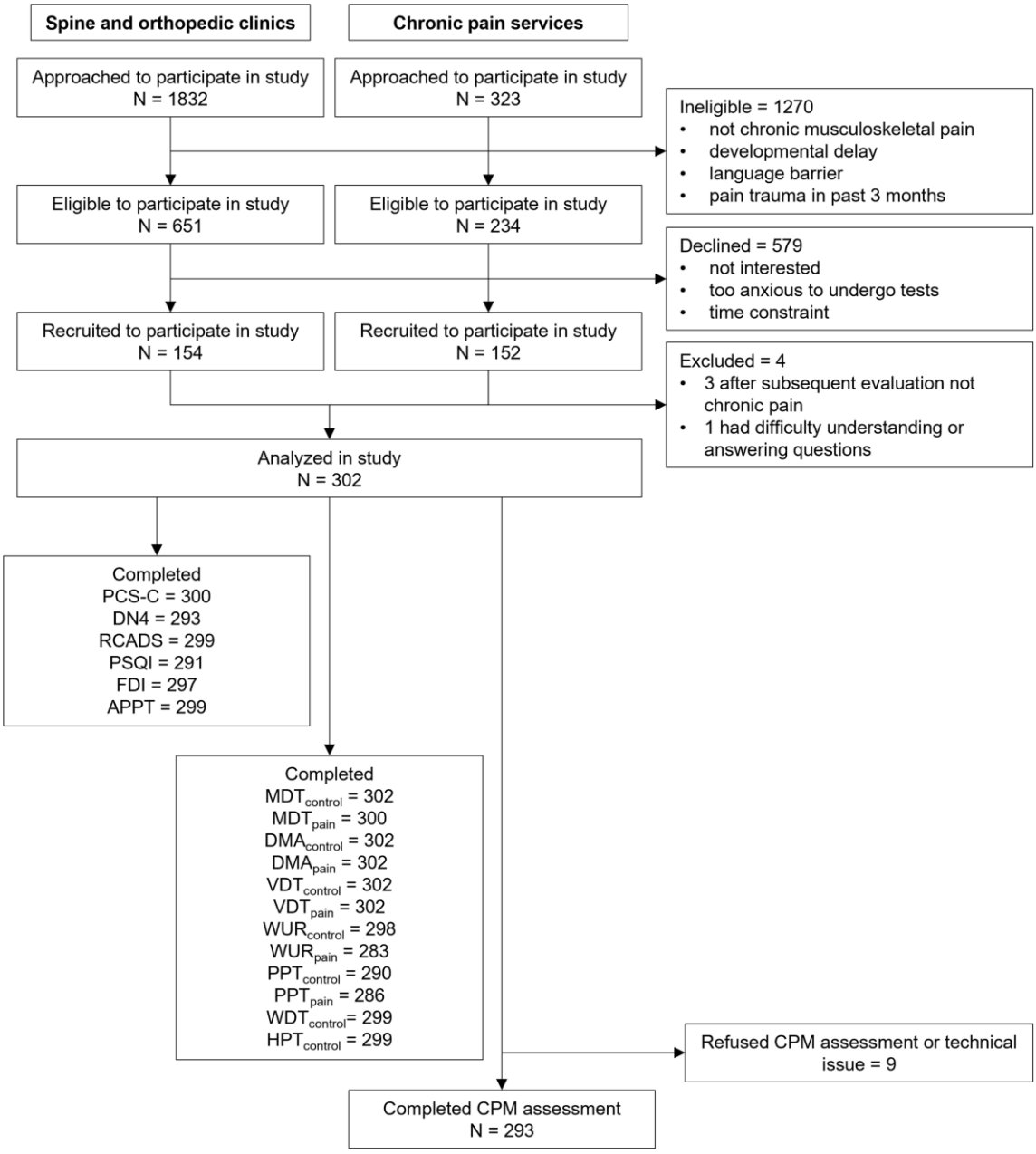


Figure 3-8. Flow chart of patient recruitment and evaluations.

Abbreviations: PCS-C, Pain Catastrophizing Scale – Child version; DN4, Douleur Neuropathique 4 questionnaire; RCADS, Revised Child Anxiety and Depression Scale; PSQI, Pittsburgh Sleep Quality Index; FDI, Functional Disability Inventory; APPT, Adolescent Pediatric Pain Tool; control, control area test site; pain, most painful location test site; MDT, mechanical detection threshold; DMA, dynamic mechanical allodynia; VDT, vibration detection threshold; WUR, wind-up ratio; PPT, pressure pain threshold; WDT, warm detection threshold; HPT, heat pain threshold; CPM, conditioned pain modulation.

Table 3-7. Characteristics of the patient and control cohorts

Variable	Chronic MSK pain patients (n = 302)	Age-matched controls (n = 80)	Test statistic	p-value	Cohen's d
Age, mean ± SD	14.93 ± 1.95	14.99 ± 1.96	0.25†	0.805	
Younger adolescent (10-13 years), n (%)	87 (28.81)	20 (25.00)	0.29*	0.593	
Older adolescent (14-18 years), n (%)	215 (71.19)	60 (75.00)		0.576	
Gender, n (%)			53.98*	**<0.001**	
Female	247 (81.79)	32 (40.00)			
Male	55 (18.21)	48 (60.00)			
Race[a], n (%)			0.41*	0.521	
Caucasian (White)	231 (76.49)	58 (72.50)			
Person of color	70 (23.18)	22 (27.50)			
Past hospitalizations (>48 hours), n (%)			4.23*	**0.040**	
No	212 (70.20)	66 (82.50)			
Yes	90 (29.80)	14 (17.50)			
Past surgeries, n (%)			1.59*	0.207	
No	182 (60.26)	55 (68.75)			
Yes	120 (39.74)	25 (21.25)			
Adolescent Pediatric Pain Tool					
Pain locations, x/67	8.78 ± 8.40	-			
Sensory descriptors, x/37 %	23.26 ± 15.36	-			
Affective descriptors, x/11 %	15.57 ± 17.41	-			
Evaluative descriptors, x/8 %	43.73 ± 24.52	-			
Temporal descriptors, x/24 %	29.01 ± 15.96	-			
Douleur Neuropatique 4 questionnaire					
Total score, mean ± SD	2.96 ± 2.03	-			
Likely neuropathic, n (%)	133 (44.04)	-			
Functional Disability Inventory					
Total score	15.79 ± 9.76	-			
No/minimal disability, n (%)	119 (39.40)	-			
Mild disability, n (%)	80 (26.49)	-			
Moderate disability, n (%)	71 (23.51)	-			
Severe disability, n (%)	27 (8.94)	-			
Pain catastrophizing scale					
Total score, mean ± SD	28.40 ± 9.98	18.55 ± 8.77	8.66†	**<0.001**	1.01
Low catastrophizers, n (%)	30 (9.93)	29 (36.25)	56.145*	**<0.001**	
Moderate catastrophizers, n (%)	84 (27.81)	36 (45.00)			
High catastrophizers, n (%)	186 (61.59)	15 (18.75)			

Variable	Chronic MSK pain patients (n = 302)	Age-matched controls (n = 80)	Test statistic	p-value	Cohen's d
Revised Child Anxiety and Depression Scale					
Total T-score, mean ± SD	52.27 ± 14.08	46.35 ± 11.59	3.87†	**<0.001**	0.44
Below clinical threshold, n (%)	244 (80.79)	74 (92.50)	5.55*	0.062	
Borderline clinical threshold, n (%)	10 (3.31)	1 (1.25)			
Above clinical threshold, n (%)	45 (14.90)	5 (6.25)			
Pittsburgh Sleep Quality Index					
Total score, mean ± SD	7.81 ± 3.77	4.88 ± 2.61	7.93†	**<0.001**	0.82
Good sleep quality, n (%)	62 (20.53)	35 (43.75)	16.43*	**<0.001**	
Poor sleep quality, n (%)	229 (75.83)	43 (53.75)			
MDT^{log} (mN), mean ± SD					
Control area	0.69 ± 1.22	0.42 ± 1.05	1.93†	0.055	
Tested area	0.67 ± 1.77	-	0.60‡	0.552	
DMA^{log} (NRS 0-10), mean ± SD					
Control area	-4.27 ± 1.18	-4.53 ± 0.48	3.01†	**0.003**	0.24
Tested area	-3.40 ± 2.07	-	7.74‡	**<0.001**	0.52
VDT (x/8), mean ± SD					
Control area	6.72 ± 0.98	7.04 ± 0.85	2.92†	**0.004**	0.34
Tested area	5.96 ± 1.35	-	17.18‡	**<0.001**	0.64
WUR^{log} (ratio), mean ± SD					
Control area	0.75 ± 0.98	0.60 ± 0.54	1.81†	0.072	
Presence of painful after sensations after 10 stimuli in the control area, n (%)	113 (37.42)	17 (21.25)	7.05*	**0.008**	
Tested area	0.66 ± 1.03	-	0.62‡	0.534	
Presence of painful after sensations after 10 stimuli in the tested area, n (%)	126 (41.72)	17 (21.25)	13.19*	**<0.001**	
PPT^{log} (kPa), mean ± SD					
Control area	5.11 ± 0.47	5.38 ± 0.54	4.01†	**<0.001**	0.55
Tested area	5.11 ± 0.65	-	2.26‡	**0.024**	<0.01
WDT^{log} (°C from baseline), mean ± SD					
Control area	0.43 ± 0.69	0.48 ± 0.66	0.64†	0.523	
HPT (°C), mean ± SD					
Control area	39.35 ± 2.73	39.02 ± 2.60	0.99†	0.324	
CPM efficiency (%), mean ± SD	-22.16 ± 44.28	-33.37 ± 33.28	2.48†	**0.014**	0.27
Inefficient, n (%)	104 (34.44)	18 (22.50)	5.56*	0.062	
Suboptimal, n (%)	60 (19.87)	16 (20.00)			
Optimal, n (%)	130 (43.05)	46 (57.50)			

Variable	Chronic MSK pain patients (n = 302)	Age-matched controls (n = 80)	Test statistic	p-value	Cohen's d
TSP (NRS -10-+10), mean ± SD	0.02 ± 2.27	0.33 ± 2.05	1.16†	0.25	
Absence, n (%)	249 (82.45)	66 (82.50)	0.09*	0.761	
Presence, n (%)	45 (14.90)	14 (17.50)			

Notes: Percentages do not always add up to 100% due to missing data for some demographic variables. [a]Due to low frequency of some racial groups, races typically identified by Statistics Canada as a visible minority group (American Indian or Alaska Native, Asian, Black or African American, Latin American, Arab, and Mixed Race) were collapsed into a single category. *Test statistic for chi-square test. †Test statistic for Student's t test between patients and controls. ‡Test statistic for Student's t test between control area and tested pain area. Significant p-values < 0.05 are bolded. Cohen's d values are displayed for significant p-values for the Student's t test (0.2 – small; 0.5 – medium, 0.8 – large).

Abbreviations: MSK, musculoskeletal; log, log-transformed data; MDT, mechanical detection threshold; DMA, dynamic mechanical allodynia; VDT, vibration detection threshold; WUR, wind-up ratio; PPT, pressure pain threshold; WDT, warm detection threshold; HPT, heat pain threshold; CPM, conditioned pain modulation; TSP, temporal summation of pain

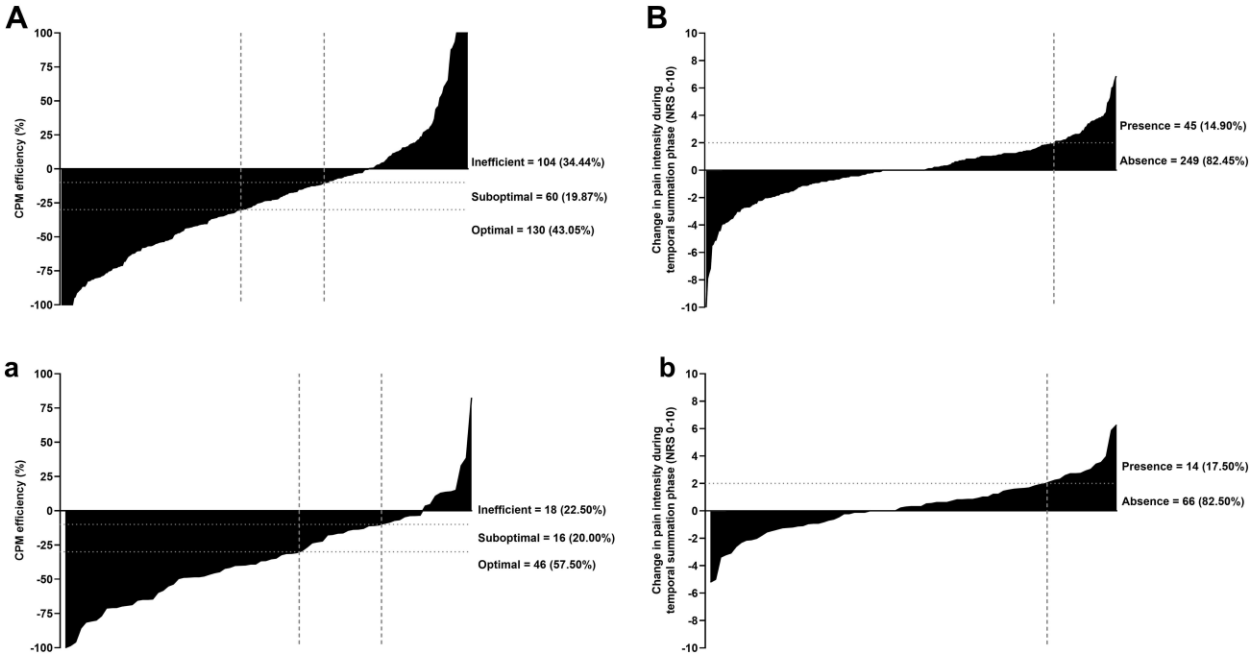


Figure 3-9. Inhibitory and facilitatory pain modulations responses in adolescents with chronic musculoskeletal pain and age-matched controls.

The distribution of conditioned pain modulation in (A) patients and (a) age-matched controls show a spectrum of individual responses. Bar = individual participants. A CPM efficiency between −100% and −30% was considered as optimal, between −30% and −10% suboptimal and between

−10% and +100% inefficient. The distribution of temporal summation of pain during the test stimulus before the conditioning stimulus in (B) patients and (b) age-matched controls also show a spectrum of individual responses. Bar = individual participants. An increase in pain intensity was determined minimum clinically significant if the change was equal or larger than 20/100 during the last 60 seconds of the first test stimulus (ie, presence of temporal summation of pain).

The primary location of pain of the patients included the head and neck (n=11), upper limbs (n=24), thorax (n=4), back (n=175), and lower limbs (n=88). Pain radiated for 48% of the patients, and the presence of a secondary pain site was reported by 52% of the patients. Mild-moderate pain intensity (3.34±2.41) was reported by the patients the day of the assessment using the NRS 0–10. Patients reported moderate intensity average pain (5.81±1.93), severe intensity worst pain (8.39±1.56), and mild intensity best pain (1.87±1.86) during the last month before the evaluation. A majority of the patients report their pain for more than 12 months (n=223), while others report pain for 3–6 months (n=29) or between 6 and 12 months (n=50). Most of the patients report pain at least once a day (n=232), while 50 patients report pain every second day and 20 patients report pain only once a week. Moreover, most of the patients reported their painful episode to be constant (n=180). Other durations of the painful episodes included a few seconds (n=5), a few minutes (n=42) and a few hours (n=75).

3.3.5.2 Differences between patients with chronic musculoskeletal pain and healthy controls

Patients reported significantly higher pain catastrophizing score, *T*-score for the RCADS, global score for the PSQI than controls (Table 3-7). Patients displayed a significantly lower vibration detection threshold and lower pressure pain threshold than controls (Table 3-7). Furthermore, patients displayed a significantly less efficient conditioned pain modulation than age-matched controls.

A significant main effect of age, gender and race was heterogeneously present across the psychosocial, QST and CPM assessment outcomes (for details see Supplementary Tables 1 and 2). However, subsequent post-hoc comparisons were not significant, except for younger adolescent (10–13 years) controls displaying a lower pressure pain threshold than the older (14-18 years) controls ($p = 0.003$).

3.3.5.3 Self-reported questionnaires identifies distinct psychosocial profiles

Based on the highest relative loss of inertia and parsimony, the best partition of psychosocial profiles of the chronic pain sample was three clusters accounting for 31.27% of the total variation in the data. Psychosocial profiles differed significantly from each other ($F_{2,2649} = 622.00$, $p < 0.001$), and psychosocial parameter × profile interaction ($F_{16,2649} = 13.87$, $p < 0.001$) was observed, meaning that a patient's response to a specific questionnaire differed based on their profile. No significant main effect of the psychosocial parameters was observed ($F_{8,2649} = 1.03$, $p = 0.412$) (Figure 3-10A).

Adaptive pain (AP) cluster: One hundred and twenty-five patients (41%) were grouped in this cluster. Patients grouped in the AP cluster reported significantly the lowest scores for pain catastrophizing, were less likely to report their pain as neuropathic in nature, report less functional disability, less locations of pain, less descriptors of pain, reported less anxiety and depression symptoms and better sleep quality than the other two clusters (see Supplementary Table 3). Patients grouped in the AP cluster reported higher scores for pain catastrophizing, but similar scores for anxiety and depression symptoms and sleep quality than controls (Figure 3-10B-D).

High pain dysfunctional (HPD) cluster: one-hundred and fifteen (38%) were grouped in this cluster. Patients in the HPD cluster 2 reported significantly higher scores for nearly all questionnaires than the AP cluster, except similar number of temporal descriptors of pain. Patients

in the HPD cluster were significantly older compared to those in the AP cluster. Moreover, patients in the HPD cluster reported significantly higher pain intensity the day of the assessment, and higher average, worst and best pain intensity over the last month compared with patients in the AP cluster (see Supplementary Table 3). Patients grouped in the HPD cluster reported higher scores for pain catastrophizing, more anxiety and depression symptoms and worst sleep quality than controls (Figure 3-10B-D).

High somatic symptoms (HSS) cluster: Sixty-two patients (21%) were grouped in this cluster. Patients in the HSS cluster reported similar scores for the Functional Disability Inventory, the Revised Child Anxiety and Depression Scale, and the Pittsburgh Sleep Quality Index, and reported a similar number of pain locations than those of the HPD cluster. However, patients grouped in the HSS cluster reported significantly higher scores for the pain catastrophizing, were more likely to report their pain as neuropathic in nature, and use more descriptors of pain (sensory, affective, evaluative, and temporal) than the HPD cluster. Patients in the HSS cluster also reported higher pain intensity the day of the assessment, in higher average, worst and best pain intensity over the last month compared with patients in the AP cluster (see Supplementary Table 3). Patients grouped in the HSS cluster reported higher scores for pain catastrophizing, more anxiety and depression symptoms and worst sleep quality than controls (Figure 3-10B-D).

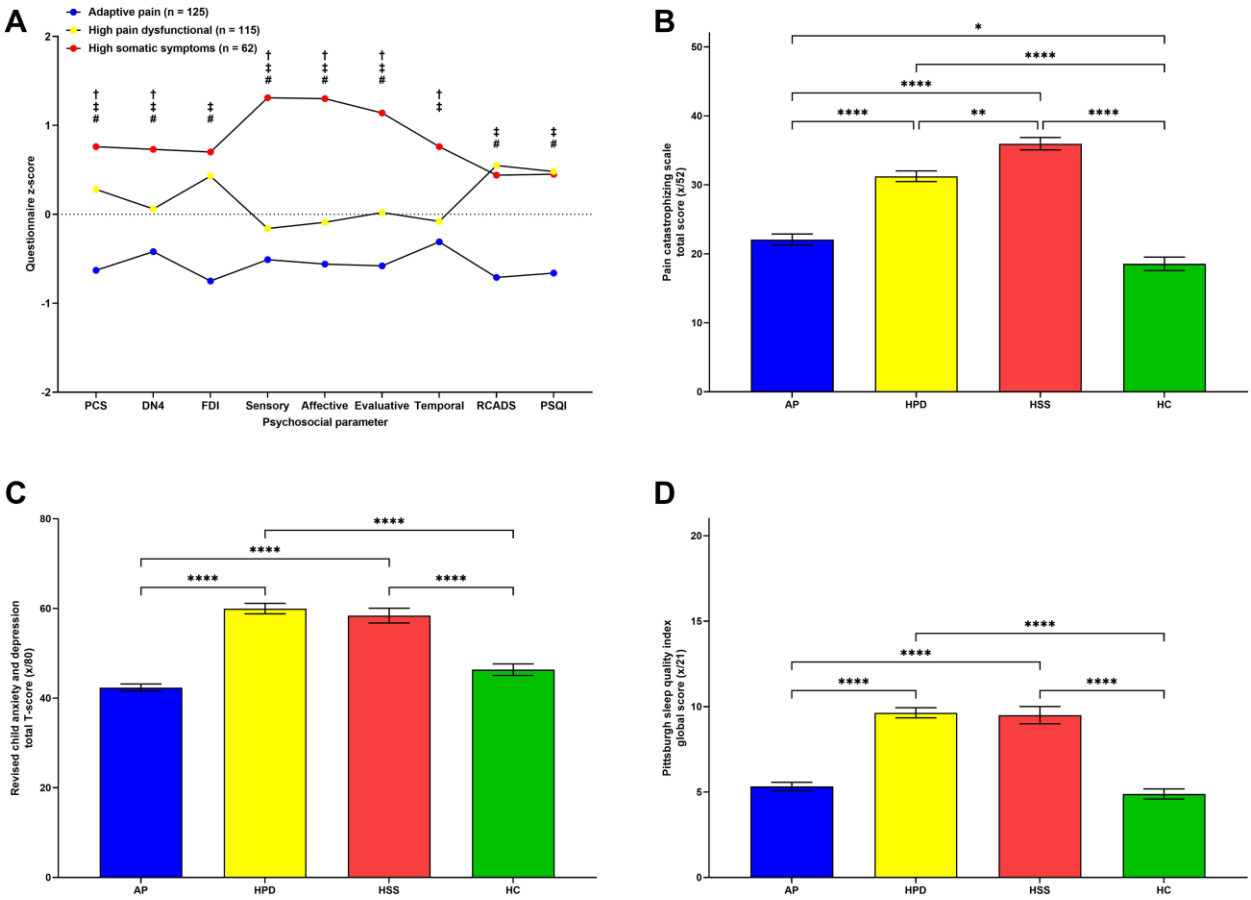


Figure 3-10. Psychosocial profiles in adolescents with chronic musculoskeletal pain.
(A) Individual patient questionnaire scores were transformed and presented as *z*-scores. Higher *z*-scores represent higher scores for the questionnaire completed. Differences are significant if $p<0.05$ Significant difference between $^{\#}$the adaptive pain and high pain dysfunctional cluster, ‡the adaptive pain and high somatic symptoms cluster or †the high pain dysfunctional and high somatic symptoms cluster. Data points = mean. (B) The pain catastrophizing score is represented by psychosocial cluster and compared with age-matched controls. Bars = mean ± SEM. (C) The Revised Child Anxiety and Depression Scale total *T*-score is represented by psychosocial cluster and compared with age-matched controls. Bars = mean ± SEM. (D) The Pittsburgh Sleep Quality Index global score is represented by psychosocial cluster and compared with age-matched controls. Bars = mean ± SEM. *$p<0.05$, **$p<0.01$, ****$p<0.0001$.
Abbreviations: PCS-C, pain Catastrophizing Scale – Child version; DN4, Douleur Neuropathique 4 questionnaire; FDI, Functional disability inventory; Sensory, sensory descriptors; Affective, affective descriptors; Evaluative, evaluative descriptors; Temporal, temporal descriptors; RCADS, Revised Child Anxiety and Depression Scale; PSQI, Pittsburgh Sleep Quality Index; AP, adaptive pain; HPD, high pain dysfunctional, HSS; high somatic symptoms; HC, healthy controls.

3.3.5.4 Quantitative sensory testing identifies distinct somatosensory profiles

For each adolescent patient, pain site *z*-scores were calculated using control measures for their forearm and for age-matched controls, and plotted across available modalities. A deterministic approach was taken for allocation to the closest matching profile including healthy controls. Profiles of sensory loss thermal hyperalgesia, mechanical hyperalgesia and normative QST differed significantly from each other, with a significant main effect of somatosensory profile ($F_{3,2043} = 39.51$, $p < 0.001$), modality ($F_{6,2043} = 37.46$, $p < 0.001$), and modality × somatosensory profile interaction ($F_{18,2043} = 14.05$, $p < 0.001$). Clinical characteristics and pain intensity did not vary across somatosensory profiles (see Supplementary Table 4).

Out of the 302 patients, 155 (51%) displayed normative QST values comparable to healthy controls. Thermal hyperalgesia was the most common profile in our cohort of adolescents with chronic MSK pain (n = 98; 32%). This included increased sensitivity to mechanical stimuli, WDT and HPT (Figure 3-11, for details, see Supplementary Table 4). Fifteen (5%) patients presented sensory loss profile with decreased sensitivity to mechanical and thermal stimuli. Mechanical hyperalgesia was observed for 34 (11%) patients with marked loss of function in HDT and HPT, and gain of function in PPT. Wind-up did not differentiate between somatosensory profiles.

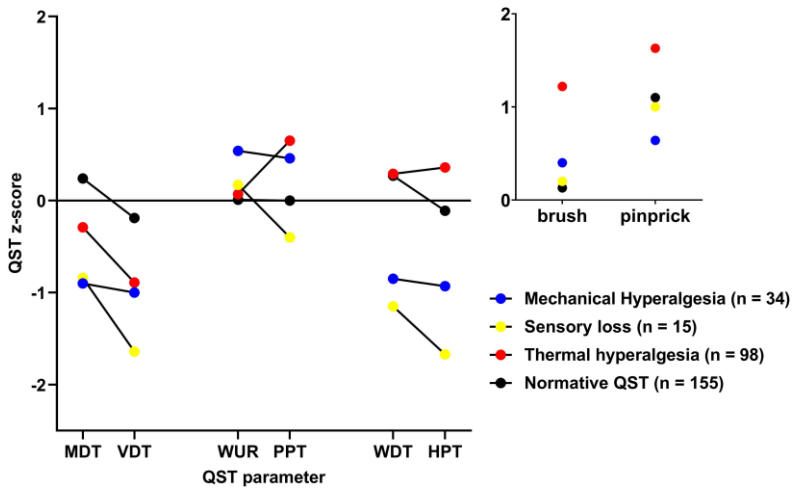


Figure 3-11. Quantitative sensory testing profiles in adolescents with chronic musculoskeletal pain.

Individual patient pain area thresholds were converted into *z*-scores calculated with reference to within-cohort control measures at the control area. Individual patient control area thresholds were converted into *z*-scores calculated with reference to between-cohort control measures at the control area. *z*-Scores for dynamic mechanical allodynia to brush and for the presence of painful after-sensations at the end of the 60-second period after 10 pinprick stimuli were calculated with reference to the pain intensity reported by the patients using the numerical rating scale (NRS 0–10). An average *z*-score for all QST parameters for the control and affected area was then calculated for each patient. The *z*-score plot for each individual patient was grouped according to the closest matching adult mechanism-related profile: mechanical hyperalgesia, sensory loss, thermal hyperalgesia or normative QST. Gain of function (hyperalgesia) is indicated as a positive *z*-score and a loss of function (sensory loss) as a negative score. Data points = mean.
Abbreviations: MDT, mechanical detection threshold; VDT, vibration detection threshold; WUR, wind-up ratio; PPT, pressure pain threshold; WDT, warm detection threshold; HPT, heat pain threshold; brush, dynamic mechanical allodynia; pinprick, painful after-sensations at the end of the 60-second period after 1 and 10 stimuli.

3.3.5.5 Conditioned pain modulation assessment identifies distinct profiles

Four distinct pain modulatory profiles within patients were observed: patients with optimal CPM efficiency and absence of temporal summation (i.e., functional central processing; n = 112), patients displaying only temporal summation of pain (i.e., facilitation; n = 18), patients displaying only suboptimal or inefficient CPM (i.e., dysfunctional inhibition; n = 136), and patients displaying both suboptimal or inefficient CPM and presence of temporal summation of pain (i.e.,

dysfunctional central processing; n = 27) (Figure 3-12). Demographic characteristics and pain intensity did not vary across pain modulatory profiles (see Supplementary Table 5).

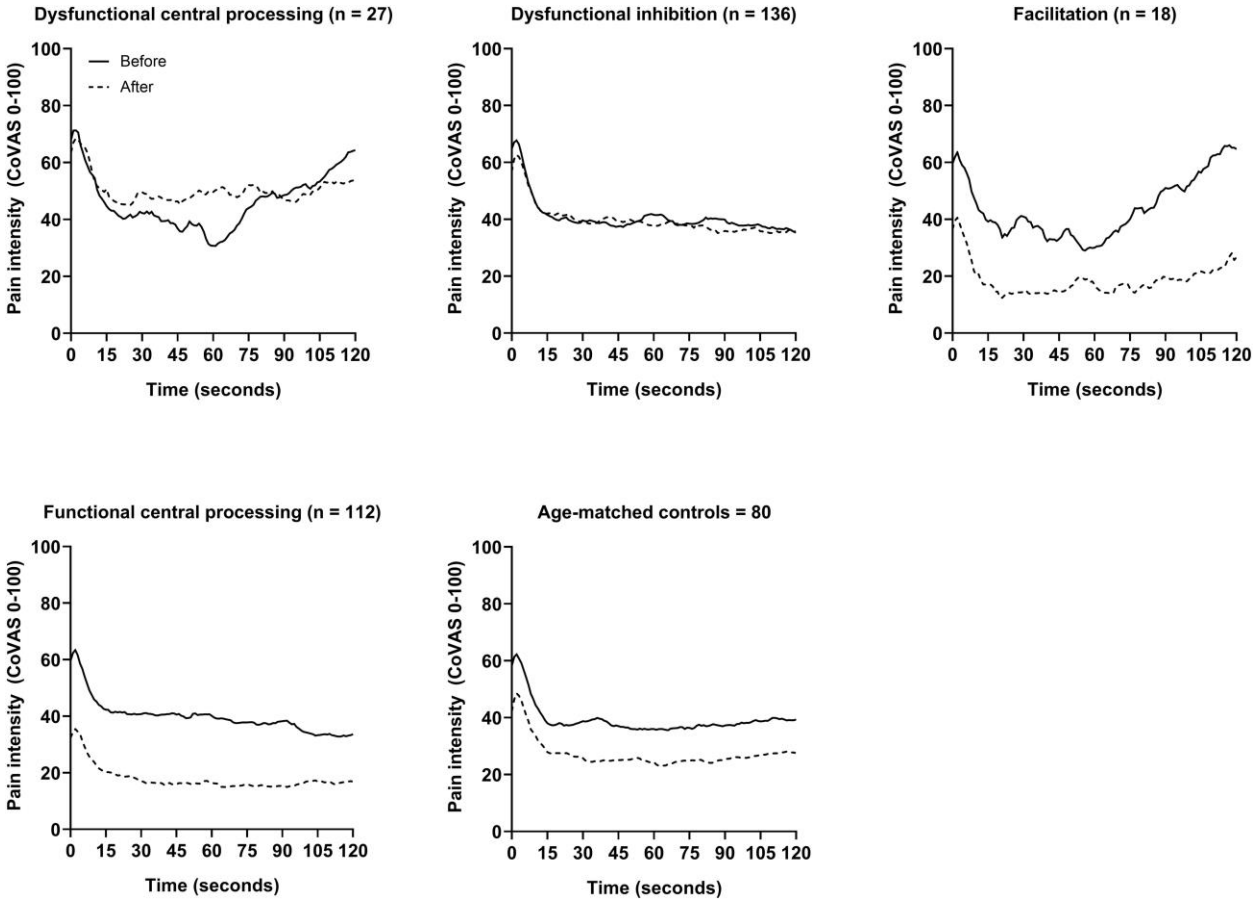


Figure 3-12. Pain modulation profiles in adolescents with chronic musculoskeletal pain and age-matched controls.

Mean pain intensity during the tonic thermal heat stimulations of the conditioned pain modulation assessment. Each individual patient was grouped according to their inhibitory and facilitatory pain modulation responses: dysfunctional central processing (suboptimal or inefficient CPM and presence of temporal summation of pain), dysfunctional inhibition (suboptimal or inefficient CPM and absence of temporal summation of pain), facilitation (optimal CPM and presence of temporal summation of pain) and functional central processing (optimal CPM and absence of temporal summation of pain). A CPM efficiency between −100% and −30% was considered as optimal, between −30% and −10% suboptimal and between −10% and +100% inefficient. Presence of temporal summation of pain was defined as an increase in pain intensity equal or larger than 20/100 (using the CoVAS) during the last 60 seconds of the first test stimulus.

Abbreviation: CoVAS, computerized visual analog scale.

3.3.5.6 Associations between psychosocial profiles and somatosensory profiles and pain modulatory profiles

As factors have been shown to influence QST and CPM in adolescents, associations between the psychosocial profiles, somatosensory profiles and pain modulatory profiles were assessed (Figure 3-13). A chi-square test revealed a significant association between the psychosocial and somatosensory profiles ($X^2 = 13.53$, $p = 0.035$) such that a larger proportion of patients in the mechanical hyperalgesia profile were grouped in the adaptive pain cluster. No association was observed between the psychosocial profiles and pain modulatory profiles ($X^2 = 6.65$, $p = 0.355$). No association between the somatosensory profiles and pain modulatory profiles was observed ($X^2 = 10.69$, $p = 0.298$). When looking at the individual outcome measures with respect to the distinct profiles, significant differences were observed.

Psychosocial profiles: Adolescent patients grouped in the HSS cluster displayed more dynamic mechanical allodynia than patients grouped in the AP cluster (see Supplementary Table 3). Moreover, more patients in the HSS clusters displayed the presence of painful after-sensations after 10 stimuli in the control and affected area tested than patients in the AP cluster. Patients in the HSS cluster also displayed a significantly higher vibration detection threshold, but lower pressure pain threshold in the affected area, when compared to patients in the AP cluster. Interestingly, patients in the HSS and AP clusters displayed more temporal summation of pain than patients in the HPD cluster.

Somatosensory profiles: Patients allocated to the thermal hyperalgesia profile reported significantly higher scores for the DN4 questionnaire than patients allocated to the normative QST subgroup. Moreover, patients allocated to the thermal hyperalgesia profile were more likely to report their pain neuropathic in nature (see Supplementary Table 4). In addition, patients allocated

to the mechanical hyperalgesia profile reported lower scores for the functional disability index than patients allocated in the thermal hyperalgesia profile.

Pain modulatory profiles: Patients allocated in the functional central processing profile reported significantly lower scores for the DN4 questionnaire and were, therefore, less likely to report their pain neuropathic in nature in comparison to patients allocated to the dysfunctional central processing, dysfunctional inhibition or facilitation profiles (see Supplementary Table 5).

3.3.6 Discussion

Youth with chronic pain are heterogeneous in regard to their clinical presentation. Therefore, the objective of the study was to subgroup pediatric patients with chronic MSK pain that will be phenotypically different from each other based on their psychosocial profile, somatosensory profile and pain modulatory profiles. Overall, patients reported higher pain catastrophizing, more anxiety and depression symptoms, and poor sleep quality than age-matched controls. Moreover, patients displayed lower pressure pain thresholds and less efficient conditioned pain modulation than controls. Our analysis revealed that pain assessment through self-reported questionnaires, quantitative sensory testing and conditioned pain modulation identified distinct psychosocial, somatosensory, and pain modulatory profiles (Figure 3-14).

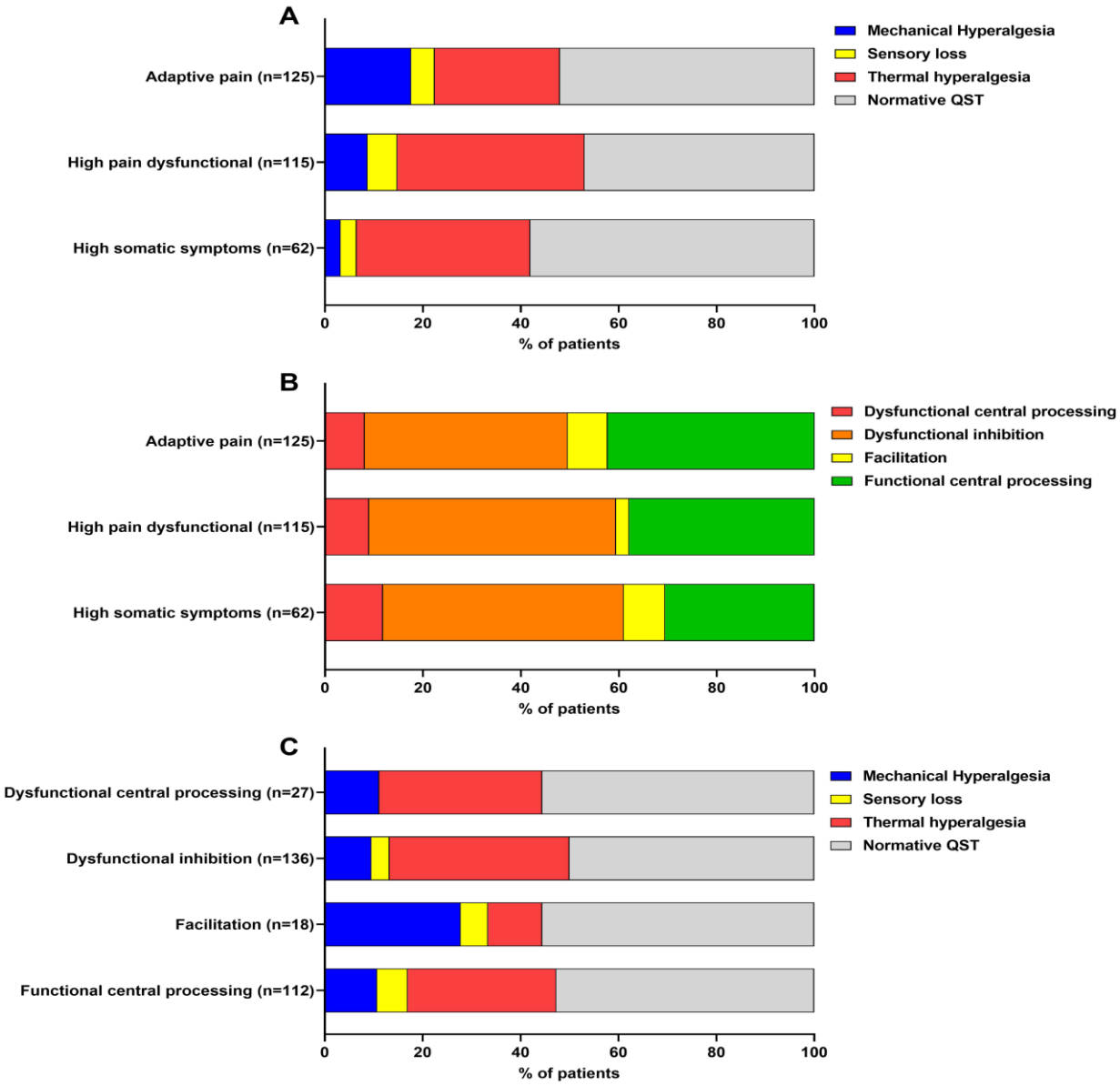
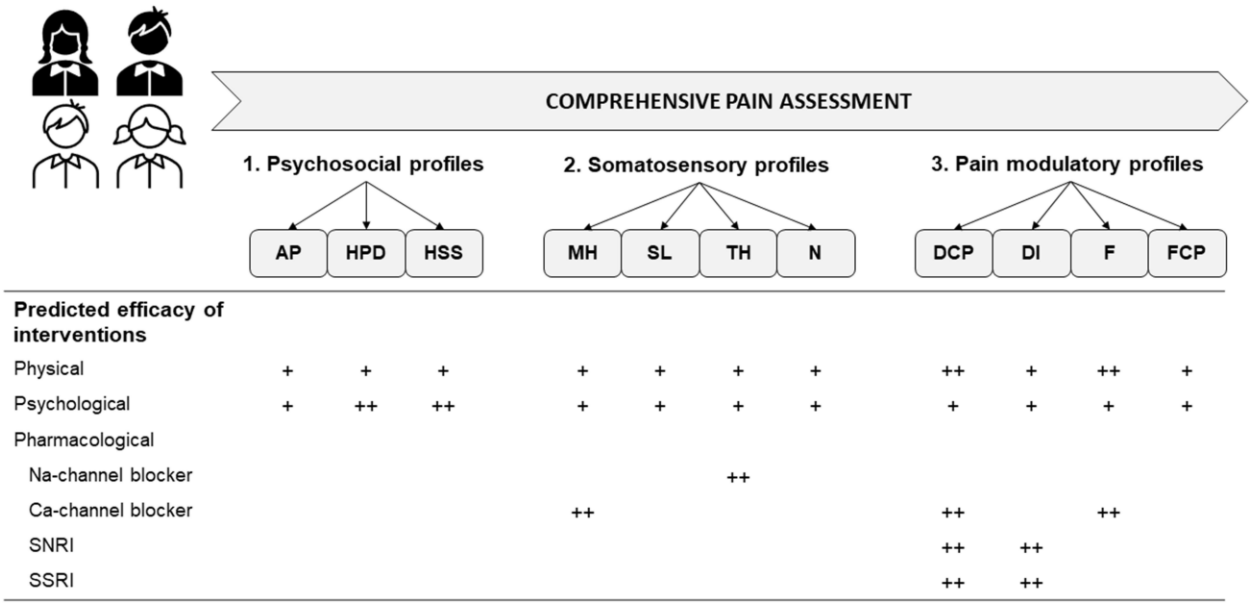


Figure 3-13. Associations between psychosocial profiles and somatosensory profiles and pain modulatory profiles.

(A) The proportion of distinct somatosensory profiles is shown divided by the identified psychosocial profiles. (B) The proportion of distinct pain modulatory profiles is shown divided by the identified psychosocial profiles. (C) The proportion of distinct somatosensory profiles is shown divided by the identified pain modulatory profiles.



Predicted efficacy of interventions											
Physical	+	+	+	+	+	+	+	++	+	++	+
Psychological	+	++	++	+	+	+	+	+	+	+	+
Pharmacological											
Na-channel blocker						++					
Ca-channel blocker				++				++		++	
SNRI								++	++		
SSRI								++	++		

Figure 3-14. Comprehensive patient pain assessment and rational predicted treatment efficacy.

Pain assessment through self-reported questionnaires, quantitative sensory testing and conditioned pain modulation identifies distinct psychosocial, somatosensory, and pain modulatory profiles. Predictions for differential efficacy of treatment approaches across profiles are depicted. + represents beneficial; ++ represents very beneficial.

Abbreviations: AP, adaptive pain; HPD; high pain dysfunctional; HSS; high somatic symptoms; MH, mechanical hyperalgesia profile; SL, sensory loss profile; TH, thermal hyperalgesia profile; N, normative QST profile; DCP, dysfunctional central processing; DI, dysfunctional inhibition; F, facilitation; FCP, functional central processing.

3.3.6.1 Psychosocial phenotyping

Studies have highlighted differences between the psychosocial characteristics of pediatric patients with chronic pain [12–16,80]. Similarly to previous cluster analyses on the psychological and behavioural characteristics of pediatric patients with chronic pain, three subgroups were identified, one with high levels of distress and disability, another with relatively low scores of distress and disability, and a third group that scored in between the other two on these measures [12,13,15,80]. In our study, three distinct profiles were identified based on cluster analysis of self-reported measures of pain catastrophizing, neuropathic pain-like experiences, functional disability, descriptors of pain, anxiety and depression symptoms and sleep quality. The subgroups identified

(adaptive pain, high pain dysfunctional, and high somatic symptoms) also differed based on their pain intensity the day of the assessment, and their average, worst and best pain over the last month. This result is important as it highlights the fear-avoidance mechanism [81,82] that may be at play in the high pain dysfunctional subgroup, but especially the high somatic symptoms subgroup. The high catastrophizing and negative affect of patients in the HPD and HSS psychosocial subgroups may lead them into a cyclical nature of prolonged avoidance of activities that is associated with increased pain, functional impairment, and disability [82,83]. Moreover, our results showed that the high somatic symptom subgroup showed more frequent dynamic mechanical allodynia and presence of painful after-sensations after pinprick stimuli. The high somatic symptom cluster also displayed a higher vibration detection threshold, but lower pressure pain threshold in their most painful location. The associations highlight that the effects of psychosocial factors on QST should not be overlooked, and identifying patients similar to those grouped in the HSS cluster would allow clinicians to intervene early to reduce pain symptoms and its negative impact on the daily lives of the patients.

3.3.6.2 Somatosensory phenotyping

Somatosensory signs vary within diagnostic characteristics of patients with neuropathic pain, and subgrouping based on different profiles may improve mechanism-based treatment [16,84]. In our sample of adolescents with chronic musculoskeletal pain, we also identified distinct sensory loss, thermal hyperalgesia, and mechanical hyperalgesia profiles, but also included a profile in which patients presented QST values closer to "healthy" controls. Although it is important to consider the sample size of our age-matched controls and methodology that may influence the *z*-scores for some modalities, our results parallel clusters reported in adolescents and adults with neuropathic pain [16,77,78]. Patients without confirmation of a lesion in the

somatosensory system but with altered sensory processing may reflect nociplastic pain as the dominant mechanism at play [85].

More than half of the patients displayed QST values that were relatively similar to "healthy" controls. Unlike Verriotis et al, whose sample consisted of adolescents with peripheral neuropathic pain [16], and our previous work in a sample of pediatric patients and young adults with chronic back pain [86], which did not include healthy controls, this study highlights that there are patients that display no gain or loss of sensory functions and, therefore, their pain may be due to other underlying mechanisms.

Sensory loss is common in children with rare conditions (e.g., postherpetic neuralgia) [78] or with conditions that produce subclinical sensory signs (e.g., diabetes) [87,88], but was relatively uncommon in our cohort of patients with chronic MSK pain (5.3%) similarly to a cohort of patients with peripheral neuropathic pain (21.2%) [16]. This sensory profile is characterized by a loss of small and large fiber function and has been described to be similar to a compression nerve block [78,89,90]. Therefore, the spontaneous pain, despite the "deafferation" or "painful hypoesthesia", may be likely due to ectopic action potentials generated in proximal sites of injured nociceptors, such as the dorsal root ganglion or the deafferented central nociceptive neurons [91].

Thermal hyperalgesia was the most common profile in our cohort of patients with chronic MSK pain displayed through increased sensitivity to mechanical and thermal stimuli. Interestingly, a higher proportion of patients in the thermal hyperalgesia profile were more likely to report their pain as neuropathic, highlighting that a change in somatosensory function may be involved in the ongoing pain. Increased thermal sensitivity has been seen in adolescents with complex regional pain syndrome [92] and chronic musculoskeletal pain [93]; however other studies in youth with functional abdominal pain have observed no difference in heat pain threshold or test temperature

when compared to pain-free youth [30,39,94]. This sensory profile is characterized by relatively preserved large and small fiber sensory functions in combination with heat hyperalgesia, which may be likely due to peripheral sensitization [78,95]. In response to a painful stimuli, sensitized nociceptors will generate an increased number of action potentials to be processed centrally and interpreted are more intense pain [96,97]. However, it is important to consider that the thermal stimulation was only conducted in a control area of the body. Sensitized nociceptors in the control area of the body may be associated with an overexpression of pronociceptive mediators, channels and receptors leading to pathological spontaneous discharges and lowered activation threshold for thermal and mechanical stimuli. Therefore, the ongoing pain experienced by the patients may be due to ongoing hyperactivity in surviving nociceptors in the affected area.

Mechanical hyperalgesia was also relatively uncommon in our cohort of patients with chronic MSK pain. This sensory profile was characterized by a loss of heat-sensitive small fiber function in combination with pressure hyperalgesia. Increased sensitivity to pressure has been in observed in a large population of adolescents with chronic pain in comparison to healthy controls, providing evidence of regional sensitization [27]. However, the dissociation of thermal and mechanical hyperalgesias may be explained by the differences in neural signaling of thermal and mechanical pain that starts with peripheral encoding in distinct subsets of nociceptors or central sensitization, which is more prominent for mechanical stimuli [95,96]. The increased excitability at the spinal level in response to stimuli may be associated with an increased in the receptive fields of the nociceptive spinal cord neurons [96,97]. The ongoing pain in this sensory profile may be due to spontaneous activity in the nociceptive system originating from the peripheral and/or central nervous system.

3.3.6.3 Pain modulation phenotyping

Improving the diagnostic process by identifying patients with chronic MSK pain based on the results of inhibitory and facilitatory pain modulation responses can provide additional standardized outcomes for clinical trials [98]. The CPM response is based on a spino-bulbar-spinal loop that involves serotonin and noradrenergic mechanisms in the descending pain inhibitory systems [99,100]. Impaired CPM has been identified in youth with chronic abdominal, neuropathic and musculoskeletal pain when compared to age-matched controls [10,30,33,38,39,82]. Facilitated TSP, involving NMDA receptors in humans [101], have been shown to be involved in some chronic pain conditions such as sickle cell disease, fibromyalgia, migraines, and functional abdominal pain [15,34–36,40,41]. Our results provide evidence of distinct combinatory profiles of facilitatory and inhibitory pain modulation responses similarly seen in adults [79]. Vaegter and Graven Nielsen (2016) observed that adult patients demonstrating impaired CPM and facilitate TSP expressed more pain areas, higher clinical pain intensity and experimental pain sensitivity than patients demonstrating normal CPM and TSP responses. Although this was not observed in our cohort and chronic widespread pain is a chronic conditioned heterogeneous with respect to pain modulation, youth grouped in the dysfunctional central processing may be important to be identified for intervention. With such manifestation of impairment in central pain modulation, these patients are suggested to be at high propensity for widespread pain and comorbidities in the future if not present already [79,102].

3.3.6.4 Clinical implications

The management and treatment of chronic pain may remain a challenge. Current pain guidelines highlight multidisciplinary management using a biopsychosocial model as the standard of care. A comprehensive use of exercises, physical therapy, cognitive behavioural therapy, and

medical treatments with active commitment of the patients and parents are associated with positive clinical outcomes [103,104]. Studies investigating quantitative sensory testing in relation to musculoskeletal pain have shown the importance of a multidimensional assessment [27,33,105,106]. Georgopoulos et al highlight that the baseline assessment with quantitative sensory testing was a valuable instrument to predict clinical outcomes including disability in patients with musculoskeletal pain. Improving the diagnostic process by identifying distinct psychosocial, somatosensory and pain modulatory profiles of patients with chronic musculoskeletal pain based on results of quantitative sensory testing, pain-related outcomes, and psychosocial factors may help clinicians provide an improved individualized care to patients [98].

Exercises, physical therapy and psychological therapies are aimed to focus on helping patients return to their desired level of functioning through progressive engagement in previously avoided activities and a self-management approach to pain [98,103]. Studies targeting the central pain processes have used physical activity to reduce the presence of temporal summation pain [107,108]. Therefore, the patients displaying facilitated TSP (i.e., grouped in the dysfunctional central processing or facilitation pain modulatory profiles) may benefit from a multidisciplinary program centered on physical activity [109].

Psychological therapies included in multidisciplinary care, delivered individually or in groups in the pediatric chronic pain population, may break the fear-avoidance cycle, reduce pain symptoms, disability and negative affect, but also modify social environmental factors to enhance functional status [110]. Hence, a multicomponent approach focused on psychological therapeutic interventions addressing anxiety, depression and poor sleep quality, and on the probable pain hypersensitivity may be more beneficial for patients that are grouped in the high pain dysfunctional

and high somatic symptoms cluster who display more functional disability, mental distress and sleep problems.

Multidisciplinary pain management centered on pharmacological treatments and interventional procedures are mainly supported through studies conducted in adults. Several trials in adults with neuropathic pain have used baseline QST phenotyping to identify predictors of treatment response that are relevant to the distinct somatosensory profiles and are supported by different pharmacological profiles [78]. Clinical trials in adults suggested that sodium channel modulators such as local anesthetics could be useful to treat pain conditions associated with peripheral sensitization, and therefore may be more beneficial for patients grouped in the thermal hyperalgesia somatosensory profile [111,112]. Moreover, patients with potential involvement of central pain processes (i.e., grouped in the mechanical hyperalgesia somatosensory profile) or displaying facilitated TSP (i.e., grouped in the dysfunctional central processing or facilitation pain modulatory profiles) could benefit more from calcium channel modulators such as gabapentinoids, inhibiting central neuronal sensitization [113]. Adult patients with a baseline QST profile similar the sensory loss somatosensory profile observed in our cohort displayed a higher efficacy in a retrospective analysis of a placebo-controlled trial with oral opioids [114]. However, studies have shown very low certainty evidence for the use of opioids for children and adolescents with chronic pain [115]. Patients with impaired CPM response (i.e. grouped in the dysfunctional central processing or dysfunctional inhibition pain modulatory profiles) could benefit more from selective serotonin reuptake inhibitors or serotonin-noradrenaline re-uptake inhibitors, which augment descending inhibition by spinal monoamine re-uptake inhibition [116,117].

The overall biopsychosocial approach management and treatment of chronic pain support the clinical relevance of the distinct profiles identified within our cohort. Our predictions for

differential efficacy of treatment approaches across profiles are summarized in Figure 3-14. However, a recent review on the efficacy and safety of pharmacological, physical, and psychological interventions for the management of chronic pain in children observed that although all interventions showed some benefit for reducing pain, most critical outcomes of pain intensity, quality of life, and physical, role and emotional functioning were rated as low or very low certainty [117]. Moreover, a recent study on children with chronic pain revealed that at their 7-year follow-up, irrespective of whether or not they experienced ongoing chronic pain, they demonstrated worse physical and mental health and continued to seek more frequent health care [118]. Therefore, the potential efficacy and size effect in treatment response between profiles remains to be proven in future prospective trials.

3.3.6.5 Limitations

Data were obtained from a heterogenous sample of patients with diverse pathological diagnoses (e.g., scoliosis, osteogenesis imperfecta, chronic widespread pain, etc.) that were not considered in this study but is important to consider in pain management. Comparisons between profiles with smaller sample of patients should be interpreted with caution. The QST protocol measures have similarities to the DFNS protocol measures [28] with modifications or exclusions. Somatosensory profiles were distinct from each other. However, although they are parallel, they do not completely mirror adult mechanism-related profiles [78]. Somatosensory profiles were based on within- and between-cohort comparisons, and additional pediatric control data will improve the sensitivity of site-, age- and sex-corrected z-scores. Only one method assessing the inhibitory and facilitatory pain modulation responses were used. Other studies have used blunt pressure as the test stimulus for the CPM paradigm and have applied a series of heat-pain stimuli of the same temperature to induce temporal summation of pain [15,29]. Medication taken by the

participants were not controlled at the time of the assessment, and medication use was variable. Confirmatory tests and biomarkers may be important to be added to further evaluate adolescents with chronic musculoskeletal pain.

3.3.7 Conclusion

Our results provide evidence that adolescents with chronic musculoskeletal pain are a heterogeneous population comprising subgroups that may reflect distinct mechanisms and may benefit from different treatment approaches. Screening self-reported questionnaires, QST, and CPM facilitate phenotyping of adolescents with chronic MSK pain in the clinical context. The combination may allow recognition of different subgroups of patients with chronic MSK pain and may ultimately contribute to personalized therapy.

3.3.8 Data Sharing Statement

The data of this study are available upon request.

3.3.9 Acknowledgements

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3.3.10 Disclosure

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3.3.12 Supplementary material

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SUPPLEMENTARY TABLES

Supplementary Table 1. ANOVA comparing age, gender, and race for psychosocial, QST and CPM assessment outcomes for the patient cohort

ANOVA	PCS	DN4	RCADS	PSQI	FDI	Sensory	Affective	Evaluative	Temporal
Main effects									
Age	0.542 (0.462)	4.647 (0.032)	4.866 (0.028)	13.556 (< 0.001)	9.397 (0.002)	4.852 (0.028)	0.148 (0.7)	4.618 (0.033)	2.989 (0.085)
Gender	4.141 (0.043)	5.538 (0.019)	0.503 (0.479)	0.761 (0.384)	2.116 (0.147)	8.241 (0.004)	7.428 (0.007)	2.653 (0.104)	1.814 (0.179)
Race	1.314 (0.253)	0.536 (0.465)	0.617 (0.433)	0.7 (0.403)	0.031 (0.859)	0.425 (0.515)	3.672 (0.056)	0.182 (0.67)	0.04 (0.841)
Interactions									
Age x Gender	3.557 (0.06)	3.369 (0.068)	1.466 (0.227)	1.142 (0.286)	3.078 (0.08)	1.174 (0.38)	0.2 (0.655)	2.403 (0.122)	0.433 (0.511)
Age x Race	0.163 (0.687)	1.173 (0.28)	1.587 (0.209)	1.316 (0.252)	0.475 (0.491)	1.079 (0.3)	0.549 (0.459)	0.001 (0.978)	0.005 (0.941)
Gender x Race	0.023 (0.88)	3.374 (0.067)	0.776 (0.376)	0.516 (0.473)	0.059 (0.808)	0.004 (0.947)	1.434 (0.232)	0.768 (0.382)	0.101 (0.751)
Age x Gender x Race	0.865 (0.353)	0.016 (0.899)	0.006 (0.937)	0.742 (0.39)	0.362 (0.548)	0.096 (0.756)	0.007 (0.933)	0.607 (0.436)	0.659 (0.418)
Estimated differences									
10-13 vs. 14-18 years	-0.925	-0.554	-3.958	-1.789	-3.780	-4.265	0.847	-6.681	-3.535
Male vs. Female	-3.018	-0.723	-1.508	-0.504	-2.132	-6.585	-7.111	-5.999	-3.262
White vs. POC	-1.545	0.202	1.514	-0.426	-0.236	1.356	-4.535	-1.423	-0.441
ANOVA	**MDTcontrol**	**MDTpain**	**DMAcontrol**	**DMApain**	**VDTcontrol**	**VDTpain**	**WURcontrol**	**WURpain**	
Main effects									
Age	2.035 (0.155)	1.302 (0.255)	0.61 (0.435)	3.618 (0.058)	0.071 (0.79)	4.116 (0.043)	0.004 (0.948)	0.231 (0.631)	
Gender	3.208 (0.074)	2.565 (0.11)	1.425 (0.234)	2.106 (0.148)	0.663 (0.416)	0.563 (0.454)	1.41 (0.236)	0.553 (0.548)	
Race	1.689 (0.195)	0.559 (0.455)	0.066 (0.797)	0.199 (0.656)	0.074 (0.785)	0.189 (0.664)	0.882 (0.348)	0.333 (0.565)	
Interactions									
Age x Gender	1.798 (0.181)	1.073 (0.301)	0.325 (0.251)	0.199 (0.656)	0.149 (0.7)	0.004 (0.95)	2.67 (0.103)	0.002 (0.962)	
Age x Race	0.424 (0.515)	0.936 (0.334)	0.52 (0.471)	4.366 (0.038)	1.307 (0.254)	4.652 (0.032)	1.864 (0.177)	0.339 (0.561)	
Gender x Race	0.63 (0.428)	0.002 (0.96)	0.176 (0.675)	1.821 (0.178)	0.144 (0.704)	0.038 (0.847)	8.735 (0.003)	3.039 (0.082)	
Age x Gender x Race	0.03 (0.862)	1.587 (0.209)	0.011 (0.917)	0.505 (0.478)	0.055 (0.816)	0.899 (0.344)	0.505 (0.478)	0.497 (0.482)	
Estimated differences									
10-13 vs. 14-18 years	0.220	0.256	0.115	0.495	0.033	0.347	0.008	0.066	
Male vs. Female	-0.327	-0.4223	-0.208	-0.446	0.120	-0.152	0.173	0.117	
White vs. POC	-0.215	-0.179	0.041	0.124	0.037	0.080	-0.125	0.084	
ANOVA	**PPTcontrol**	**PPTpain**	**WDTcontrol**	**HPTcontrol**	**CPM**	**TSP**			
Main effects									
Age	3.307 (0.07)	0.01 (0.921)	2.586 (0.109)	4.104 (0.044)	0.073 (0.788)	1.538 (0.216)			
Gender	6.15 (0.014)	2.384 (0.124)	6.057 (0.014)	0.43 (0.513)	1.816 (0.179)	3.246 (0.073)			
Race	0.547 (0.46)	0.659 (0.418)	3.115 (0.079)	0.317 (0.574)	0.215 (0.643)	7.013 (0.009)			
Interactions									
Age x Gender	4.63 (0.032)	1.59 (0.208)	1.136 (0.288)	1.879 (0.176)	0.393 (0.531)	0.002 (0.966)			
Age x Race	0.098 (0.755)	0.091 (0.763)	0.078 (0.78)	2.914 (0.089)	0.045 (0.832)	0.168 (0.682)			
Gender x Race	1.311 (0.253)	0.855 (0.356)	0.011 (0.916)	2.861 (0.092)	4.35 (0.038)	0.099 (0.753)			

Age x Gender x Race	0.106 (0.745)	0.785 (0.376)	2.334 (0.128)	5.595 (0.019)	0.022 (0.882)	0.843 (0.359)
Estimated differences						
10-13 vs. 14-18 years	-0.109	0.009	0.140	-0.693	1.544	0.362
Male vs. Female	0.179	0.159	0.251	0.263	9.131	-0.621
White vs. POC	-0.047	-0.075	-0.163	-0.206	-2.831	0.823

The first part of this table comprises of the F test statistic (p-values) derived from the three way ANOVA. The second part of this table displays estimated group differences for the main effects of age, gender and race. The reference group is the first group in each case. The effects refer to log-transformed QST values except VDT and HPT. POC, person of color; control, control area test site; pain, most painful location test site; PCS, pain catastrophizing scale; RCADS; revised child anxiety and depression scale; PSQI, Pittsburgh sleep quality index; MDT, mechanical detection threshold; VDT, vibration detection threshold; DMA, dynamic mechanical allodynia; WUR, wind-up ratio; PPT, pressure pain threshold; WDT, warm detection threshold; HPT, heat pain threshold; CPM; conditioned pain modulation; TSP, temporal summation of pain.

Supplementary Table 2. ANOVA comparing age, gender, and race for psychosocial, QST and CPM assessment outcomes for the age-matched control cohort

ANOVA	PCS	RCADS	PSQI		
Main effects					
Age	1.289 (0.26)	0.602 (0.441)	1.379 (0.244)		
Gender	0.494 (0.485)	0.94 (0.335)	0.2 (0.656)		
Race	1.588 (0.212)	0 (0.995)	0.653 (0.422)		
Interactions					
Age x Gender	2.118 (0.15)	1.636 (0.205)	0.166 (0.685)		
Age x Race	0.315 (0.576)	1.162 (0.285)	5.475 (0.022)		
Gender x Race	0.011 (0.919)	2.231 (0.14)	7.663 (0.007)		
Age x Gender x Race	2.097 (0.152)	0.312 (0.578)	0.113 (0.737)		
Estimated differences					
10-13 vs. 14-18 years	2.491	2.262	-0.754		
Male vs. Female	-1.380	2.532	0.250		
White vs. POC	-2.752	-0.019	0.504		
ANOVA	**MDTcontrol**	**DMAcontrol**	**VDTcontrol**	**WURcontrol**	
Main effects					
Age	3.505 (0.065)	0.096 (0.578)	2.843 (0.096)	0.652 (0.422)	
Gender	7.317 (0.009)	0.676 (0.414)	8.771 (0.004)	0.001 (0.97)	
Race	1.68 (0.199)	5.436 (0.023)	0.295 (0.589)	1.02 (0.316)	
Interactions					
Age x Gender	0.195 (0.66)	0.013 (0.91)	1.305 (0.257)	0.873 (0.353)	
Age x Race	0.366 (0.547)	0.109 (0.742)	0.172 (0.68)	0.802 (0.373)	
Gender x Race	0.714 (0.401)	2.053 (0.156)	5.026 (0.028)	0.285 (0.595)	
Age x Gender x Race	0.005 (0.944)	0.029 (0.866)	2.95 (0.09)	0.045 (0.833)	
Estimated differences					
10-13 vs. 14-18 years	0.472	0.037	-0.332	-0.112	
Male vs. Female	-0.611	0.088	0.523	0.005	
White vs. POC	-0.326	-0.277	-0.107	-0.139	
ANOVA	**PPTcontrol**	**WDTcontrol**	**HPTcontrol**	**CPM**	**TSP**
Main effects					
Age	25.499 (< 0.001)	0.041 (0.839)	0.252 (0.617)	0.862 (0.356)	1.514 (0.223)
Gender	7.064 (0.01)	11.053 (0.001)	0.138 (0.711)	0.229 (0.634)	0.099 (0.754)
Race	6.812 (0.011)	2.42 (0.124)	0.115 (0.735)	0.028 (0.867)	0.816 (0.369)
Interactions					
Age x Gender	0.074 (0.787)	0.344 (0.559)	0.932 (0.337)	0.15 (0.7)	3.431 (0.068)
Age x Race	2.117 (0.15)	0.154 (0.696)	0.157 (0.693)	0.925 (0.508)	0.207 (0.65)
Gender x Race	1.049 (0.309)	0.05 (0.825)	0.142 (0.707)	0.15 (0.339)	1.094 (0.229)
Age x Gender x Race	0.001 (0.979)	0.153 (0.697)	0.289 (0.289)	0.522 (0.472)	0.365 (0.547)
Estimated differences					
10-13 vs. 14-18 years	-0.564	0.032	-0.338	-7.967	0.631
Male vs. Female	0.266	0.472	0.224	3.675	-0.145
White vs. POC	0.290	-0.246	-0.228	1.431	-0.461

The first part of this table comprises of the F test statistic (p-values) derived from the three way ANOVA. The second part of this table displays estimated group differences for the main effects of age, gender and race. The reference group is the first group in each case. The effects refer to log-transformed QST values except VDT and HPT. POC, person of color; control, control area test site; PCS, pain catastrophizing scale; RCADS; revised child anxiety and depression scale; PSQI, Pittsburgh sleep quality index; MDT, mechanical detection threshold; VDT, vibration detection threshold; DMA, dynamic mechanical allodynia; WUR, wind-up ratio; PPT, pressure pain threshold; WDT, warm detection threshold; HPT, heat pain threshold; CPM; conditioned pain modulation; TSP, temporal summation of pain.

Supplementary Table 3. Characteristics of psychosocial profiles in adolescents with chronic musculoskeletal pain

Variable	Adaptive pain (n = 125)	High pain dysfunctional (n = 115)	High somatic symptoms (n = 62)	Test statistic	p-value	Subgroup comparison
Age, mean ± SD	14.52 ± 2.05	15.22 ± 1.72	15.22 ± 2.03	4.81†	0.009	HDP > AP
Younger adolescent (10-13 years), n (%)	47 (37.60)	24 (20.87)	16 (25.81)	8.51*	0.014	
Older adolescent (14-18 years), n (%)	78 (62.40)	91 (79.13)	46 (74.19)			
Gender, n (%)				7.15*	0.028	ND
Female	95 (76.00)	95 (82.61)	57 (91.94)			
Male	30 (24.00)	20 (17.39)	5 (8.06)			
Race, n (%)				5.39*	0.068	ND
Caucasian (White)	101 (81.45)	80 (69.57)	50 (80.65)			
Person of color	23 (18.55)	35 (30.43)	12 (19.35)			
Past hospitalizations, n (%)				1.00*	0.607	ND
No	91 (72.80)	77 (66.96)	44 (70.97)			
Yes	34 (27.20)	38 (33.04)	18 (29.03)			
Past surgeries, n (%)				1.30*	0.523	ND
No	80 (64.00)	67 (58.26)	35 (56.45)			
Yes	45 (36.00)	48 (41.74)	27 (43.55)			
Primary location of pain (Tested pain area), n (%)				16.89*	0.031	ND
Head/Neck	4 (3.20)	6 (5.22)	1 (1.61)			
Upper limbs	8 (6.40)	6 (5.22)	10 (16.13)			
Thorax	3 (2.40)	0	1 (1.61)			
Back	76 (60.80)	73 (63.48)	26 (41.94)			
Lower limbs	34 (27.20)	30 (26.09)	24 (38.71)			
Presence of radiating pain, n (%)	52 (41.60)	58 (50.43)	36 (58.06)	4.82*	0.090	ND
Presence of secondary pain sites, n (%)	59 (47.20)	63 (54.78)	36 (58.06)	2.41*	0.299	ND
Pain now (NRS 0-10), mean ± SD	2.67 ± 2.17	3.57 ± 2.42	4.29 ± 2.51	10.84†	<0.001	HSS & HPD > AP
Average pain over the last month (NRS 0-10), mean ± SD	5.32 ± 1.93	5.89 ± 1.88	6.68 ± 1.71	11.14†	<0.001	HSS > HPD & AP
Worst pain over the last month (NRS 0-10), mean ± SD (n = 301)	7.85 ± 1.63	8.60 ± 1.49	9.08 ± 1.16	16.09†	<0.001	HSS & HPD > AP
Best pain over the last month (NRS 0-10), mean ± SD (n = 301)	1.47 ± 1.65	2.06 ± 1.79	2.33 ± 2.21	5.52†	0.004	HSS & HPD > AP
Duration of pain, n (%)				1.28*	0.864	ND
3 to 6 months	11 (8.80)	13 (11.30)	5 (8.06)			
6 to 12 months	20 (16.00)	21 (18.26)	9 (14.52)			
More than 12 months	94 (75.20)	81 (70.43)	48 (42)			
Frequency of pain, n (%)				8.98*	0.062	ND
Once a day	87 (69.60)	90 (78.26)	55 (88.71)			
Every second day	28 (22.40)	17 (14.78)	5 (8.06)			
Once a week	10 (8.00)	8 (6.96)	2 (3.23)			
Duration of painful episode, n (%)				16.58*	0.011	HSS > AP
Few seconds	1 (0.80)	3 (2.61)	1 (1.61)			
Few minutes	23 (18.40)	17 (14.78)	2 (3.23)			

Few hours	39 (31.20)	24 (20.87)	12 (19.35)			
Constant	62 (49.60)	71 (61.74)	47 (75.81)			
Pain catastrophizing scale, mean ± SD						
Total score	22.08 ± 8.85	31.24 ± 8.23	35.96 ± 7.06	69.02†	<0.001	HSS > HPD > AP
Low catastrophizers, n (%)	29 (23.20)	1 (0.87)	0	71.00*	<0.001	HSS > HPD > AP
Moderate catastrophizers, n (%)	48 (38.40)	30 (26.09)	6 (9.68)			
High catastrophizers, n (%)	48 (38.40)	82 (71.30)	56 (90.32)			
Douleur Neuropatique 4 questionnaire						
Total score, mean ± SD	2.10 ± 1.65	3.08 ± 2.07	4.44 ± 1.77	33.14†	<0.001	HSS > HPD > AP
Likely neuropathic, n (%)	22 (17.60)	47 (40.87)	44 (70.97)	50.90*	<0.001	HSS > AP
Functional Disability Inventory						
Total score	8.50 ± 6.43	20.00 ± 7.29	22.65 ± 9.77	100.40†	<0.001	HSS & HPD > AP
No/minimal disability, n (%)	89 (71.20)	17 (14.78)	13 (20.97)	120.58*	<0.001	HSS > HPD > AP
Mild disability, n (%)	27 (21.60)	44 (38.26)	9 (14.52)			
Moderate disability, n (%)	7 (5.60)	38 (33.04)	26 (41.94)			
Severe disability, n (%)	0	13 (11.30)	14 (22.58)			
Adolescent Pediatric Pain Tool						
Pain locations, x/67	6.26 ± 6.83	9.59 ± 7.85	12.39 ± 10.50	12.83†	<0.001	HSS & HPD > AP
Sensory descriptors, x/37 %	15.48 ± 9.20	20.80 ± 10.12	43.37 ± 15.73	133.40†	<0.001	HSS > HPD > AP
Affective descriptors, x/11 %	5.75 ± 8.29	13.96 ± 11.05	38.27 ± 19.83	142.40†	<0.001	HSS > HPD > AP
Evaluative descriptors, x/8 %	29.50 ± 16.06	44.20 ± 19.85	71.57 ± 22.20	102.70†	<0.001	HSS > HPD > AP
Temporal descriptors, x/24 %	24.07 ± 14.66	27.76 ± 12.67	41.20 ± 17.63	29.02†	<0.001	HSS > HPD & AP
Revised Child Anxiety and Depression Scale						
Total T-score, mean ± SD	42.33 ± 9.24	59.97 ± 12.35	58.42 ± 12.95	83.71†	<0.001	HSS & HPD > AP
Below clinical threshold, n (%)	124 (99.20)	76 (66.09)	44 (70.97)	44.68*	<0.001	HSS & HPD > AP
Borderline clinical threshold, n (%)	0	7 (6.09)	3 (4.84)			
Above clinical threshold, n (%)	1 (0.80)	29 (25.22)	15 (24.19)			
Pittsburgh Sleep Quality Index						
Total score, mean ± SD	5.32 ± 2.69	9.64 ± 3.06	9.50 ± 3.96	65.64†	<0.001	HSS & HPD > AP
Good sleep quality, n (%)	53 (42.40)	4 (3.48)	5 (8.06)	62.99*	<0.001	HSS & HPD > AP
Poor sleep quality, n (%)	68 (54.40)	105 (91.30)	56 (90.32)			
MDT^{log} (mN), mean ± SD						
Control area	0.63 ± 1.25	0.82 ± 1.26	0.55 ± 1.06	1.22†	0.296	ND
Tested area	0.78 ± 1.80	0.69 ± 1.74	0.39 ± 1.77	1.01†	0.364	ND
Z-score	0.14 ± 1.09	0.19 ± 1.14	-0.06 ± 1.01	1.06†	0.347	ND
DMA^{log} (NRS 0-10), mean ± SD						
Control area	-4.41 ± 0.91	-4.23 ± 1.24	-4.05 ± 1.49	2.05†	0.131	ND
Tested area	-3.77 ± 1.75	-3.23 ± 2.16	-2.95 ± 2.37	3.96†	0.020	HSS > AP
Z-score	0.36 ± 0.77	0.59 ± 0.93	0.72 ± 1.00	3.94†	0.020	HSS > AP
VDT (x/8), mean ± SD						
Control area	6.70 ± 0.86	6.68 ± 1.02	6.84 ± 1.12	0.563†	0.570	ND
Tested area	5.79 ± 1.10	5.91 ± 1.49	6.39 ± 1.47	4.35†	0.014	HSS > AP
Z-score	-0.68 ± 0.93	-0.63 ± 1.25	-0.29 ± 1.31	2.56†	0.079	ND
WUR^{log} (ratio), mean ± SD						
Control area	0.80 ± 1.10	0.78 ± 0.96	0.61 ± 0.76	0.86†	0.424	ND

Presence of painful after sensations after 10 stimuli in the control area, n (%)	35 (28.00)	44 (38.26)	34 (54.84)	13.23*	0.001	HSS > AP
Tested area	0.83 ± 1.20	0.52 ± 0.88	0.58 ± 0.84	2.86†	0.059	ND
Presence of painful after sensations after 10 stimuli in the tested area, n (%)	33 (26.40)	56 (48.70)	37 (59.68)	27.95*	< 0.001	HSS > AP
Z-score	0.20 ± 1.39	0.05 ± 1.01	-0.04 ± 0.92	0.95†	0.387	ND
PPT^{log} (kPa), mean ± SD						
Control area	5.13 ± 0.43	5.12 ± 0.49	5.05 ± 0.49	0.69†	0.504	ND
Tested area	5.18 ± 0.59	5.14 ± 0.67	4.90 ± 0.71	3.69†	0.026	HSS < AP
Z-score	-0.15 ± 0.92	-0.20 ± 1.08	-0.53 ± 1.10	2.78†	0.064	ND
WDT^{log} (°C from baseline), mean ± SD						
Control area	0.51 ± 0.68	0.39 ± 0.69	0.35 ± 0.69	1.49†	0.226	ND
Z-score	0.04 ± 1.03	-0.14 ± 1.05	-0.21 ± 1.05	1.49†	0.226	ND
HPT (°C), mean ± SD						
Control area	39.56 ± 2.78	39.05 ± 2.66	39.45 ± 2.74	1.07†	0.346	ND
Z-score	0.21 ± 1.07	0.01 ± 1.02	0.17 ± 1.06	1.07†	0.346	ND
CPM efficiency (%), mean ± SD	-28.10 ± 42.54	-19.29 ± 43.47	-15.21 ± 48.41	2.09†	0.126	ND
Inefficient, n (%)	37 (29.60)	42 (36.52)	25 (40.32)	4.12*	0.390	ND
Suboptimal, n (%)	24 (19.20)	25 (21.74)	11 (17.74)			
Optimal, n (%)	62 (49.60)	45 (39.13)	23 (37.10)			
TSP (NRS -10-+10), mean ± SD	0.32 ± 2.00	-0.53 ± 2.45	0.40 ± 2.31	5.31†	0.005	HSS & AP > HPD
Absence, n (%)	103 (82.40)	98 (85.22)	48 (77.42)	2.21*	0.331	ND
Presence, n (%)	20 (16.00)	13 (11.30)	12 (19.35)			

Percentages do not always add up to 100% due to missing data for some demographic variables.
*Test statistic for chi-square test. †Test statistic for one-way ANOVA.
AP indicates adaptive pain profile; HPD, high pain dysfunctional profile; HSS, high somatic symptoms profile; ND, no statistically significant difference between psychosocial profiles; log, log-transformed data; MDT, mechanical detection threshold; DMA, dynamic mechanical allodynia; VDT, vibration detection threshold; WUR, wind-up ratio; PPT, pressure pain threshold; WDT, warm detection threshold; HPT, heat pain threshold; CPM indicates conditioned pain modulation; TSP, temporal summation of pain.

Supplementary Table 4. Characteristics of quantitative sensory testing profiles in adolescents with chronic musculoskeletal pain

Variable	Normative QST (n = 147)	Mechanical hyperalgesia (n = 31)	Sensory loss (n = 16)	Thermal hyperalgesia (n = 108)	Test statistic	p-value	Subgroup comparison
Age, mean ± SD	15.05 ± 1.82	14.56 ± 2.24	15.59 ± 1.93	14.77 ± 2.03	1.39†	0.245	ND
Younger adolescent (10-13 years), n (%)	41 (26.45)	14 (41.18)	2 (13.33)	30 (30.61)	4.86*	0.182	ND
Older adolescent (14-18 years), n (%)	114 (73.55)	20 (58.82)	13 (86.67)	68 (69.39)			
Gender, n (%)					3.91*	0.271	ND
Female	127 (81.94)	24 (70.59)	12 (80.00)	84 (85.71)			
Male	28 (18.06)	10 (29.41)	3 (20.00)	14 (14.29)			
Race, n (%)					3.00*	0.392	ND
Caucasian (White)	123 (79.35)	28 (82.35)	11 (73.33)	69 (71.13)			
Person of color	32 (20.65)	6 (17.65)	4 (26.67)	28 (28.87)			
Past hospitalizations, n (%)					10.28*	0.016	ND
No	112 (72.26)	20 (58.82)	6 (40.00)	74 (75.51)			
Yes	43 (27.74)	14 (41.18)	9 (60.00)	24 (24.49)			
Past surgeries, n (%)					2.72*	0.436	ND
No	91 (58.71)	18 (52.94)	8 (53.33)	65 (66.33)			
Yes	64 (41.29)	16 (47.06)	7 (46.67)	33 (33.67)			
Primary location of pain (Tested pain area), n (%)					9.69*	0.644	ND
Head/Neck	7 (4.52)	2 (5.88)	0	2 (2.04)			
Upper limbs	11 (7.10)	1 (2.94)	0	12 (12.24)			
Thorax	2 (1.29)	0	0	2 (2.04)			
Back	91 (58.71)	18 (52.94)	11 (73.33)	55 (56.12)			
Lower limbs	44 (28.39)	13 (38.24)	4 (26.67)	27 (27.55)			
Presence of radiating pain, n (%)	72 (44.12)	15 (44.12)	8 (53.33)	51 (52.04)	1.15*	0.765	ND
Presence of secondary pain sites, n (%)	80 (51.61)	21 (61.76)	6 (40.00)	51 (52.04)	2.16*	0.539	ND
Pain now (NRS 0-10), mean ± SD	3.16 ± 2.43	2.94 ± 2.23	2.10 ± 1.80	3.96 ± 2.42	4.18†	0.006	TH > SL
Average pain over the last month (NRS 0-10), mean ± SD	5.69 ± 1.91	5.47 ± 1.97	6.33 ± 1.71	6.05 ± 1.97	1.44†	0.231	ND
Worst pain over the last month (NRS 0-10), mean ± SD (n = 301)	8.41 ± 1.52	8.16 ± 1.67	8.20 ± 1.39	8.45 ± 1.62	0.38†	0.771	ND
Best pain over the last month (NRS 0-10), mean ± SD (n = 301)	1.68 ± 1.65	2.00 ± 1.99	0.67 ± 1.11	2.31 ± 2.09	4.71†	0.003	TH > SL
Duration of pain, n (%)					7.33*	0.292	ND
3 to 6 months	15 (9.68)	2 (5.88)	0	12 (12.24)			
6 to 12 months	26 (16.77)	2 (5.88)	4 (26.67)	18 (18.37)			
More than 12 months	114 (73.55)	30 (88.24)	11 (73.33)	68 (69.39)			

Frequency of pain, n (%)					5.97*	0.427	ND
Once a day	119 (76.77)	25 (73.53)	9 (60.00)	79 (80.61)			
Every second day	26 (16.77)	7 (20.59)	3 (20.00)	14 (14.29)			
Once a week	10 (6.45)	2 (5.88)	3 (20.00)	5 (5.10)			
Duration of painful episode, n (%)					11.98*	0.215	ND
Few seconds	1 (0.65)	0	0	4 (4.08)			
Few minutes	22 (14.19)	6 (17.65)	2 (13.33)	12 (12.24)			
Few hours	32 (20.65)	9 (26.47)	7 (46.67)	27 (27.55)			
Constant	100 (64.52)	19 (55.88)	6 (40.00)	55 (56.12)			
Pain catastrophizing scale							
Total score, mean ± SD	27.39 ± 10.11	27.07 ± 9.75	31.43 ± 8.66	30.00 ± 9.89	2.04†	0.108	ND
Low catastrophizers, n (%)	18 (11.61)	4 (11.76)	0	8 (8.16)	4.24*	0.644	ND
Moderate catastrophizers, n (%)	47 (30.32)	9 (26.47)	4 (26.67)	24 (24.49)			
High catastrophizers, n (%)	89 (57.42)	21 (61.76)	11 (73.33)	65 (66.33)			
Douleur Neuropatique 4 questionnaire							
Total score, mean ± SD	2.70 ± 2.06	2.40 ± 1.69	3.20 ± 2.31	3.25 ± 1.94	4.27†	0.006	TH > N
Likely neuropathic, n (%)	52 (33.55)	6 (17.65)	7 (46.67)	48 (48.98)	11.63*	0.009	TH > N & MH & SL
Functional Disability Inventory							
Total score	15.67 ± 9.30	10.58 ± 8.74	15.87 ± 8.93	17.68 ± 10.38	4.41†	0.005	TH > MH
No/minimal disability, n (%)	58 (37.42)	23 (67.65)	6 (40.00)	32 (32.65)	20.71*	0.014	N & SL & TH > MH
Mild disability, n (%)	3 (8.82)	49 (31.61)	4 (26.67)	24 (24.49)			
Moderate disability, n (%)	32 (20.65)	5 (14.71)	3 (20.00)	31 (31.63)			
Severe disability, n (%)	14 (9.03)	1 (2.94)	2 (13.33)	10 (10.20)			
Adolescent Pediatric Pain Tool							
Pain locations, x/67	9.68 ± 9.38	6.79 ± 6.27	7.20 ± 5.61	8.26 ± 7.59	1.52†	0.209	ND
Sensory descriptors, x/37 %	24.59 ± 16.66	17.77 ± 12.46	19.82 ± 10.99	23.54 ± 14.33	2.07†	0.104	ND
Affective descriptors, x/11 %	14.99 ± 18.93	9.64 ± 9.63	17.58 ± 17.00	18.18 ± 16.65	2.15†	0.094	ND
Evaluative descriptors, x/8 %	46.27 ± 26.51	35.61 ± 18.78	35.00 ± 18.42	43.81 ± 23.11	2.43†	0.066	ND
Temporal descriptors, x/24 %	30.40 ± 16.64	23.97 ± 10.62	26.67 ± 10.00	28.87 ± 16.86	1.61†	0.187	ND
Revised Child Anxiety and Depression Scale							
Total T-score, mean ± SD	51.46 ± 13.80	51.48 ± 15.07	53.13 ± 17.39	53.70 ± 13.73	0.55†	0.646	ND
Below clinical threshold, n (%)	129 (83.23)	26 (76.47)	12 (80.00)	77 (78.57)	2.58*	0.860	ND
Borderline clinical threshold, n (%)	4 (2.58)	1 (2.94)	0	5 (5.10)			
Above clinical threshold, n (%)	21 (13.55)	6 (17.65)	3 (20.00)	15 (15.31)			

Pittsburgh Sleep Quality Index							
Total score, mean ± SD	7.82 ± 3.83	6.62 ± 2.69	7.50 ± 3.72	8.23 ± 3.92	1.44†	0.232	ND
Good sleep quality, n (%)	36 (23.23)	7 (20.59)	2 (13.33)	17 (17.35)	1.96*	0.581	ND
Poor sleep quality, n (%)	114 (73.55)	23 (67.65)	12 (80.00)	80 (81.63)			
MDT^{log} (mN), mean ± SD							
Control area	0.37 ± 1.20	1.11 ± 1.11	1.15 ± 1.76	0.97 ± 1.05	7.75†	<0.001	MH & TH > N
Tested area	0.16 ± 1.59	2.08 ± 1.45	1.89 ± 1.98	0.78 ± 1.76	15.91†	<0.001	MH & SL & TH > N MH > TH
Z-score	0.24 ± 0.96	-0.90 ± 1.01	-0.84 ± 1.49	-0.29 ± 1.03	16.50†	<0.001	MH & SL & TH < N MH < TH
DMA^{log} (NRS 0-10), mean ± SD							
Control area	-4.53 ± 0.54	-4.32 ± 1.17	-4.36 ± 0.96	-3.82 ± 1.71	7.76†	<0.001	TH > N
Tested area	-4.29 ± 1.19	-3.68 ± 1.87	-4.40 ± 0.79	-1.74 ± 2.35	46.67†	<0.001	TH > N & MH & SL
Z-score	0.13 ± 0.52	0.40 ± 0.85	0.20 ± 0.77	1.22 ± 0.97	44.57†	<0.001	TH > N & MH & SL
VDT (x/8), mean ± SD							
Control area	6.97 ± 0.88	6.54 ± 0.78	6.08 ± 1.61	6.48 ± 0.96	8.58†	<0.001	N > SL & TH
Tested area	6.43 ± 1.23	5.35 ± 0.88	4.63 ± 1.60	5.64 ± 1.34	17.69†	<0.001	N > MH & TH > SL
Z-score	-0.19 ± 1.04	-1.00 ± 0.73	-1.64 ± 1.68	-0.89 ± 1.12	15.97†	<0.001	N > MH & SL & TH
WUR^{log} (ratio), mean ± SD							
Control area	0.67 ± 0.78	1.14 ± 1.50	0.72 ± 1.10	0.74 ± 1.01	2.13†	0.096	ND
Presence of painful after sensations after 10 stimuli in the control area, n (%)	55 (35.48)	8 (23.53)	3 (20.00)	47 (47.96)	10.2*†	0.016	TH > N & MH & SL
Tested area	0.67 ± 1.00	0.81 ± 1.60	0.88 ± 0.61	0.57 ± 0.84	0.68†	0.566	ND
Presence of painful after sensations after 10 stimuli in the tested area, n (%)	58 (37.42)	7 (20.59)	7 (46.67)	54 (55.10)	19.84*	<0.001	TH > N & MH & SL
Z-score	0.01 ± 0.99	0.54 ± 1.85	0.17 ± 1.14	0.07 ± 1.11	1.88†	0.132	ND
PPT^{log} (kPa), mean ± SD							
Control area	5.20 ± 0.42	5.00 ± 0.39	5.41 ± 0.59	4.96 ± 0.48	8.33†	<0.001	SL > MH N & SL > TH
Tested area	5.26 ± 0.60	5.00 ± 0.79	5.46 ± 0.47	4.87 ± 0.63	9.26†	<0.001	N & SL > TH
Z-score	0.00 ± 0.93	0.46 ± 1.10	-0.40 ± 0.89	0.65 ± 1.01	11.09†	<0.001	SL < MH N & SL < TH
WDT^{log} (°C from baseline), mean ± SD							
Control area	0.31 ± 0.61	1.04 ± 1.34	1.24 ± 0.46	0.29 ± 0.52	22.58†	<0.001	TH & N < MH & SL
Z-score	0.27 ± 0.92	-0.85 ± 1.45	-1.15 ± 0.69	0.29 ± 0.79	22.58†	<0.001	TH & N > MH & SL
HPT (°C), mean ± SD							
Control area	39.30 ± 2.48	41.44 ± 1.88	43.35 ± 2.19	38.09 ± 2.41	31.51†	<0.001	MH & SL > N > TH
Z-score	-0.11 ± 0.96	-0.93 ± 0.72	-1.67 ± 0.84	0.36 ± 0.93	31.51†	<0.001	MH & SL < N < TH
CPM efficiency (%), mean ± SD	-23.08 ± 42.68	-28.14 ± 52.39	-35.10 ± 31.38	-16.89 ± 45.15	1.05†	0.373	ND
Inefficient, n (%)	52 (33.55)	10 (29.41)	3 (20.00)	39 (39.80)	4.25*	0.643	ND
Suboptimal, n (%)	31 (20.00)	6 (17.65)	2 (13.33)	21 (21.43)			

Optimal, n (%)	69 (44.52)	17 (50.00)	8 (53.33)	36 (36.73)			
TSP (NRS -10-+10), mean ± SD	0.08 ± 2.29	0.56 ± 2.21	-0.82 ± 2.71	-0.15 ± 2.19	1.42†	0.236	ND
Absence, n (%)	127 (81.94)	25 (73.53)	12 (80.00)	85 (86.73)	3.86*	0.277	ND
Presence, n (%)	25 (16.13)	8 (23.53)	1 (6.67)	11 (11.22)			

Percentages do not always add up to 100% due to missing data for some demographic variables.
*Test statistic for chi-square test. †Test statistic for one-way ANOVA.
QST indicates quantitative sensory testing; log, log-transformed data; MDT, mechanical detection threshold; DMA, dynamic mechanical allodynia; VDT, vibration detection threshold; WUR, wind-up ratio; PPT, pressure pain threshold; WDT, warm detection threshold; HPT, heat pain threshold; N, normative QST profile; MH, mechanical hyperalgesia profile; SL, sensory loss profile; TH, thermal hyperalgesia profile; ND, no statistically significant difference between somatosensory profiles; CPM indicates conditioned pain modulation; TSP, temporal summation of pain.

Supplementary Table 5. Characteristics of pain modulation profiles in adolescents with chronic musculoskeletal pain

Variable	Dysfunctional central processing (n = 27)	Dysfunctional inhibition (n = 136)	Facilitation (n = 18)	Functional central processing (n = 112)	Test statistic	p-value	Subgroup comparison
Age, mean ± SD	15.01 ± 1.76	14.94 ± 1.99	14.87 ± 2.42	14.90 ± 1.86	0.03†	0.992	ND
Younger adolescent (10-13 years), n (%)	6 (22.22)	39 (28.68)	6 (33.33)	33 (29.46)	0.77*	0.856	ND
Older adolescent (14-18 years), n (%)	21 (77.78)	97 (71.32)	12 (66.67)	79 (70.54)			
Gender, n (%)					2.76*	0.430	ND
Female	23 (85.19)	106 (77.94)	15 (83.33)	96 (85.71)			
Male	4 (14.81)	30 (22.06)	3 (16.67)	16 (14.29)			
Race, n (%)					1.85*	0.605	ND
Caucasian (White)	20 (74.07)	99 (73.33)	15 (83.33)	89 (79.46)			
Person of color	7 (25.93)	36 (26.67)	3 (16.67)	23 (20.54)			
Past hospitalizations, n (%)					0.81*	0.847	ND
No	18 (66.67)	94 (69.12)	14 (77.78)	80 (71.43)			
Yes	9 (33.33)	42 (30.88)	4 (22.22)	32 (28.57)			
Past surgeries, n (%)					1.79*	0.616	ND
No	18 (66.67)	79 (58.09)	13 (72.22)	68 (60.71)			
Yes	9 (33.33)	57 (41.91)	5 (27.78)	44 (39.29)			
Primary location of pain (Tested pain area), n (%)					7.69*	0.807	ND
Head/Neck	1 (3.70)	7 (5.15)	0	3 (2.68)			
Upper limbs	4 (14.81)	10 (7.35)	1 (5.56)	7 (6.25)			
Thorax	0	1 (0.74)	0	3 (2.68)			
Back	13 (48.15)	76 (55.88)	12 (66.67)	68 (60.71)			
Lower limbs	9 (33.33)	42 (30.88)	5 (27.78)	31 (27.68)			
Presence of radiating pain, n (%)	14 (51.85)	63 (46.32)	10 (55.56)	56 (50.00)	0.83*	0.843	ND
Presence of secondary pain sites, n (%)	15 (55.56)	75 (55.15)	7 (38.89)	59 (52.68)	1.76*	0.624	ND
Pain now (NRS 0-10), mean ± SD	3.80 ± 1.95	3.34 ± 2.53	3.22 ± 2.01	3.27 ± 2.43	0.37†	0.777	ND
Average pain over the last month (NRS 0-10), mean ± SD	6.28 ± 1.89	5.81 ± 1.96	5.50 ± 1.73	5.70 ± 1.91	0.80†	0.495	ND
Worst pain over the last month (NRS 0-10), mean ± SD (n = 301)	8.50 ± 1.45	8.44 ± 1.62	7.83 ± 1.64	8.41 ± 1.46	0.87†	0.456	ND
Best pain over the last month (NRS 0-10), mean ± SD (n = 301)	2.31 ± 1.79	1.92 ± 1.96	1.83 ± 1.78	1.70 ± 1.69	0.90†	0.441	ND
Duration of pain, n (%)					2.43*	0.876	ND
3 to 6 months	4 (14.81)	11 (8.09)	2 (11.11)	12 (10.71)			
6 to 12 months	5 (18.52)	20 (14.71)	3 (16.67)	21 (18.75)			
More than 12 months	18 (66.67)	105 (77.21)	13 (72.22)	79 (70.54)			

Frequency of pain, n (%)					1.07*	0.983	ND
Once a day	22 (81.48)	104 (76.47)	13 (72.22)	87 (77.68)			
Every second day	3 (11.11)	23 (16.91)	4 (22.22)	18 (16.07)			
Once a week	2 (7.41)	9 (6.62)	1 (5.56)	7 (6.25)			
Duration of painful episode, n (%)					3.16*	0.957	ND
Few seconds	0	2 (1.47)	0	3 (2.68)			
Few minutes	3 (11.11)	21 (15.44)	2 (11.11)	15 (13.39)			
Few hours	8 (29.63)	33 (24.26)	3 (16.67)	27 (24.11)			
Constant	16 (59.26)	80 (58.82)	13 (72.22)	67 (59.82)			
Pain catastrophizing scale							
Total score, mean ± SD	28.70 ± 11.62	28.65 ± 9.92	28.72 ± 9.60	27.67 ± 9.92	0.22†	0.881	ND
Low catastrophizers, n (%)	3 (11.11)	12 (8.82)	3 (16.67)	12 (10.71)	3.86*	0.696	ND
Moderate catastrophizers, n (%)	7 (25.93)	38 (27.94)	2 (11.11)	35 (31.25)			
High catastrophizers, n (%)	17 (62.96)	84 (61.76)	13 (72.22)	65 (58.04)			
Douleur Neuropatique 4 questionnaire							
Total score, mean ± SD	3.80 ± 1.73	3.17 ± 2.18	2.75 ± 1.83	2.56 ± 1.88	3.41†	0.018	ND
Likely neuropathic, n (%)	15 (55.56)	57 (41.91)	7 (38.89)	31 (27.68)*	11.04*	0.012	DCP & DI & F > FCP
Functional Disability Inventory							
Total score	15.19 ± 9.19	17.21 ± 9.93	15.00 ± 9.76	14.19 ± 9.47	2.04†	0.109	ND
No/minimal disability, n (%)	11 (40.74)	43 (31.62)	9 (50.00	53 (47.32)	12.09*	0.208	ND
Mild disability, n (%)	10 (37.04)	39 (28.68)	2 (11.11)	28 (25.00)			
Moderate disability, n (%)	4 (14.81)	40 (29.41)	5 (27.78)	20 (17.86)			
Severe disability, n (%)	2 (7.41)	12 (8.82)	2 (11.11)	9 (8.04)			
Adolescent Pediatric Pain Tool							
Pain locations, x/67	8.89 ± 7.68	8.90 ± 9.28	7.78 ± 6.94	8.83 ± 7.47	0.10†	0.961	ND
Sensory descriptors, x/37 %	26.93 ± 14.56	23.07 ± 15.51	23.27 ± 21.62	22.71 ± 14.61	0.56†	0.645	ND
Affective descriptors, x/11 %	17.85 ± 17.56	16.08 ± 17.90	19.19 ± 23.72	13.56 ± 15.48	0.95†	0.417	ND
Evaluative descriptors, x/8 %	46.30 ± 27.04	44.31 ± 23.83	36.11 ± 31.47	43.97 ± 23.07	0.71†	0.545	ND
Temporal descriptors, x/24 %	31.31 ± 17.89	27.07 ± 14.21	32.32 ± 21.20	30.6 ± 15.46	1.45†	0.230	ND
Revised Child Anxiety and Depression Scale							
Total T-score, mean ± SD	50.63 ± 10.99	53.40 ± 14.91	54.28 ± 15.88	51.17 ± 13.79	0.74†	0.529	ND
Below clinical threshold, n (%)	25 (92.59)	107 (78.68)	12 (66.67)	92 (82.14)	8.32*	0.216	ND
Borderline clinical threshold, n (%)	1 (3.70)	6 (4.41)	0	3 (2.68)			
Above clinical threshold, n (%)	1 (3.70)	21 (15.44)	6 (33.33)	17 (15.18)			

Pittsburgh Sleep Quality Index							
Total score, mean ± SD	8.50 ± 4.11	7.98 ± 3.77	6.88 ± 3.62	7.52 ± 3.68	0.93†	0.425	ND
Good sleep quality, n (%)	5 (18.52)	29 (21.32)	5 (27.78)	22 (19.64)	0.84*	0.840	ND
Poor sleep quality, n (%)	21 (77.78)	103 (75.74)	12 (66.67)	87 (77.68)			
MDT^{log} (mN), mean ± SD							
Control area	0.87 ± 0.93	0.64 ± 1.15	0.46 ± 1.17	0.72 ± 1.38	0.48†	0.694	ND
Tested area	0.72 ± 1.66	0.55 ± 1.77	1.47 ± 1.53	0.69 ± 1.79	1.46†	0.226	ND
Z-score	0.23 ± 0.91	0.05 ± 1.04	0.34 ± 1.08	0.14 ± 1.19	0.54†	0.656	ND
DMA^{log} (NRS 0-10), mean ± SD							
Control area	-4.45 ± 0.79	-4.18 ± 1.28	-4.61 ± 1.10	-4.34 ± 1.08	1.12†	0.341	ND
Tested area	-2.99 ± 2.26	-3.23 ± 2.21	-3.74 ± 1.69	-3.71 ± 1.83	1.65†	0.179	ND
Z-score	0.59 ± 0.84	0.60 ± 0.97	0.33 ± 0.64	0.40 ± 0.78	1.33†	0.264	ND
VDT (x/8), mean ± SD							
Control area	6.50 ± 0.89	6.76 ± 0.97	6.81 ± 0.87	6.72 ± 0.92	0.62†	0.601	ND
Tested area	5.73 ± 1.59	6.02 ± 1.37	6.07 ± 1.24	5.96 ± 1.21	0.39†	0.760	ND
Z-score	-0.83 ± 1.25	-0.52 ± 1.16	-0.47 ± 1.08	-0.58 ± 1.02	0.60†	0.618	ND
WUR^{log} (ratio), mean ± SD							
Control area	0.79 ± 1.00	0.71 ± 0.91	0.99 ± 0.89	0.75 ± 1.06	0.46†	0.711	ND
Presence of painful after sensations after 10 stimuli in the control area, n (%)	16 (59.26)	50 (36.76)	5 (27.78)	38 (33.93)	6.57*	0.087	ND
Tested area	0.41 ± 0.55	0.55 ± 0.85	0.52 ± 0.52	0.86 ± 1.29	2.48†	0.062	ND
Presence of painful after sensations after 10 stimuli in the tested area, n (%)	14 (51.85)	56 (41.18)	7 (38.89)	44 (39.29)	1.70*	0.637	ND
Z-score	0.03 ± 1.00	0.02 ± 1.11	0.26 ± 0.87	0.17 ± 1.32	0.46†	0.711	ND
PPT^{log} (kPa), mean ± SD							
Control area	5.13 ± 0.49	5.10 ± 0.51	5.23 ± 0.38	5.09 ± 0.41	0.49†	0.691	ND
Tested area	4.92 ± 0.70	5.13 ± 0.73	5.12 ± 0.44	5.14 ± 0.57	0.83†	0.480	ND
Z-score	-0.43 ± 1.14	-0.23 ± 1.16	-0.12 ± 0.63	-0.24 ± 0.89	0.35†	0.787	ND
WDT^{log} (°C from baseline), mean ± SD							
Control area	0.31 ± 0.65	0.42 ± 0.76	0.68 ± 0.50	0.41 ± 0.61	1.15†	0.331	ND
Z-score	-0.27 ± 0.98	-0.10 ± 1.15	0.30 ± 0.76	-0.11 ± 0.93	1.15†	0.331	ND
HPT (°C), mean ± SD							
Control area	39.14 ± 1.98	39.13 ± 2.72	40.45 ± 2.17	39.39 ± 2.90	1.34†	0.262	ND
Z-score	0.05 ± 0.76	0.04 ± 1.05	0.55 ± 0.84	0.14 ± 1.12	1.34†	0.262	ND
CPM efficiency (%), mean ± SD	13.29 ± 30.55	6.60 ± 35.02	-58.53 ± 21.30	-59.86 ± 20.67	177.3†	<0.001	DCP & DI > F & FCP
Inefficient, n (%)	22 (81.48)	82 (60.29)	0	0	300.87*	<0.001	DCP & DI > F & FCP
Suboptimal, n (%)	5 (18.52)	54 (39.71)	0	0			DCP & DI > F & FCP
Optimal, n (%)	0	0	18 (100)	112 (100)			DCP & DI < F & FCP

TSP (NRS -10-+10), mean ± SD	3.31 ± 1.2	-0.57 ± 1.95	3.47 ± 1.38	-0.63 ± 1.73	63.07†	<0.001	DCP & F > DI & FCP
Absence, n (%)	0	136 (100)	0	112 (100)	293*	<0.001	DCP & F < DI & FCP
Presence, n (%)	27 (100)	0	18 (100)	0			DCP & F > DI & FCP

Percentages do not always add up to 100% due to missing data for some demographic variables.
*Test statistic for chi-square test. †Test statistic for one-way ANOVA.
log, log-transformed data; MDT, mechanical detection threshold; DMA, dynamic mechanical allodynia; VDT, vibration detection threshold; WUR, wind-up ratio; PPT, pressure pain threshold; WDT, warm detection threshold; HPT, heat pain threshold; CPM indicates conditioned pain modulation; TSP, temporal summation of pain; DCP, dysfunctional central processing; DI, dysfunctional inhibition; F, facilitation; FCP, functional central processing; ND, no statistically significant difference between pain modulation response profiles.

Manuscript 4 – Electroencephalographic characteristics of children and adolescents with chronic musculoskeletal pain

(Under review, February 2022)

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3.4.1 Abstract

The pathophysiology of pediatric musculoskeletal (MSK) pain is unclear, contributing to persistent challenges to its management. This study hypothesizes that children and adolescents with chronic MSK pain (CPs) will show differences in electroencephalography (EEG) features at rest and during thermal pain modalities when compared to age-matched controls. One hundred and forty-two CP patients and forty-five age-matched healthy controls (HCs) underwent a standardized thermal tonic heat and cold stimulations, while a 21-electrode headset collected EEG data. Cohorts were compared with respect to their EEG features of spectral power, peak frequency, permutation entropy, weight phase-lag index, directed phase-lag index and node degree at four frequency bands, delta (1-4Hz), theta (4-8Hz), alpha (8-13Hz) and beta (13-30Hz), at rest and during the thermal conditions. At rest, CPs showed increased global delta ($p=0.0493$) and beta ($p=0.0002$) power in comparison with HCs. These findings provide further impetus for the investigation and prevention of long-lasting developmental sequalae of early life chronic pain processes. Though no cohort differences in pain intensity scores were found during the thermal pain modalities, CPs and HCs showed significant difference in changes in EEG spectral power, peak frequency, permutation entropy, and network functional connectivity during the tonic heat and cold stimulations. This suggests that EEG can characterize subtle differences in heat and cold pain sensitivity in CPs. The complementation of EEG and evoked-pain in the clinical assessment of pediatric chronic MSK pain can better detect underlying pain mechanisms and changes in pain sensitivity.

Keywords

Pediatric pain, clinical pain assessment, chronic musculoskeletal pain, electroencephalography, sensory testing, non-invasive neuroimaging

3.4.2 Introduction

Musculoskeletal (MSK) pain is a common pediatric pain presentation [1-4] that elicits disabling and distressing impacts on the daily lives of children and adolescents by limiting school attendance and social participation when chronic [5, 6]. The pathophysiology of pediatric chronic pain is not fully understood, contributing to persistent challenges in its management such as determining which characteristics associated with treatment responses [7]. This elicits significant burdens, as poorly managed pediatric pain can lead to continued pain and disability in adulthood [8].

Advances in non-invasive neuroimaging techniques such as electroencephalography (EEG) present opportunities to better characterize the neurological processes underlying pediatric chronic pain. EEG is a safe, reliable and portable neuroimaging tool that is well-positioned to measure electrical activity patterns on the scalp surface at the point-of-care [9]. Previous studies have identified that adults with and without chronic pain show distinct EEG patterns [10-12]. Spectral power and peak frequency, measures of oscillatory neural activity generated by transforming EEG waves from the time to frequency domain [13], are the most commonly assessed parameters in the chronic pain literature. Adult chronic pain patients demonstrate increased resting EEG theta power (4-8 Hz) and a slowing of the peak frequency of the power spectra to lower frequencies [14]. Studies have also identified that changes in the pain connectome among adult chronic pain patients [15, 16], as measured through altered functional connectivity between the EEG captured over different scalp areas, and that anesthetic gases alter waveform permutation entropy, a measure of EEG information content quantifying the regularity of the continuous EEG time series [4, 17].

However, there is a paucity of neuroimaging studies investigating children and adolescents with chronic pain [18]. The pediatric neuroimaging literature has concentrated on employing fMRI to investigate changes in functional connectivity and brain regional activation of adolescents with complex regional pain syndromes (CRPS) [19-21], identifying that pediatric and adult CRPS patients show different patterns of functional connectivity changes [22]. This neuroimaging finding corroborates with a host of experimental and clinical studies that have identified age-dependent developmental changes in pediatric pain processing, perception and responses [23-26], suggesting that children and adolescents are not merely 'little adults'. There is thus substantial impetus for extending the findings of the adult chronic pain EEG literature into pediatric populations to identify objective, dynamic, and age-related cerebral biomarkers of pediatric chronic pain. This study employed EEG to interrogate brain activity and connectivity changes in children and adolescents with chronic MSK pain at rest and during thermal experimental pain modalities previously demonstrated to elicit altered pain responses in pediatric patients with MSK impairments [27], to assess differences in a participant's pain responses to two forms of tonic noxious stimuli (tonic heat and cold pressor task). The hypothesis was that children and adolescents with chronic MSK pain will show developmental patterns of EEG neural activity and connectivity differences to age-matched pain-free healthy controls at rest and an increased sensitivity to acute tonic pain experiences during the thermal experimental pain modalities.

3.4.3 Material and methods

3.4.3.1 Participants

Participant recruitment occurred between October 2018 and June 2021. Children and adolescents with chronic MSK pain (CP) from the spine and orthopedic outpatient clinics and from

the Chronic Pain Services of our institution were approached by a research assistant to participate in the study and to confirm eligibility criteria prior to receiving signed consent. Inclusion criteria for patients include being between 10-18 years of age, reporting MSK pain at least once weekly and lasting 3 months or longer, and demonstrating the ability to adequately understand and respond to the study's outcome measures. Exclusion criteria included children unable to speak, write or read English or French, children with pain due to an acute trauma occurring in the past 3 months (e.g. fracture), children diagnosed with developmental delay, and children with any severe systemic disease with some functional limitations will be excluded from the study. Age-matched healthy controls (HC) with no chronic pain in the last three months, between 10 and 18 years old, were recruited through word of mouth, recruitment advertisements in local magazines and social media. As suggested by Gierthmühlen et al., a screening checklist for recruitment was completed by a research assistant to ensure eligibility of "healthy" subjects [28]. Ethics approval was obtained prior to the beginning of the recruitment from the Research Ethics Board of McGill University (A09-M17-17B). Participants received a written informed consent prior to inclusion in the study and a signature was obtained by the participant or their parent/legal guardian, if the participant was under the age of 14 years old, prior to the beginning of the study.

3.4.3.2 Sociodemographic characteristics and pain history

The age, gender, ethnicity and dominant hand of all participants were collected through face-to-face interviews by a research assistant on a standardized participant history collection form. All CP participants were asked for their medical history and to describe the location(s), duration and frequency of their pain. The Douleur Neuropathique 4 (DN4) questionnaire was used to assess the neuropathic component of their pain [29]. Prior to the assessment, all participants

were asked to verbally rate their current pain intensity with a numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain imaginable).

The Pain Catastrophizing Scale for Children (PCS-C) was completed by all participants to assess the degree to which they experienced negative thoughts or feelings while experiencing pain [30]. The PCS-C is a 13-item scale and can be divided into three subscales: rumination, magnification and helplessness. Responses for each statement are done using a Likert-type rating scale, ranging from 0 (not at all) to 4 (extremely) for a maximum score of 52 [31]. The Pittsburgh Sleep Quality Index (PSQI) questionnaire was completed by all participants to assess sleep quality, in which a global score of 5 or higher indicated poor sleep quality [32]. The PSQI is the most commonly used measure in clinical and research settings and has been validated in clinical and non-clinical groups of adolescents [33, 34]. The Revised Child Anxiety and Depression Scale (RCADS) questionnaire was completed by all participants to assess children's self-report of depression and anxiety [35]. Based on the patient's age and grade in school, their total scores are converted into a T score (≤64 below, 65-69 borderline, and ≥70 above clinical threshold).

3.4.3.3 Thermal experimental pain modalities

Each participant underwent two specific thermal experimental pain modalities from a conditioned pain modulation assessment previously described by our research group [27, 36]. Pain perception during the experimental tonic heat pain procedure was recorded using a computerized visual analogue scale (CoVAS) scale ranging from 0 (no pain) to 100 (worst pain imaginable). For the tonic heat test stimulus, a 9 cm2 warm calibrated thermode connected to a Q-sense apparatus (Medoc, Israel) was placed on the right volar forearm and was set to a pre-determined test temperature eliciting a 50/100 pain intensity rating for the individual participant. The target temperature then remained constant for 120 seconds. To avoid expectation effects, participants

were told that the temperature of the thermode could increase, remain stable or decrease and that they would have to evaluate their pain with the CoVAS throughout the test. All participants were blinded to the temperature used. At the end of the 120 seconds of the tonic heat test stimulus, the average pain intensity during the 120 second period was calculated. Each participant then performed a cold pressor task (CPT), with complete immersion of their left forearm in cold water (12°C) for 2 min while rating their pain with a NRS ranging from 0 (no pain) to 10 (worst pain imaginable) every fifteen seconds. If a participant removed their arm before the end of the 120 seconds, an average pain intensity score of 10/10 was given.

3.4.3.4 Electroencephalography (EEG) recording

Brain activity was recorded with a dry EEG headset (DSI-24 from Wearable Sensing) using 21 electrodes located at standard 10-20 system coordinates. This headset was selected for its high portability and feasibility for routine use in clinical settings. Data was sampled at 300 Hz. All EEG electrodes were referenced to Pz. Recordings were performed at resting-state with eyes opened and during the thermal experimental pain modalities (tonic heat and cold pressor task conditions). Two different baseline EEG recordings were conducted on two groups of participants: resting-state with eyes open or resting-state with eyes open while moving the COVAS to control for the motor aspect of the thermal heat pain modality.

3.4.3.5 EEG preprocessing

The EEG was preprocessed in EEGlab (A Delorme & S Makeig, 2004). The EEG was bandpass filtered between 0.1 and 50 Hz, and re-referenced to A1 and A2 electrodes. This resulted in 19 referenced EEG channels corresponding to the Fp1/2, F3/4/7/8/z, C3/4/z, T3/4/5/6, P3/4/z, and O1/2 electrodes. Independent component analysis was performed in order to identify and

remove electrooculogram (EOG) and electromyogram (EMG) components in the signal, artifacts of eye movement and facial muscle activity, respectively. The data were visually inspected and the remaining bad segments were manually removed. The cleaned EEG data was segmented into three conditions of interest: the resting state, the tonic heat stimulation and the CPT. All EEG segments were then exported in a custom MATLAB plug-in EEGapp (EEGapp, BIAPT lab, McGill University) for further analysis [37].

3.4.3.6 EEG feature extraction

All EEG features were calculated at four frequency bands —delta (1 – 4Hz), theta (4-8Hz), alpha (8-13Hz) and beta (13-30Hz)— on 10-second EEG segments. Six EEG features were calculated: global spectral power, global peak frequency, permutation entropy, weighted phase-lag index, directed phase-lag index and node degree.

To assess the oscillatory neural activity, the spectral powers of each channel were calculated on the average spectrogram for a given window using the *spectopo* function in EEGlab [38]. Spectrograms across all channels were calculated using the multitaper method with 3 tapers and a time bandwidth product of 2; global spectral power was calculated for each participant by averaging the spectral power across all channels within each frequency band. Global peak frequency was identified as the frequency with the largest power amplitude within each frequency range of interest.

To investigate the information content of the EEG waveform, permutation entropy was calculated by fragmenting the continuous EEG waveform into a sequence of motifs according to their shape (slopes, peaks, and troughs) and generating a probability distribution of their representation in the EEG with two parameters, embedding dimension (d_E) and time delay (τ) [39]. Guided by previous studies, we used $d_E = 5$ and $\tau = 4$ to provide a sufficient deployment of the

trajectories within the state space of the EEG beta activity [40]. A normalized permutation entropy value approaching 1 indicates that the EEG waveform is dominated by higher frequency signals, while a normalized permutation entropy value approaching its theoretical minimum of 0 suggests that the EEG waveform is primarily composed of low frequency signals. Global permutation entropy was calculated for each participant by averaging the permutation entropy across all channels within each frequency band.

To characterize the neural communication processes detected as the relationships between EEG signals measured by electrodes overlying neighboring cortical areas, functional connectivity was estimated with the weighted phase lag index [41], a method that is not susceptible to the effects of volume conduction (43). A wPLI value close to 1 indicates complete phase locking between the two EEG signals. Conversely, a wPLI value of 0 indicates that the phase lead/lag relationship between the signals is random. To characterize the temporal precedence between two EEG signals, directed functional connectivity was estimated with the directed phase lag index [42]. A dPLI value between 0.5 and 1 indicates that the EEG signal from electrode 1 leads the signal from electrode 2. Conversely, a dPLI value between 0 and 0.5 indicates that the EEG signal from electrode 2 leads the signal from electrode 1, and a dPLI value of 0.5 indicates that there is no phase lead or lag relationship between the signals. Both the wPLI and dPLI functional connectivity measures between every pair of electrodes was computed, resulting in a 19 x 19 channel connectivity matrix, with each single value corresponding to the strength of connection between the cortical activity detected by 2 channels over the 10-second EEG segments. The average wPLI and dPLI functional connectivity measures was calculated by averaging the measure within each condition and each frequency band.

Graph analysis was used to further characterize the functional connectivity network for each condition (rest, tonic heat, cold pressor task) [43]. A minimally spanning graph using individually set thresholds for each patient was used to characterize the node degree of each electrode; in other words, the total number of other electrodes to which a given electrode was functionally connected. The average node degree was calculated for each channel by averaging the node degree within each condition and each frequency band.

3.4.3.7 Data analysis and statistics

Statistical analysis was performed using R Studio software (RStudio Team, Boston, MA, USA). The demographic and clinical pain characteristics of participants in the CP and HC groups were analyzed for differences with independent samples t-testing and Chi-squared tests. All EEG feature variables were visually and statistically assessed for normality with Q-Q plots and Kolmogorov-Smirnov tests, and were subsequently all transformed into Z-scores to provide more uniform distributions. Pearson's correlation analyses were performed to assess associations between participant age, pain catastrophizing, anxiety and depression, and sleep quality, with baseline EEG features. The EEG features of global spectral power, global peak frequency and global permutation entropy across each frequency band were investigated with two-way analyses of variance (ANOVA) of generalized linear mixed models (GLMMs) with cohort (CP and HC) and thermal stimulus (resting, tonic heat, and CPT) as fixed effects, resting-state recording type as a moderator (resting-state with eyes open or resting-state with eye open while moving the COVAS to control for the motor aspect of the thermal heat pain modality), and participants as random effects, to account for the within-participant variability inherent to the experiment's repeated measures design. Main effects identified through ANOVAs on the GLMMs were further analyzed using least squares means post hoc testing with Tukey corrections for multiple comparisons to

identify specific cohort and thermal stimulus-related group differences in EEG features. Since wPLI and dPLI functional connectivity, as well as node degree, were calculated for each channel, they were analyzed using least squares means comparing the average channel measures during each thermal stimulus (tonic heat and CPT) with resting measures, with p-values adjusted for multiple comparisons with the Benjamini-Hochberg procedure with a False Discovery Rate (FDR), the expected proportion of type I error, of 0.05. All data are presented as the mean +/- standard error of the mean, unless indicated otherwise. Statistical significance was set at $p<0.05$.

3.4.4 Results

3.4.4.1 Demographic and clinical pain characteristics of participants

A total of one hundred and fifty-one children and adolescents with chronic MSK pain and forty-five age-matched healthy controls were recruited and completed the EEG and thermal experimental pain modalities simultaneously. However, after subsequent evaluation, two patients did not experience pain at least once a week, and six patients did not have usable baseline resting-state EEG data. Therefore, one hundred and forty-two patients with chronic MSK pain were included in the analysis. Demographic and clinical pain characteristics for the study participants are presented in Table 3-8. No significant differences were observed in age and dominant handedness of the children and adolescents with and without chronic MSK pain. However, there was a higher proportion of females (83.92% vs. 42.22%, $p<0.001$) and a different distribution of ethnicity ($\chi 2=5.67$, $p=0.017$) in the CP group compared to the HCs. No significant differences in the outcome measures from the thermal experimental pain modalities were identified between CPs and their age-matched HCs.

3.4.4.2 Associations between demographic characteristics and resting EEG global spectral power

Pearson's correlation analyses showed significant age-related decreases in resting global theta power in CPs, but this negative correlation was not significant for the global theta power of HCs (Figure 3-15). No significant age-related differences in resting delta, alpha and beta power were observed. No significant correlation was observed between pain catastrophizing or sleep quality and resting EEG global spectral power (Figure S1 and S2). However, a significant positive correlation between anxiety and depression and resting global beta power was observed in CPs, but not HCs (Figure S3D).

Table 3-8 Demographics and Characteristics of sample

Variable	CP (n = 143)	HC (n = 45)	Test statistic	p-value
Age, mean ± SD	14.93 ± 1.99	14.91 ± 2.23	t = 0.05	0.963
Gender, n (%)			χ^2 = 28.75	**<0.001**
Female	120 (83.92)	19 (42.22)		
Male	23 (16.08)	26 (57.78)		
Race*, n (%)			χ^2 = 5.67	**0.017**
White	123 (86.01)	31 (68.89)		
Person of color	20 (13.99)	14 (31.11)		
Past hospitalizations, n (%)			χ^2 = 1.90	0.169
No	97 (67.83)	36 (80.00)		
Yes	46 (32.17)	9 (20.00)		
Past surgeries, n (%)			χ^2 = 0.01	0.926
No	89 (62.24)	27 (60.00)		
Yes	54 (37.76)	18 (40.00)		
Dominant hand, n (%)			χ^2 = 0.37	0.544
Left	16 (11.19)	3 (6.67)		
Right	126 (88.11)	42 (93.33)		
Primary location of pain, n (%)				
Head/Neck	6 (4.20)	-		
Upper limbs	17 (11.89)	-		
Thorax	2 (1.40)	-		
Back	76 (53.15)	-		
Lower limbs	42 (29.37)	-		
Presence of radiating pain, n (%)	69 (48.25)	-		
Presence of secondary pain sites, n (%)	74 (51.75)	-		
Pain now (NRS 0-10), mean ± SD	3.60 ± 2.38	0	t = 16.22	**<0.001**

Variable	CP (n = 143)	HC (n = 45)	Test statistic	p-value
Average pain over the last month (NRS 0-10), mean ± SD	5.99 ± 1.91	-		
Worst pain over the last month (NRS 0-10), mean ± SD	8.49 ± 1.49	-		
Best pain over the last month (NRS 0-10), mean ± SD	2.03 ± 1.85	-		
Duration of pain, n (%)				
3 to 6 months	19 (13.29)	-		
6 to 12 months	26 (18.18)	-		
More than 12 months	98 (68.53)	-		
Frequency of pain, n (%)				
Once a day	117 (81.82)	-		
Every second day	19 (13.29)	-		
Once a week	7 (4.90)	-		
Duration of painful episode, n (%)				
Few seconds	1 (0.70)	-		
Few minutes	17 (11.89)	-		
Few hours	30 (20.98)	-		
Constant	95 (66.43)	-		
Douleur Neuropatique 4 questionnaire				
Total score, mean ± SD	3.16 ± 1.99	-		
Likely neuropathic, n (%)	62 (44.29)	-		
Pain catastrophizing scale, mean ± SD				
Total score	29.35± 10.10	17.33 ± 7.86	t = 8.31	**<0.001**
Revised Child Anxiety and Depression Scale				
Total T-score, mean ± SD	52.56 ± 13.90	44.82 ± 11.02	t = 3.84	**<0.001**
Below clinical threshold, n (%)	115 (80.42)	42 (93.33)	χ^2 = 4.34	0.114
Borderline clinical threshold, n (%)	5 (3.50)	1 (2.22)		
Above clinical threshold, n (%)	23 (16.08)	2 (4.44)		
Pittsburgh Sleep Quality Index				
Total score, mean ± SD	7.88 ± 3.59	4.35 ± 2.48	t = 7.30	**<0.001**
Good sleep quality, n (%)	26 (18.18)	27 (60.00)	χ^2 = 25.98	**<0.001**
Poor sleep quality, n (%)	112 (78.32)	18 (40.00)		
Tonic heat				
Pain intensity (CoVAS 0-100), mean ± SD	40.36 ± 21.29	39.22 ± 15.74	t = 0.38	0.701
Cold pressor task				
Pain intensity (NRS 0-10), mean ± SD	7.01 ± 2.45	6.26 ± 2.34	t = 1.84	0.070

Percentages do not always add up to 100% due to missing data for some demographic variables.
*Due to low frequency of some racial groups, races typically identified by Statistics Canada as a visible minority group (American Indian or Alaska Native, Asian, Black or African American, Latin American, Arab, and Mixed Race) were collapsed into a single category.

Variable	CP (n = 143)	HC (n = 45)	Test statistic	p-value

The Douleur Neuropatique 4 questionnaire was only completed by n=140 CPs. The Pain Catastrophizing Scales was only completed by n=142 CPs. The Pittsburgh Sleep Quality Index was only completed by n=138 CPs.
CP, children and adolescents with chronic MSK pain; HC, age-matched healthy controls; NRS, numerical rating scale; CoVAS, computerized visual analog scale.

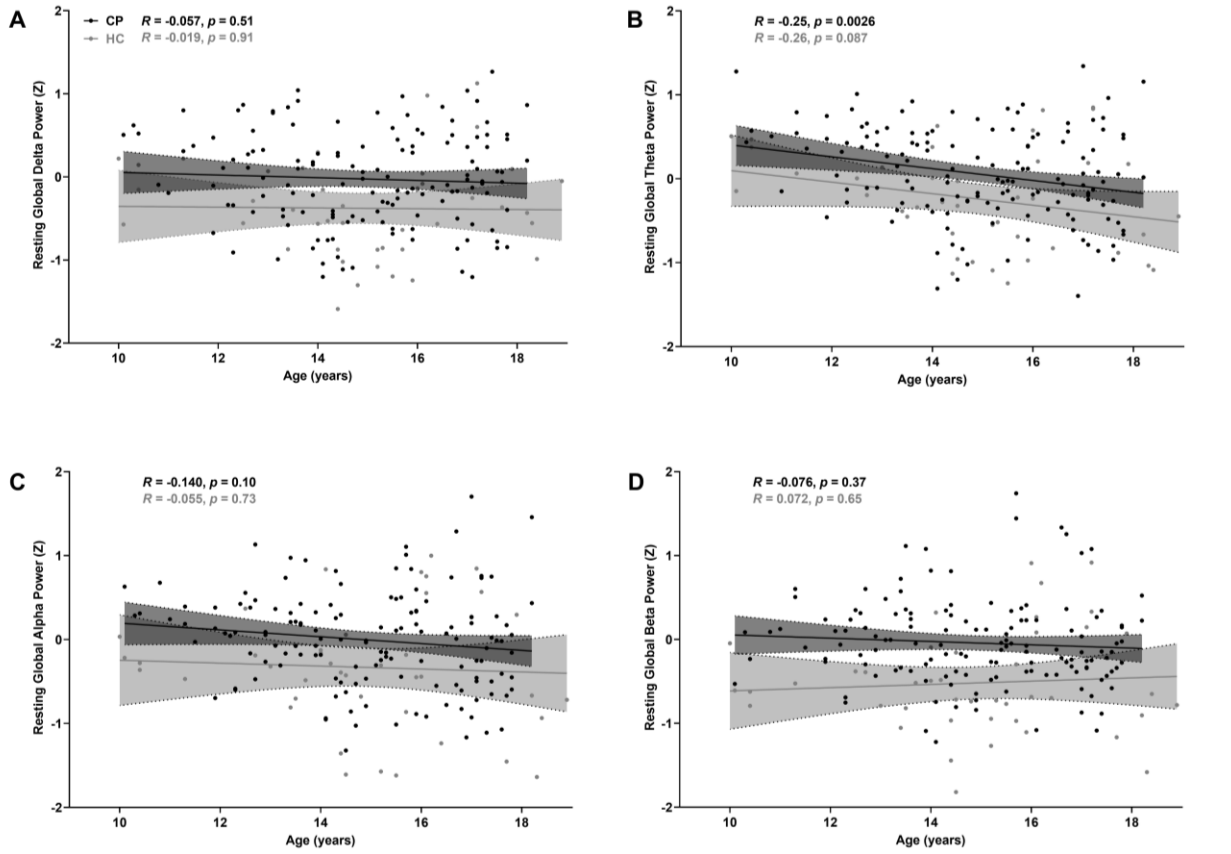

Figure 3-15. Associations between age and resting EEG global spectral power at rest
Associations between age and resting EEG global delta (A), theta (B), alpha (C), and beta (D) spectral power at rest of children and adolescents with chronic MSK pain (CP) and age-matched healthy controls (HC). Pearson's rank correlation analysis R values and p-values are shown.

3.4.4.3 Changes in EEG global spectral powers

Children and adolescents with chronic MSK pain showed global changes in oscillatory brain activity at rest and in response to the different thermal stimuli. Two-way ANOVAs on the GLMMs of global spectral powers showed no interaction effect, but showed main effects of cohort

in the delta ($F_{1,179}$=10.82, p=0.0012), theta ($F_{1,179}$=6.11, p=0.0144), alpha ($F_{1,179}$=7.19, p=0.0080) and beta ($F_{1,179}$=21.87, p<0.0001) frequency bands and thermal stimulus in the delta ($F_{2,331}$=111.19, p<0.0001), theta ($F_{2,331}$=44.00, p<0.0001), alpha ($F_{2,331}$=40.78, p<0.0001) and beta ($F_{2,331}$=197.02, p<0.0001) frequency bands (Figure 3-16). CPs showed increased resting global delta power relative to HCs (p=0.0493, Figure 3-16A). No significant cohort-related differences in global theta or alpha powers measured at rest and during tonic noxious thermal stimulations were observed between CPs and HCs (Figure 3-16B-C). Moreover, CPs showed increased global beta power relative to HCs at rest (p=0.0002), and during the tonic heat (p=0.0070) and cold (p=0.0010) pain modalities (Figure 3-16D). Post hoc testing to assess the main effect of the thermal modalities stimulus revealed decreased global spectral powers in the delta (p=0.0190) and theta (p=0.0007) bands in CPs during the tonic heat condition relative to resting measurements (Figure 3-16A-B). No differences in global spectral powers during the tonic heat condition relative to resting measurements were found in the HCs (p>0.05). In addition, CPs and HCs showed increased global spectral powers across all frequency bands during the CPT in comparison with resting and tonic heat conditions (p<0.05; Figure 3-16A-D). In summary, CPs showed increased resting EEG global delta and beta power and a differential response of suppressed global spectral powers across delta and theta bands to the tonic heat thermal stimulus in comparison with their age-matched HC counterparts.

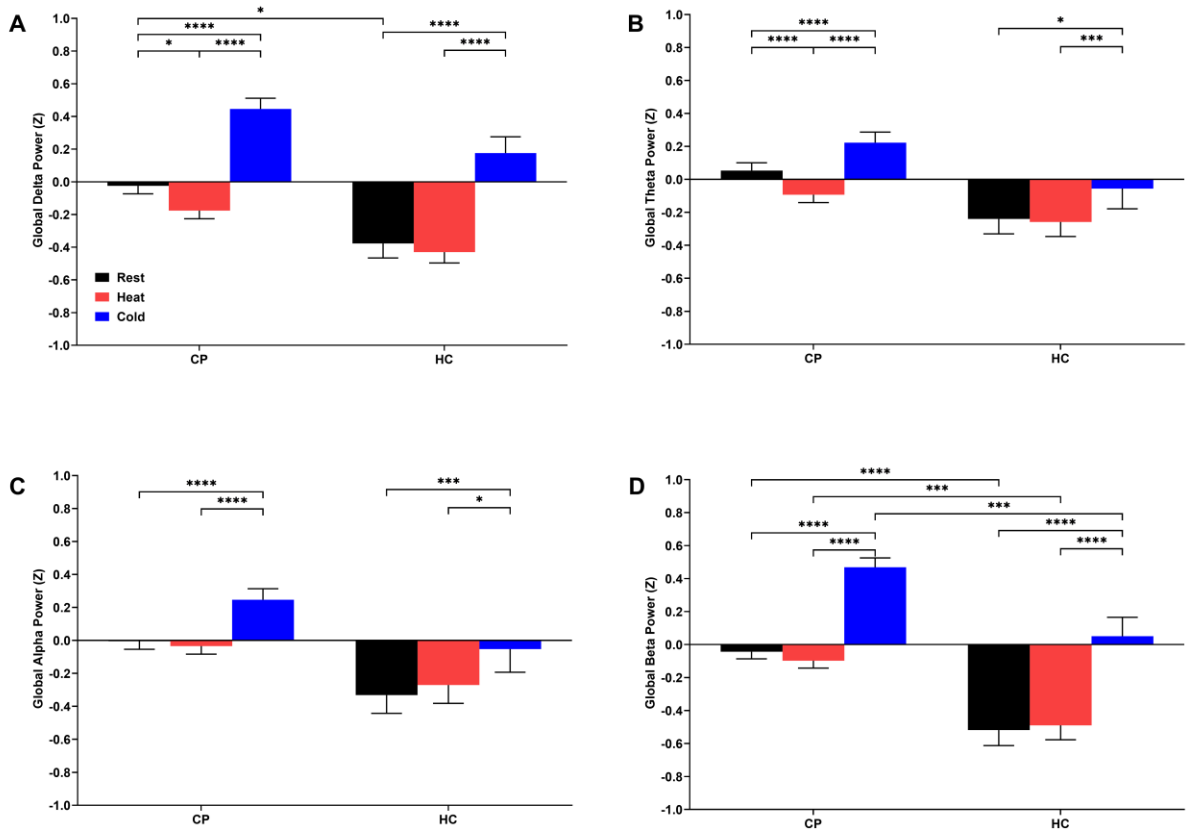

Figure 3-16. Changes in EEG global spectral power during thermal quantitative sensory testing assessments

Changes in EEG global delta (A), theta (B), alpha (C), and beta (D) spectral power during thermal quantitative sensory testing assessments of children and adolescents with chronic MSK pain (CP) and age-matched healthy controls (HC). Statistically significant differences related to thermal quantitative sensory testing condition identified through least squares means testing with Tukey post hoc pairwise comparisons are shown by *p<0.05, **p<0.01, ***p<0.005, ****p<0.001. Data are presented as Mean +/- standard error of the mean (SEM).

3.4.4.4 Changes in EEG global peak frequencies

Children and adolescents with chronic MSK pain showed global changes in peak oscillatory brain activity in response to the different thermal stimuli. Two-way ANOVAs on the GLMMs of global peak frequencies showed a main effect of thermal stimulus in the delta ($F_{2,331}$=11.84, p<0.0001), theta ($F_{2,331}$=7.54, p=0.0006), alpha ($F_{2,331}$=7.17, p=0.0009) and beta ($F_{2,331}$=18.16, p<0.0001) frequency bands (Figure 3-17). Post hoc Tukey testing revealed statistically significant decreases in global peak delta frequency during the CPT for CPs in comparison with resting measurements (p=0.0136) and the tonic heat condition (p=0.0073; Figure 3-17A). Significant decreases in global peak theta frequency were observed during the CPT relative rest (p=0.0086) and the tonic heat condition (p=0.0346; Figure 3-17C) in CPs. CPs showed significant increases in global peak alpha frequency during the tonic heat condition (p=0.0093; Figure 3-17C) relative to resting measurements. Statistically significant increases in global peak beta frequency were identified in CPs during the CPT in comparison with resting measurements (p<0.0001) and the tonic heat condition (p<0.0001; Figure 3-17D). Similar condition-related differences in global peak frequencies were not found in HCs across all frequency bands (p>0.05). In summary, while no differences were found in HCs, EEG assessment of CPs showed increased global peak alpha frequency during the tonic heat conditions, and decreased global peak delta and theta frequencies and increased global peak beta frequency during the CPT.

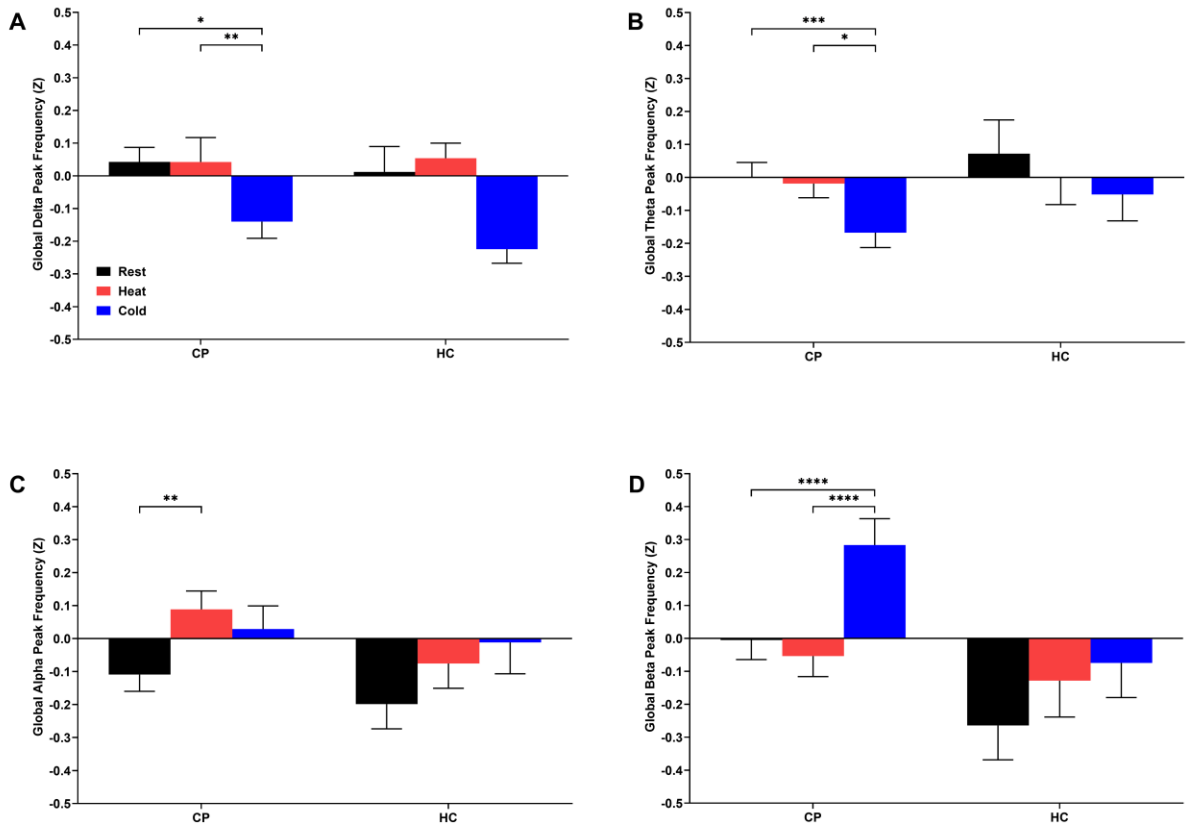

Figure 3-17. Changes in EEG global peak frequency during thermal quantitative sensory testing assessments

Changes in EEG global peak delta (A), theta (B), alpha (C), and beta (D) frequency during thermal quantitative sensory testing assessments of children and adolescents with chronic MSK pain (CP) and age-matched healthy controls (HC). Statistically significant differences related to thermal quantitative sensory testing condition identified through least squares means testing with Tukey post hoc pairwise comparisons are shown by *p<0.05, **p<0.01, ***p<0.005, ****p<0.001. Data are presented as Mean +/- standard error of the mean (SEM).

3.4.4.5 Changes in EEG global permutation entropy

Children and adolescents with chronic MSK pain showed global changes in permutation entropy in response to the different thermal stimuli. Two-way ANOVAs on the GLMMs of global permutation entropies showed a main effect of thermal stimulus in the delta ($F_{2,331}$=48.35, p<0.0001), theta ($F_{2,331}$=139.66, p<0.0001), alpha ($F_{2,331}$=131.33,p<0.0001) and beta ($F_{2,331}$=112.84, p<0.0001) frequency bands and a main effect of cohort in the delta ($F_{1,179}$=5.22, p=0.0235), theta ($F_{1,179}$=7.10, p=0.0084), and alpha ($F_{1,179}$=7.03, p=0.0088) bands (Figure 3-18). Post hoc testing revealed no significant cohort-related differences in global permutation entropy measured at rest and during tonic noxious thermal stimulations between CPs and HCs. Significant increases in global permutation entropy in the delta frequency band during the CPT (p<0.0001) and the tonic heat condition (p<0.05) relative to resting measurements were found in CPs and HCs (Figure 3-18A). However, CPs only showed increased global delta permutation entropy during the CPT (p=0.0006) relative to the tonic heat condition. Both CPs and their age-matched HCs showed increased global permutations entropy during the CPT across the theta (p<0.001; Figure 3-18B), alpha (p<0.001; Figure 3-18C) and beta (p<0.001; Figure 3-18D) frequency bands relative to resting measurements and the tonic heat conditions. A significant increase in global permutation in the theta frequency band during the CPT (p=0.0051) relative to the tonic heat condition was only found in CPs. In summary, while the CPT elicited significant increases in global permutation entropy across the frequency bands in both CPs and HCs, only CPs showed increased global delta and theta permutation entropy during the tonic heat thermal condition.

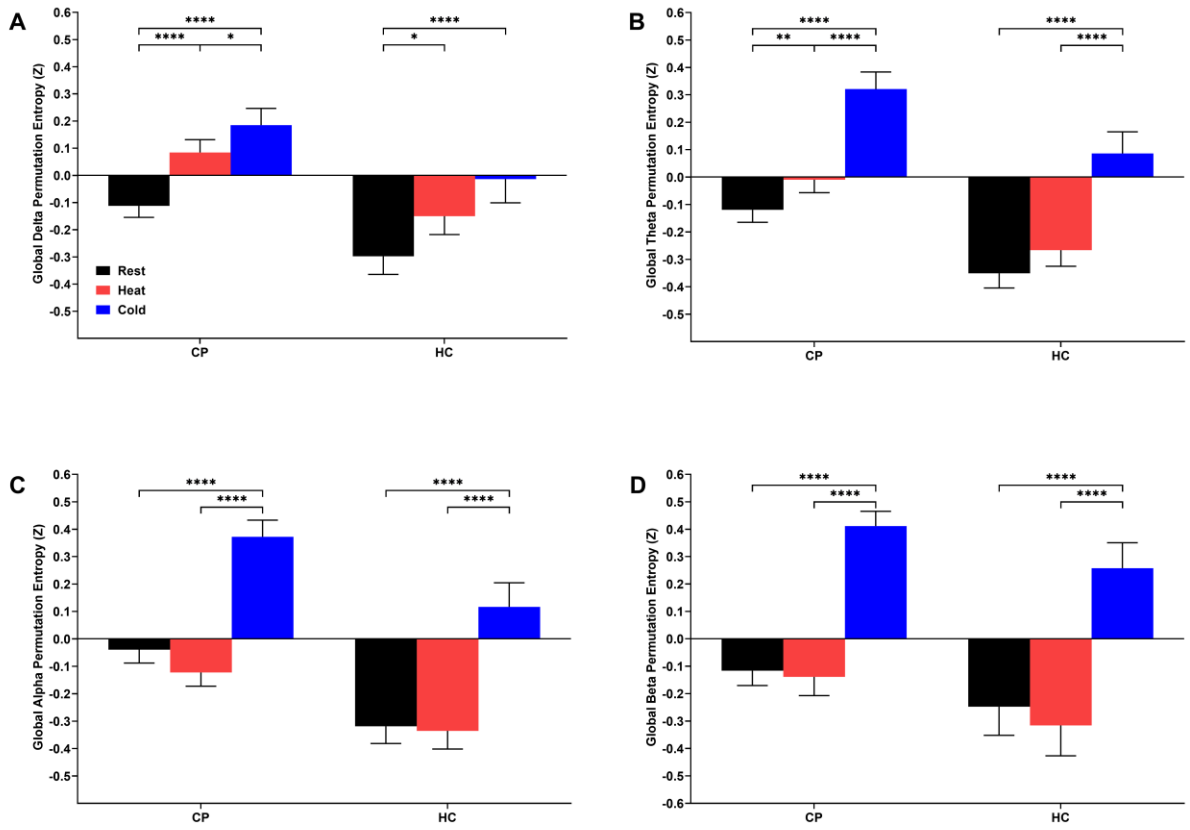

Figure 3-18. Changes in EEG global permutation entropy during thermal quantitative sensory testing assessments

Changes in EEG global delta (A), theta (B), alpha (C), and beta (D) permutation entropy during thermal quantitative sensory testing assessments of children and adolescents with chronic MSK pain (CP) and age-matched healthy controls (HC). Statistically significant differences related to thermal quantitative sensory testing condition identified through least squares means testing with Tukey post hoc pairwise comparisons are shown by *p<0.05, **p<0.01, ***p<0.005, ****p<0.001. Data are presented as Mean +/- standard error of the mean (SEM).

3.4.4.6 Changes in EEG functional connectivity

Children and adolescents with chronic MSK pain showed a different profile of changes in functional connectivity in response to the different thermal stimuli. The tonic heat condition increased the wPLI functional connectivity of CPs at the C3, T3 and T5 channels in the alpha frequency band (Figure 3-19A). Similar comparisons of network wPLI functional connectivity measured during the tonic heat condition relative to resting measurements in HCs showed increased network wPLI connectivity at the T6 channel in the delta frequency band, and at the T3 channel in the alpha frequency band (Figure 3-19B). CPs showed significant increase in network wPLI functional connectivity during the CPT globally across all channels except for C4, F8, O2, P3, and T3 in the delta frequency band. The CPT also significant increased theta network wPLI connectivity in the F4, F8, Fp1, T5 and T6 channels and increased alpha network wPLI connectivity at the F3, T5 and T6 channels. The tonic heat condition also increased the network wPLI connectivity of CPs at the frontal F3, F7, F8, Fp1, Fp2, Fz channels, as well at the P3, T4, T5 and T6 channels. Age-matched HCs showed significant increase in network wPLI functional connectivity during the CPT across the F7, F8, Fp1, Fp2, Fz, Pz, T5 and T6 channels in the delta frequency band, at the C3, T3 and T6 channels in the theta frequency band, and at the C3, O1, P3, and T5 channels in the beta frequency band.

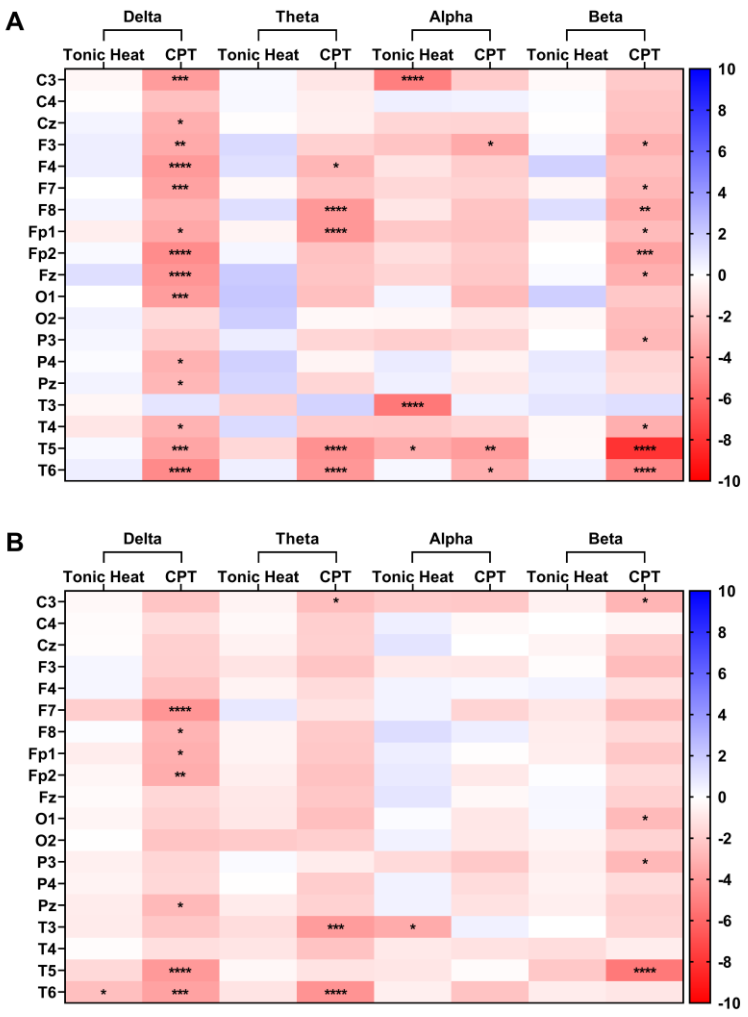

Figure 3-19. Changes in EEG network functional connectivity as measured by comparing the weighted phase-lag index (wPLI) at each channel during each thermal condition

Changes in EEG network functional connectivity as measured by comparing the weighted phase-lag index (wPLI) at each channel in the delta, theta, alpha, and beta frequency band during each thermal condition with resting measurements in (A) children and adolescents with chronic MSK pain and (B) age-matched healthy controls. Statistically significant differences related to thermal condition identified through least squares means testing with p-values adjusted for multiple comparisons with the Benjamini-Hochberg procedure with a FDR of 0.05 are shown by *p<0.05, **p<0.01, ***p<0.005, ****p<0.001. Data shown are t ratios, which represent the estimate difference between the average network functional connectivity measured at rest and during the thermal condition divided by the standard error. A negative t ratio represents an increase in network wPLI functional connectivity, while a positive t ratio represents a decrease in network wPLI functional connectivity.

When investigating the temporal precedence between two EEG signals, the tonic heat condition increased network dPLI functional connectivity of CPs at the F8 channel in the theta frequency band, but decreased network dPLI functional connectivity at the T3 channel in the alpha frequency band (Figure S4A). Similar comparisons of network dPLI functional connectivity measured during the tonic heat condition relative to resting measurements in HCs showed a decrease in network wPLI connectivity at the T5 channel in the delta frequency band (Figure S4B). CPs showed significant reduction in network dPLI functional connectivity during the CPT at the P3 channel in the theta frequency band, at the T5 and T6 channel in the alpha frequency band, and at the T5 channel in the beta frequency band. Age-matched HCs showed significant decrease in network dPLI functional connectivity during the CPT at the O1 and T5 channels in the delta frequency band, and at the occipital O1, O2, T5, and T6 channels in the alpha frequency band.

3.4.4.7 Changes in EEG node degree

When evaluating the node degree at each electrode, the tonic heat condition increased the node degree functional connectivity of CPs at the T3 channel in the theta frequency band, and at the C3 and T3 channels in the alpha frequency band (Figure S5A). Age-matched controls only showed increased node degree functional connectivity at the T3 channel in the alpha frequency band (Figure S5B). CPs showed significant increase in node degree functional connectivity during the CPT at the T5 channel in the beta frequency band. Similar comparisons of node degree functional connectivity measured during the CPT relative to resting measurements in HCs showed no significant differences across all channels in all frequency bands.

3.4.5 Discussion

In this study, children and adolescents with chronic MSK pain and age-matched healthy controls showed different EEG phenotypes while undergoing detailed thermal experimental pain modalities. At rest, CPs showed increased global delta and beta power and an altered developmental pattern of theta spectral power changes relative to age-matched HCs. Tonic heat stimulation elicited more significant changes in EEG spectral power, peak frequency, waveform permutation entropy and functional connectivity in CPs, but not HCs. Though CPs and HCs showed many parallel cortical activity changes during the CPT; only CPs showed changes in global peak frequencies during the cold stimulation.

CPs showed increased resting global delta and beta power which aligns with previous studies in adult patients with chronic neurogenic pain [44, 45]. Therefore, resting global delta and beta power may have potential as a useful EEG-derived biomarker for chronic pediatric MSK pain conditions. In addition, though age-correlated reductions in theta and delta power have been observed in previous studies of EEG spectral power changes in healthy pediatric cohorts [46, 47], this trend was only found in the theta power of CPs. This lack of a well-characterized EEG developmental pattern linked to gray matter tissue loss and synaptic pruning [48-50] in our HCs may be due to a diversity of neuroplasticity processes involved in the normal trajectory of brain maturation. However, the lack of EEG developmental pattern in our CPs may provide evidence for persistent changes in central sensitivity, a key feature of chronic pain [51]. Changes in microglial function and activity, with a well-established role in developmental synaptic pruning, elicited by the long-term release of stress hormones and immune mediators in chronic pain may underlie this EEG finding of altered brain development [52, 53]. This highlights the need for

effective detection and management of persistent pain in childhood and adolescence to intervene against and prevent long-lasting developmental consequences of chronic pain.

Although no diagnosis-related differences in thermal pain responses were found, tonic heat stimulation decreased global spectral powers across delta and theta frequency bands and increased global peak alpha frequency in CPs but not in HCs. Global spectral power and peak alpha frequency have been shown to be negatively- [54-59] and positively-correlated [60], respectively, with perceptions of tonic heat pain; thus, these observations suggest an increased thermal pain sensitivity in CPs. The CPT increased global spectral powers across all frequency bands in both CPs and age-matched HCs groups; however, only CPs showed decreased global peak delta and theta frequencies and increased global peak beta frequency during CPT. Taken together with evidence that peak frequency decelerations in the low frequency delta and theta bands and peak frequency accelerations in the high frequency beta and alpha bands are associated with reduced pain tolerance [61], these observations also suggest increased sensitivity to cold pain in CPs. These observed spectral power changes between CPs and HCs extends the findings of spectral power pattern differences in adult patients with different chronic pain presentations [12, 14, 62, 63].

CPs and HCs showed increased EEG global permutation entropy across the frequency bands during the CPT; however, only CPs showed increased global delta and theta permutation entropy during the tonic heat stimulations. Permutation entropy has been correlated with changes in levels of consciousness and depth of sedation, as the EEG loses its high frequency components and assumes a low frequency delta wave pattern due to anesthesia [4, 17]. It may be expected that pain processes would increase permutation entropy as ascending spinal pain fibers first pass through the brainstem reticular formation, where diffuse pain-associated increased wakefulness and alertness are generated [64]. The observation of EEG of CPs gaining high frequency

components during tonic heat exposure provides additional evidence of an increase sensitivity to tonic thermal pain. CPs also showed a different network functional connectivity profile in response to the thermal conditions, through wPLI, extending previous work in adult patients with chronic pain syndromes [16, 65]. CPs showed increases in network functional connectivity particularly in the beta bands of the bilateral temporal and frontal scalp channels during the CPT that were not seen in HCs. While it is difficult to draw conclusions about the underlying brain networks from EEG findings, this scalp distribution of beta network functional connectivity roughly overlies the dorsolateral prefrontal cortex (DLPFC), primary somatosensory cortex (S1) and anterior cingulate cortex (ACC), which is consistent with previous adult studies that have found altered resting functional connectivity in the PFC and the ACC [66, 67]. Pain is a complex, multi-dimensional experience that manifests as the integration of at least three dimensions: 1) sensory, which determines pain localization and intensity; 2) affective, which determines pain unpleasantness; and 3) cognitive, which determines how pain is expressed and responded to. The brain regions with observed increase in functional connectivity are implicated in sensory pain processing pathways as well as the circuits mediating the affective and cognitive aspects of the chronic pain experience [63, 68, 69]. As prefrontal regions mediate executive control functions which permit cognitive reappraisals of pain and pain-associated emotions [70, 71] and that stimulating the ACC may attenuate the emotional component of pain unpleasantness [72], dysregulations in the signalling within their inhibitory circuits may increase engagement of the subcortical limbic regions such as the amygdala that manifest maladaptive responses to pain stimuli [73]. Taken together with the increased S1 functional connectivity, these observed alterations in network functional connectivity support the hypothesis that chronic pediatric MSK pain is mediated and maintained by a dysfunctional reorganization in brain signalling patterns that shifts from the superficial brain

regions primarily encoding pain sensation to subcortical regions which encode pain emotionality [69, 74, 75]. In addition, diffuse suppressions of alpha network functional connectivity were found in response to tonic heat stimulations in CPs, but not HCs. These observed changes in permutation entropy and functional connectivity EEG measures suggests that dynamic perturbations in the flow of information in the brain connectome underlie the sensory, affective, and cognitive pain experiences of youth with chronic MSK pain undergoing the thermal pain modalities.

The observed cortical activity changes in response to tonic heat and cold stimuli, despite no differences in the thermal pain assessment, suggests that EEG is a low-cost, clinical-accessible, and non-invasive brain imaging tool that is more sensitive to the detection and interpretation of the pain mechanisms underlying pediatric chronic MSK pain than the thermal pain modalities. EEG may enhance the clinical pain assessment of children and adolescents with suspected or diagnosed chronic MSK pain conditions, particularly those who are non-verbal or developmentally unable to articulate their pain experience. This cross-sectional study complementing EEG measurements during thermal pain assessments of youth with chronic MSK pain should be followed-up with a prospective cohort study to identify if pharmacological or behavioural pain management influences or normalizes the perturbed brain signalling patterns observed in this study. In addition, this study identified that tonic heat and cold pain stimuli conditions produced divergent EEG power spectra, waveform and network functional connectivity changes, suggesting that EEG may be sensitive in interrogating differences in the pain experience that are elicited by distinct experimental noxious modalities.

There were several limitations in our study. First, cohort composition differences may have introduced confounders into our cross-sectional study, as the pain experience is modified by a spectrum of biopsychosocial factors. However, exploratory GLMMs showed that sex and ethnicity

were statistically insignificant fixed factors ($p>0.05$; data not shown). Second, the heterogenous composition of our CPs, with representation from a diversity of pediatric pain diagnoses, locations, severities, and neuropathic-like characteristics, may have reduced our likelihood to detect differences between the CPs and HCs. However, our sample's heterogeneity promotes the external validity of our findings to clinicians caring for children and adolescents with a diversity of chronic MSK pain clinical presentations. Third, our EEG findings could only infer the specific neurological substrates that may be responsible for the observed EEG cortical activity patterns. Future application of low resolution brain electromagnetic tomography (LORETA) could estimate the source localization of brain electrical activity underlying the observed EEG scalp recordings during the thermal conditions [76]. Fourth, the different baseline conditions may have influenced the significance of our results. However, this difference was statistically controlled. A notable strength of this study is its large sample size of children and adolescents with chronic MSK pain and HCs. Though it was not possible to perform a priori sample size calculation due to the paucity of effect sizes and variances reported in the EEG literature [77], this study's statistical power qualitatively exceeds that of most previously published EEG studies with sample sizes typically between 10-20 participants per cohort.

In this study, children and adolescents with chronic MSK pain and age-matched healthy controls showed differences in resting EEG features and differential changes in EEG activity while undergoing thermal experimental pain modalities. Continuous EEG enhances the ability of thermal modalities to reveal the underlying pain mechanisms and detect changes in pain sensitivity in children and adolescents with chronic MSK pain.

3.4.6 Acknowledgements

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3.4.8 Supplementary material

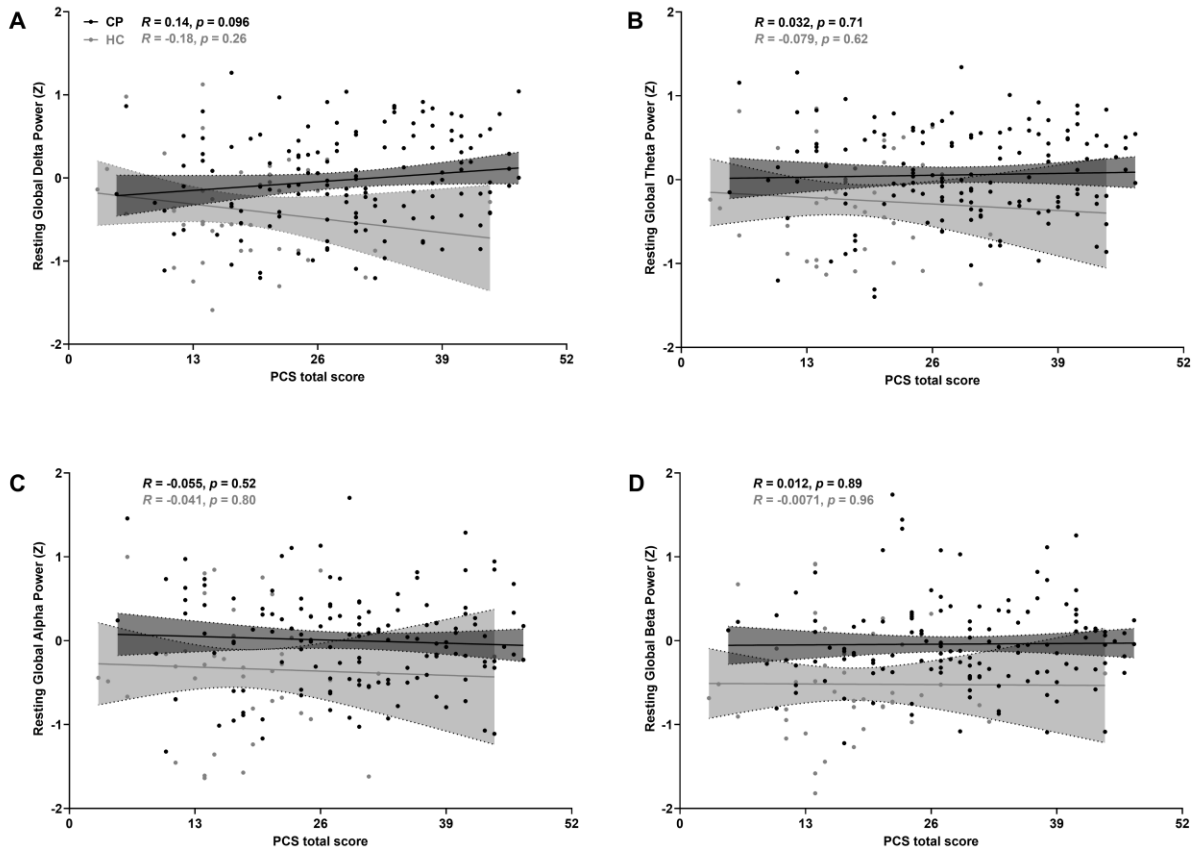

Figure S1. Associations between the total score of the pain catastrophizing scale (PCS) and resting EEG global spectral power at rest

Associations between the total score of the pain catastrophizing scale (PCS) and resting EEG global delta (A), theta (B), alpha (C), and beta (D) spectral power at rest of children and adolescents with chronic MSK pain (CP) and age-matched healthy controls (HC). Pearson's rank correlation analysis R values and p-values are shown.

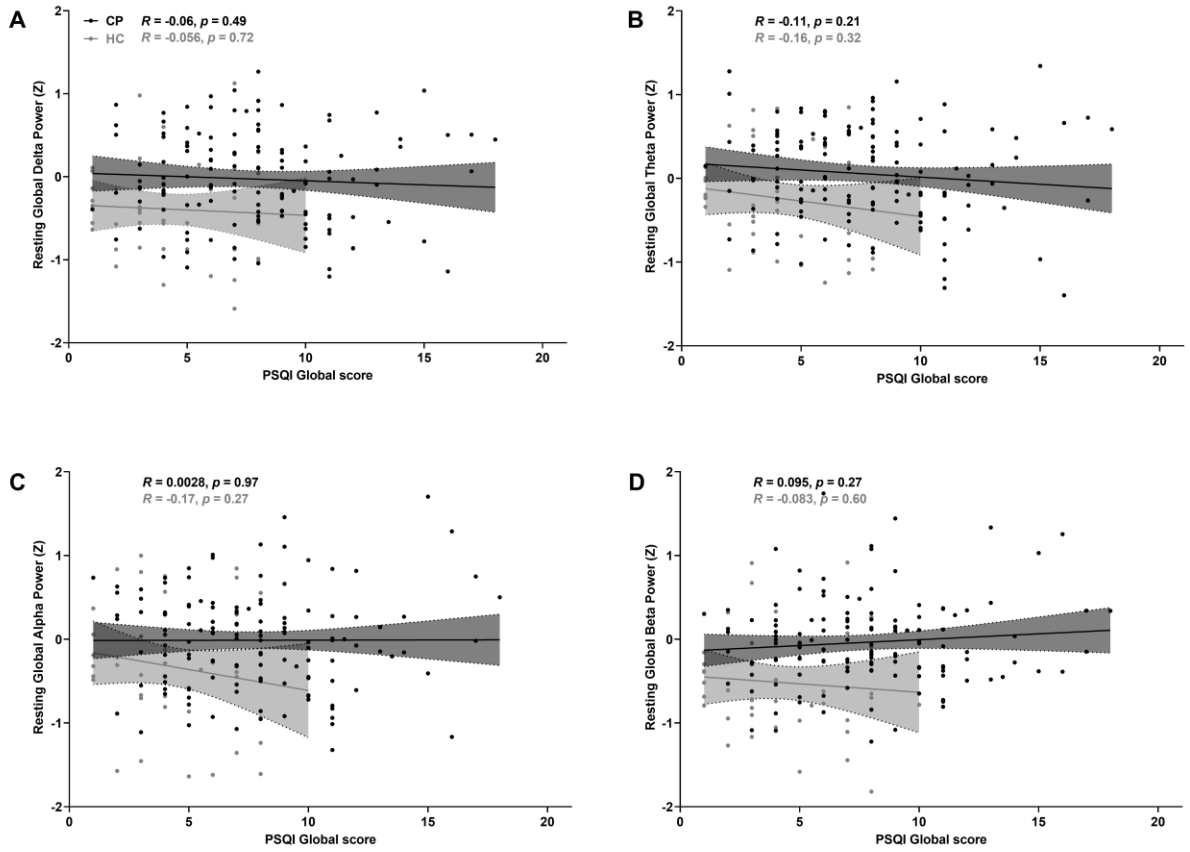

Figure S2. Associations between the global score of the Pittsburgh sleep quality index (PSQI) and resting EEG global spectral power at rest

Associations between the global score of the Pittsburgh sleep quality index (PSQI) and resting EEG global delta (A), theta (B), alpha (C), and beta (D) spectral power at rest of children and adolescents with chronic MSK pain (CP) and age-matched healthy controls (HC). Pearson's rank correlation analysis R values and p-values are shown.

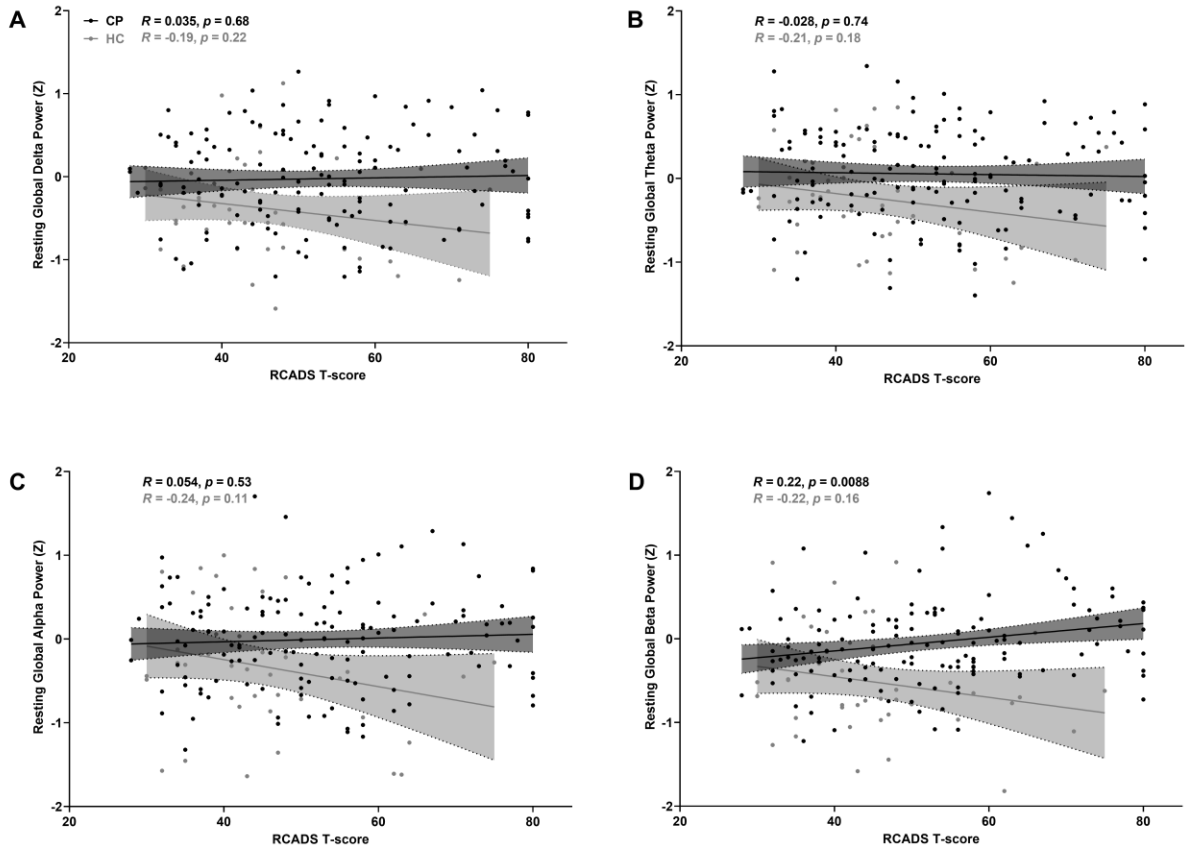

Figure S3. Associations between the T-score of the revised child anxiety and depression scale (RCADS) and resting EEG global spectral power at rest

Associations between the T-score of the revised child anxiety and depression scale (RCADS) and resting EEG global delta (A), theta (B), alpha (C), and beta (D) spectral power at rest of children and adolescents with chronic MSK pain (CP) and age-matched healthy controls (HC). Pearson's rank correlation analysis R values and p-values are shown.

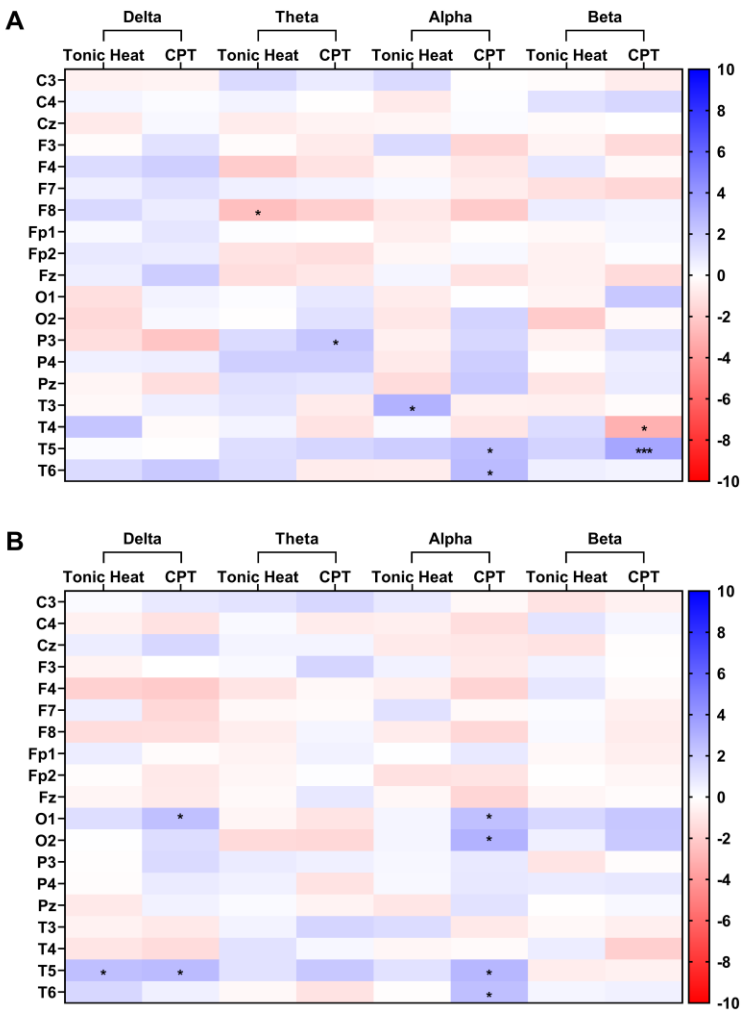

Figure S4. Changes in EEG network functional connectivity as measured by comparing the directed phase-lag index (dPLI) at each channel during each thermal condition

Changes in EEG network functional connectivity as measured by comparing the directed phase-lag index (dPLI) at each channel in the delta, theta, alpha, and beta frequency band during each thermal condition with resting measurements in (A) children and adolescents with chronic MSK pain and (B) age-matched healthy controls. Statistically significant differences related to thermal condition identified through least squares means testing with p-values adjusted for multiple comparisons with the Benjamini-Hochberg procedure with a FDR of 0.05 are shown by *p<0.05, **p<0.01, ***p<0.005, ****p<0.001. Data shown are t ratios, which represent the estimate difference between the average network functional connectivity measured at rest and during the thermal condition divided by the standard error. A negative t ratio represents an increase in network dPLI functional connectivity, while a positive t ratio represents a decrease in network dPLI functional connectivity.

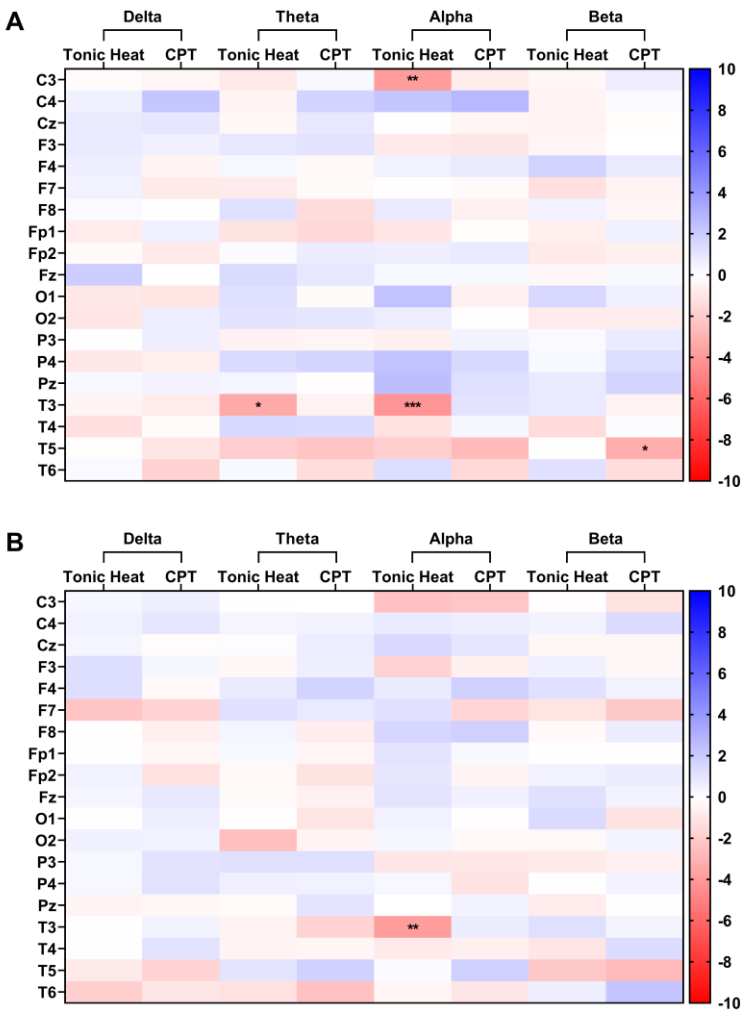

Figure S5. Changes in EEG network functional connectivity as measured by comparing the node degree at each channel during each thermal condition

Changes in EEG network functional connectivity as measured by comparing the node degree at each channel in the delta, theta, alpha, and beta frequency band during each thermal condition with resting measurements in (A) children and adolescents with chronic MSK pain and (B) age-matched healthy controls. Statistically significant differences related to thermal condition identified through least squares means testing with p-values adjusted for multiple comparisons with the Benjamini-Hochberg procedure with a FDR of 0.05 are shown by *p<0.05, **p<0.01, ***p<0.005, ****p<0.001. Data shown are t ratios, which represent the estimate difference between the average network functional connectivity measured at rest and during the thermal condition divided by the standard error. A negative t ratio represents an increase in network node degree functional connectivity, while a positive t ratio represents a decrease in network node degree functional connectivity.

CHAPTER 4 GENERAL DISCUSSION

Due to the heterogeneity within chronic pain conditions and that different chronic pain conditions may share similar characteristics [204], researchers and clinicians have turned to identifying subgroups with distinct psychosocial and psychophysical profiles in different samples of patients with chronic pain. Subgroups of pediatric patients with peripheral neuropathic pain [135], recurrent or functional abdominal pain [152, 206, 208] and other chronic pain conditions [205, 207] have been successfully identified using a combination of psychosocial factors and/or QST. However, most of these studies strictly investigated pain qualities, sleep, and psychosocial characteristics in their cluster analysis and there is limited data evaluating subgroups based on the somatosensory and pain modulatory profiles of pediatric chronic pain patients. To our current knowledge, only one other study phenotyped a cohort of pediatric patients, but with peripheral neuropathic pain, based on their pain descriptors, somatosensory profile, CPM and child-parent reported disability [135]. Moreover, there is also limited data in larger pediatric samples investigating neuroimaging findings in relation to pain. The overall objective of this thesis is to better understand chronic pain in youth to improve the clinical assessment of pain processes in pediatric patients with chronic MSK pain. Results from all projects of this thesis highlight that pediatric patients with chronic pain have their own way of integrating and experiencing pain when compared to healthy controls, and that questionnaires, quantitative sensory testing, and electroencephalography can be implemented in clinical practice to gain as much information on their full pain experience and narrative and be considered in clinical decision-making in regards to pain management.

4.1 Sensitivity and specificity of the clinical assessment conducted

Clinical tools for pain assessment, such as pain scales, self-report questionnaires and QST are a result of rigorous research to identify and validate key behaviours that are indicative of pain, psychosocial domains, and somatosensory function. Like all scientifically robust measures, these tools undergo several steps of validation to ensure that they produce consistent results when repeated over time (reliability) and they measure what is intended to measure (validity) to have a critical impact on clinical trials. Recommended outcome domains and specific measures for chronic pain trials have been published by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) and Pediatric IMMPACT (PedIMMPACT) [209, 210]. However, there is limited knowledge on the adequacy of the domains and specific measures for specific contexts of use which may be variable due to the multiple elements contributing to chronic pain, and the different chronic pain conditions.

4.1.1 Self-reported questionnaires

The work in this thesis included multiple self-report questionnaires recommended by the PedIMMPACT for chronic pain trials [210], such as the Functional Disability Inventory (FDI) [211-213] and Revised Child Anxiety and Depression (RCADS) [93, 214]. However, the work in this thesis also included self-report questionnaires recommended by the PedIMMPACT for acute pain trials, such as the Adolescent Pediatric Pain Tool (APPT) [215, 216], or not recommended, such as the Pain Catastrophizing Scale (PCS) [80, 96], the *Douleur Neuropathique 4* questionnaire (DN4) [217, 218] and the Pittsburgh Sleep Quality Index (PSQI) [102, 104, 108, 109]. Despite not recommended by the PedIMMPACT, these measures showed good reliability and validity in pediatric chronic pain populations and are important for decision-making pertaining to pain management [80, 109, 215, 217]. With scientific knowledge on pediatric chronic pain evolving

with time, the core outcome set for pediatric chronic pain clinical trials have been updated [219], but questionnaire recommendations by the PedIMMPACT published over 10 years ago also need to be re-evaluated in order to not hinder comparative research and further improving the assessment of pain in children and adolescents and ultimately pain management. The two psychosocial profiles (high somatic symptoms cluster vs low somatic symptoms from the pain-sensitive and adaptive pain cluster) identified in the first article of this thesis was further subdivided into three profiles in the third article of this thesis when strictly investigating the psychosocial factors. Previous cluster analyses based on the psychological and behavioural characteristics of pediatric patients with chronic pain have also identified three subgroups qualitatively similar to those observed in the third article of this thesis: one with high levels of distress and disability, another with relatively low scores of distress and disability, and a third group that scored in between the other two on these measures [152, 205-208]. Despite the use of some different measures in those previous studies in comparison to the self-reported measures included in the studies of this thesis, the classification system focusing on pain qualities and psychosocial factors can be evaluated for application to multiple pain conditions other than chronic MSK pain. The identification of specific psychosocial profiles based on self-reported questionnaires narrows the gap in the literature to identify patient-specific factors associated with favorable responsiveness to specific psychosocial treatments. A recent study conducted by Walker et al. (2021) observed that youth with functional abdominal pain grouped into a high pain dysfunctional profile displayed greater reduction in gastrointestinal symptoms and abdominal pain youth than youth grouped into the high pain adaptive or low pain adaptive profile after cognitive behavioral therapy [220]. Ultimately, matching psychosocial profiles like those observed in the work of this thesis to targeted interventions may improve patient outcomes.

4.1.2 Static quantitative sensory testing

The static QST measures included in the work of this thesis were adapted from the standardized protocol from the DFNS [50, 110, 158] and the QST guidelines developed by an initiative of the Quebec Pain Research Network (QPRN) which includes six independent laboratories with expertise in QST and one pain clinic across four academic institutions (McGill University, Université Laval, Université de Montréal and Université de Sherbrooke). The specific protocol of mechanical and thermal QST in the third study of the work of this thesis consisted of seven parameters over two tests areas. However, it is unknown if the addition of other static QST measures in the somatosensory phenotyping of patients would lead to different results. The thermal QSTs were conducted after the mechanical QSTs in the work of this thesis, unlike the protocol established by the DFNS. Cold detection and pain thresholds were not assessed in the work of this thesis, although there are neurons in the dorsal horn that receives input from C fibers that are activated distinctively by intense cold. Moreover, the number of paradoxical heat sensations, usually assessed through a thermal sensory limen procedure (bidirectional heating or cooling stimulation alternately applied between the cold and warm detection thresholds that patients), was not measured. The reversal of testing order and exclusion of some thermal QST measures was due to the thermal measures being assessed simultaneously during the CPM paradigm which was conducted after the mechanical sensory assessment. The reversal of testing order may have been beneficial in our results as a study investigating the test order of QST in healthy adult subjects observed mechanical hyperalgesia following thermal testing [221]. Other mechanical QSTs such as mechanical pain threshold and mechanical pain sensitivity were not measured. However, these specific tests require a set of weighted pinprick mechanical stimulators which was not available for our study. Nevertheless, the somatosensory phenotyping of youth may have been different if

mechanical pain sensitivity was included since it is one of the two parameters that explain a large variance between the phenotypes observed in adults [222]. The somatosensory profiles of the patients in the third article of this thesis, were based on the closest matching profiles reported in adults with neuropathic pain who underwent a DFNS QST protocol consisting of thirteen parameters [222, 223]. The modifications to the QST protocol of the DFNS and QPRN were done for the assessment to fit within the time restraints of clinical routines. Vollert et al. (2017) observed that a simplified deterministic approach, using only two QST parameters (warm detection threshold and mechanical pain sensitivity), showed low sensitivity due to the dependency on a combination of the phenotype of interest and the clinical entity under study [222, 223]. Yet, studies are turning to implement more routine clinical screening and profiling of pain mechanisms in chronic pain patients by developing a simple to use and clinical applicable, bedside tool-kits [134, 224, 225]. Using machine learning techniques, Sachau et al. (2022) observed that only three easy-to-use sensory tests were needed to identify sensitization in a sample of adult patients with osteoarthritis or chronic knee pain after total knee replacement. In the pediatric chronic pain population, the utility of an office adaptation of laboratory QST was evaluated to be complementary to the standard biopsychosocial assessment of pediatric chronic pain [134]. Other studies are also turning to implement a qualitative component to QST to add valuable information contributing to the detection of sensory abnormalities [226]. Hence, future studies applying the same static protocol from the work of the thesis, or a modified protocol are warranted to evaluate the applicability of bedside sensory testing tools in a clinical context, and the reproducibility of our results.

Although healthy controls were included in the work of this thesis, the small sample size of age-matched controls in comparison to the patient samples is a limitation, especially as the QST

z-scores for the control area for patients with chronic MSK pain in the third article of this thesis was calculated based on between-cohort control measures at the control area. In epidemiological studies, having more than one control for every case increases the power of the study, with 2 controls for every case being optimal [227]. Age-matched controls only represented 9-23% of the whole sample in the last three articles of the thesis. Moreover, healthy volunteers in QST-based studies are not often systematically investigated before inclusion. Despite the age-matched controls in the work of this thesis underwent a screening process before inclusion in the study, the low sample size of controls may have led to individuals with unrecognized medical conditions, but who consider themselves "healthy" to skew the QST z-scores of the patients. QST z-scores of the control area of patients depends on the mean and standard deviation of QST scores of the control area of the age-matched controls which can be affected by extreme outliers. Therefore, inclusion of more healthy controls may shift certain patients from one somatosensory profile to another in the third article of this thesis or may reveal that some patients display normative QST values. A second-level of screening has been suggested [228] to excluded participants in unknown neuropathies using warm, cold, mechanical, and vibration detection threshold, especially as 5% of healthy controls may present with abnormal QST values per parameter for statistical reasons. Moreover, conducting their four suggested QST subtests, the expected probability of assessing a value outside the 95% confidence interval for at least one of the four tests increases to $1 - 0.95^4 =$ 19%. However, if values outside the reference interval are not tolerated at all, an artificial reduction of the variance of the QST results would occur. Therefore, inclusion of all QST results of large- and small-fiber functions are needed to determine whether the "healthy" participant should be excluded. Future studies investigating the effect of recommendations on considering who is

healthy on the generation of a valid reference data is warranted to improve the quality of future studies including QST to identify somatosensory profiles in patients.

4.1.3 Dynamic quantitative sensory testing

The dynamic QST measures, conditioned pain modulation and temporal summation of pain, included in the work of the thesis were chosen based on the study by Tousignant-Laflamme et al. [130] who developed a relatively simple experimental design to measure both excitatory and inhibitory pain mechanisms. The specific dynamic QST assessment in the first three studies of this thesis was chosen to fit within the time constraints of clinical routines. However, although recommendations for CPM have been established [229], a review by Hwang et al. highlighted the lack of consensus in CPM assessment in pediatrics due to the various approaches used for the test stimulus, conditioning stimulus, and the calculation of CPM efficacy [159]. Multiple modalities have been used such as pressure, heat, cold and electrical stimulation and different combinations of test stimulus versus conditioning stimulus have been studied as well [38]. The most used test stimuli are pressure pain threshold and contact heat, while the most used conditioning test stimulus is the cold pressor task [230]. However, within these modalities there are still differences such as using heat pain threshold or tonic heat pain as the test stimulus, or the temperature at which the cold bath was set or the duration the hand or arm was immersed in the cold bath. Temporal summation can also be assessed by applying a series of heat-pain stimuli of the same temperature (e.g., 47°C) or a series of mechanical-pain stimuli of the same weight [50, 152]. It is unknown whether the use of another experimental pain procedure would have produced different results in the work of this thesis. A study conducted by Nahman-Averbuch et al. (2013) investigated healthy adult subjects undergoing six CPM paradigms differing by test stimuli (heat pain threshold, pressure pain threshold, heat pain, pressure pain, thermal and mechanical temporal summation). To their

surprise, no correlations were observed between the various CPM responses [231]. In the third article of this thesis, a mechanical modality of temporal summation was investigated through mechanical pain summation and determined with the wind-up ratio (WUR). However, to our surprise, WUR was not significantly different between the pain modulatory profiles. WUR is calculated as the mean pain rating of repetitive stimuli divided by the mean pain rating of a single stimuli, while the thermal temporal summation of pain was defined as an increase of two points over ten (or twenty points over one hundred) in pain intensity during the last 60 seconds of a tonic noxious heat stimulation that lasted two minutes. Therefore, since only thermal modalities was used for the CPM paradigm, the pain modulatory profiles identified in the second and third article of this thesis may only suggest one multifaceted trait of each participant's capacity of pain modulation. Although the main strength of the current experimental CPM procedure used in the work of the thesis allows to elicit and measure multiple pain modulation responses in a short period of time, adding another CPM paradigm (e.g. a mechanical test stimuli) and TSP paradigm in future studies is recommended [229] and may further strengthen or validate our findings.

The discriminative power of CPM paradigm conducted in the studies presented in this thesis was previously evaluated in a cohort of adults with fibromyalgia and healthy controls [131]. They observed that the CPM procedure had good specificity (78.9%) but low sensitivity (45.7%). Results in the second article of this thesis did not show any difference in CPM efficiency between patients (n=608) and controls (n=60), but results from the third article of this thesis showed a significant difference, but of small effect size (cohen's d = 0.27) between patients (n=302) and controls (n=80). These results highlight that investigating pain modulatory responses should not be discriminative, but informative. No reference values for CPM efficiency have been established in the pediatric population due to the heterogeneity observed in the healthy population and the

various CPM paradigms conducted. A hypothesis would be significant neural development particularly in brain regions associated with cognitive-affective processing which occurs as children age which can shape the functional integrity of the descending inhibitory systems [232]. A previous study in young children observed that prematurity and exposure to numerous painful interventions after birth lead to alterations in the endogenous pain modulatory mechanisms [69]. However, no significant correlation was observed between the pain modulatory profiles identified in the second and third articles of the thesis and the participants' age. Additional studies investigating the role of development and pain modulatory systems is therefore warranted.

4.1.4 Electroencephalography

In the last study of this thesis, a dry-EEG headset was used and suggested as a non-invasive, safe, and reliable measurement of electrical patterns at the surface of the scalp, which reflect cortical activity related to pain. Previous studies using EEG have also shown that nociception is encoded differently between adults and children [233]. Therefore, EEG may be used to objectively reveal the underlying pain mechanisms and detect changes in pain sensitivity in non-verbal children and adolescents with chronic pain. In the fourth study of this thesis, at rest, only significant differences in spectral power, more specifically global beta and delta frequencies were observed between youth with chronic MSK pain and age-matched controls. Studies in adults employing EEG to investigate differences between patients with neurogenic pain (i.e., pain due to dysfunction of the peripheral or central nervous system) and healthy controls mainly revealed an increase in theta and beta frequency ranges at rest [234, 235]. These EEG differences in the adult studies were mainly located in the insular cortex and anterior cingulate cortex. Although only global spectral power was investigated in the fourth study of this thesis and the location of the spectral power changes were not investigated, it may be hypothesized that the overactivation of theta and beta

frequency range are associated with the overaction of affective-emotional and cognitive-evaluative systems characteristic of youth with chronic pain.

Previous studies have demonstrated that functional magnetic resonance imaging, which investigates functional and structural brain activity through blood flow, can detect brain activity changes elicited by acute painful stimuli in pediatric populations [236-239]. A study by Simons et al. (2014) revealed that youth with complex regional pain syndromes (CRPS) displayed greater functional connectivity compared to controls for the prefrontal cortex, cingulate cortex, thamalus, amygdala and somatosensory cortex [236]. In the fourth study of this thesis, we primarily observed changes in functional connectivity primarily in youth with chronic MSK pain during a cold pressor task that was not seen in controls. While it is not possible to draw conclusions on the underlying networks due to the low spatial resolution of EEG data, the distribution of functional connectivity changes overlapped with brain areas involved in all three pain perception systems (sensory, affective, and cognitive) as observed by Simons et al. (2014). Therefore, our findings highlight that youth with chronic pain integrate and experience pain differently than controls and suggest that pediatric chronic pain is mediated and maintained by a dysfunctional reorganization in brain signalling patterns.

Whether there are distinct subgroups of changes in brain activity or functional connectivity within the pediatric chronic pain population is still unknown. The study by Stern et al. (2006), who observed overactivation of theta and beta frequency ranges at rest in adult patients with neurogenic pain, also observed differential patterns between patients reporting trigeminal pain (n=5) and those reporting lower limb pain (n=5), such that patients with trigeminal pain displayed more homogeneous overactivation, while patients with lower limb pain displayed more diffuse patterns [235]. The effect of primary location of pain on the EEG patterns observed in the patients in the

fourth article of this thesis was not investigated. However, as observed in the large sample size of the third article of this thesis where no correlation was observed between the primary location of pain and the patients' psychosocial, somatosensory or pain modulatory profile, we hypothesize that no correlation may be observed between the primary location of pain and EEG patterns of youth with chronic pain. On another hand, with the differential changes in EEG frequency bands and functional connectivity observed in the patients of the fourth article of this thesis which may reflect dysfunctional reorganization in brain signalling patterns, we hypothesize that EEG patterns may correlate with the psychosocial, somatosensory or pain modulatory profiles identified in the first three studies of this thesis. For example, we may hypothesize that patients grouped in the high somatic symptoms profile in the first and third study of this thesis may display more increased global delta and beta power at rest than patients grouped in the adaptive pain or high pain dysfunctional psychosocial subgroups. We may also hypothesize that patients that do not display normative QST values or functional central processing may display more increased global delta and beta power at rest, and greater functional connectivity during experimental pain. Therefore, future analysis combining our phenotyping results with the EEG patterns observed is warranted to better understand our pediatric chronic pain population.

4.2 Location of study site

The patients recruited from the studies included in the work of this thesis included patients referred from the orthopedic outpatient clinics of the Shriners Hospitals for Children - Canada and from the Edwards Family Interdisciplinary Center for Complex Pain of the Montreal Children's Hospital. The location of the assessment of chronic pain was strategic to accelerate patient recruitment for the projects of this thesis. However, the location of recruitment is important to be considered in the interpretation of our findings, due to the difference in the progression of chronic

pain of patients seeking treatment for their pain at center for complex pain instead at an outpatient clinic. In the second article of this thesis, the average pain intensity prior to the assessment was statistically significantly higher in patients recruited from the center for complex pain when compared to patients recruited from the orthopedic outpatient clinics. This observation may be relevant to be considered, as the presence, duration and/or intensity of pain during the assessment may have influenced the patients' responses to the questionnaires, QST and EEG recordings. For example, a study investigating the prediction of pain scores of adults during thermal noxious stimulations using electroencephalography frequency bands observed an accuracy of 89.45% for a 10-way classification (i.e., 1-10 pain score) [241]. The fourth study of this thesis demonstrated that youth with chronic pain showed increased global delta and beta power at rest relative to age-matched healthy controls. However, it is unknown if there were distinct EEG patterns within the cohort of youth with chronic pain whether they were experiencing none, mild (i.e., 1-3/10), moderate (i.e., 4-6/10), or severe (i.e., 7-10/10) pain prior to the assessment. Chronic pain clinical trials usually require a minimum baseline pain of ≥4 on a 0-10 numerical rating scale (or its equivalent) for the recruitment of patients with chronic pain (i.e., for longer than 3 months) [242]. However, to our current knowledge, no set minimum baseline pain intensity is recommended for cross-sectional studies on chronic pain. A minimum baseline pain intensity ≥4 is generally recommended to limit the "floor effect" of participants not having enough pain for group differences in improvement to be detected [242], but a reduction of two points (on ten) or a reduction of 30% represents a clinically important difference [243]. Results from the first and third study of this thesis showed that patients reporting lower average, worst or best pain intensity the past month prior to the assessment were mainly grouped in the "adaptive" psychosocial cluster. However, our results also highlight that although this subgroup of patients may not display

significant improvement in response to psychological therapies, patients profiled in an "adaptive" psychosocial cluster could be further evaluated, through QST alongside neuroimaging, to determine which underlying mechanisms may be targeted for pain management.

Studies on chronic pain typically require a minimum pain duration of three months, which is consistent with the existing definition from the IASP [18, 82]. In the projects included in this thesis, no significant differences were observed in the duration of pain between the subgroups or profiles identified. However, only 6.6-13.3% of the patient cohorts in the articles presented in this thesis reported their duration of pain between three to six months. The difference is group sizes may explain the lack of significant differences between patients with various duration of pain. Therefore, it is unknown whether recruiting patients with a minimum pain duration of six months would produce different results, especially when there may be an appreciable percentage of patients that may experience pain resolution before six months due to the natural history of the pathological condition of the patient [242]. Replication of the analysis with a larger and diverse sample of patients with various duration of pain or using a continuous measure to report the duration of pain in the analysis of future studies is warranted.

4.3 Medical history of participants

We observed in the third project of this thesis that younger patients were grouped in the "adaptive" psychosocial cluster, similarly seen in previous studies investigating psychosocial subgroups of pediatric patients with chronic pain [152, 208]. This result highlights the developmental differences in pediatric patients [15, 51] which was not fully discussed in the article. It has been shown that the perception of pain in children and adolescents follow the Piagetian stages and findings on their understanding of illness [15]. It may be hypothesized that the developmental differences in pain perception may explain why older youth are clustered in the

"high pain dysfunctional" or "high somatic symptoms" subgroup. Despite our findings, these developmental differences found in these subgroups need to be taken into account for interventions to improve patient outcomes [16].

The work of this thesis included primarily patients with chronic musculoskeletal pain that was primary or secondary in nature. However, the pathology of the patients is only reported in the first article presented in this thesis, which included patients diagnosed with scoliosis, disc protrusion, mechanical back pain, spondylolysis/spondylolisthesis, etc. The other three articles presented in this thesis only reported the primary location of pain of the patients, but included a diversity of diagnosis such as scoliosis, patellofemoral pain syndrome, chronic widespread pain, etc. Building on prior work identifying distinct informative subgroups or phenotypic profiles of adult patients with chronic overlapping pain conditions [244-247], our findings highlight that if anatomically classified pediatric pain disorders were classified using biopsychosocial criteria, pediatric pain management should also be tailored to address these underlying biopsychosocial mechanisms. The primary location of the pain of the patients and the presence and location of secondary pain sites is important to consider in relation to the psychosocial profiles of the patients. For example, in the FDI questionnaires, there are specific questions pertaining to any physical trouble or difficulty walking up stairs and walking or running the length of a football field. Therefore, patients reporting pain primarily in their lower limbs may report higher scores for functional disability than patients reporting pain primarily in their upper limbs. In the first study of this thesis, a significant correlation was observed between the clusters identified and the presence of radiating back pain down the patients' legs, such that a high proportion of patients in the high somatic symptoms cluster also reported radiating pain than patients in the pain sensitive or adaptive pain cluster. However, in the third article of this thesis, no association was observed

between the psychosocial profiles and the primary location of pain, the presence of secondary pain sites or radiating pain. The primary location of the pain of the patients and the presence and location of secondary pain sites is also important to consider in relation to the psychophysical profiles of the patients. Patients in all studies in this thesis included some patients with chronic widespread pain or persistent pain in upper limbs leading to pain in their forearms which was used as the "control" site for the mechanical QST and the location for stimulation during the CPM paradigms. QST z-scores for patients with chronic musculoskeletal pain in the third article of this thesis was calculated as the average z-score for the QST parameters of the control and affected area, which were based on between-cohort control measures and within-cohort control measures at the control area, respectively. Although this gives sensitive within-patient and between-cohort comparisons for clinical testing, different somatosensory profiles may arise if strictly pain-free control areas were used, which may be challenging in patients with chronic widespread pain. Further establishment for reference values for QST for body sites relevant to musculoskeletal pain is needed in the literature. There is still a gap in the literature concerning investigating QST in healthy children and adolescents in body sites, other than the face, hand and foot [50]. A study investigating QST profiles on the back in healthy adult subjects observed lower sensitivity on the upper back than the hand, and higher sensitivity in the lower back than the foot [248]. Hence, there is a need to extend the existing reference database to include other body sites, especially relevant to musculoskeletal pain such as the back, shoulder, and knees. With the recent introduction of nociplastic pain, which is defined as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage […] or evidence for disease or lesion of the somatosensory system causing the pain" [249], it is therefore important to note that the somatosensory and pain modulatory profiles may not be exclusive categorical labels and may

represent one of a combination of mechanisms at play in the genesis and maintenance of chronic pain in pediatric patients depending on the location the sensory tests were applied and the number of pain locations reported by the patient.

Regular or intermitted analgesia intake by the patients after recruitment in the studies presented in the thesis was noted. However, its potential contribution in the variability in the outcomes was not assessed. The extent to which an analgesic drug taken regularly or intermittently can affect one individual, in comparison to another, was not effectively accounted for in our statistical analysis. Some patients across all four studies of this thesis were taking intermittent or regular analgesics such as acetaminophen or ibuprofen to relieve pain. Some have taken or were currently taking muscle relaxants or gabapentin, which is an anti-epileptic, and others were taking anti-depressants for depression, but may also have an effect on the descending inhibitory control of patients [250, 251]. Moreover, some participants were taking stimulants, such as Concerta, for attention-deficit/hyperactivity disorder. A study in adults did not observe any differences in QST results in individuals after analgesic intake (1 dose of aspirin, acetaminophen, or acetaminophen and codeine) when compared to a placebo [252]. Another study in adults highlighted how the use of non-steroidal anti-inflammatory drugs can inhibit the expression of genes encoding for cytokines, which are involved in pain perception [253]. Studies on EEG in youth with attention-deficit/hyperactivity disorder observed that stimulants increase their cortical arousal normalising their EEG [254-256]. Although the effect of medication on the distinct psychosocial, somatosensory or pain modulatory profiles or on the EEG patterns was not investigated, they are worthy to take into consideration. Stone et al. (2020) observed in their study that pediatric patients grouped into a high pain dysfunctional psychosocial profile reported a higher number of prescription medications, specifically pain medication and antidepressants, than patients grouped

in the high pain adaptive or low pain adaptive psychosocial profile [208]. Therefore, we may also hypothesize that the patients grouped in the high somatic symptoms cluster identified in the first and third article of this thesis may also have reported a high number of intermitted or regular analgesic intake than the rest of the cohort. The effect of antidepressants on the descending inhibitory control of individuals may have had a significant effect on the pain modulatory profiles of patients in the second and third article of this thesis. Whether patients who took anti-depressants prior to the study assessment were grouped in the functional central processing pain modulatory profile or if they would change profile if they were not taking antidepressants the day of the assessment is unknown. Moreover, at rest, youth with chronic pain showed increased global delta and beta power and an altered developmental pattern of theta spectral power changes relative to age-matched controls. No other differences in EEG patterns were observed at rest. Whether the lack of difference may be attributed to analgesic or stimulant intake is unknown. There is still a paucity of studies investigating the effect of regular or intermittent medication intake on QST or neuroimaging results of youth. Nevertheless, the complexity of chronic pain is acknowledged such that future studies investigating subgroups or profiles of patients alongside their medical history and analgesia intake is warranted.

4.5 Other limitations

The generalizability of our findings to all children, and adolescents with chronic pain should be interpreted considering certain limitations.

4.5.1 Participant environment

A biopsychosocial approach to chronic pain has been adopted as it results from the interactions between multiple elements, including, nociceptive, affective, sociocultural,

behavioural, and cognitive factors [46]. Although the work of the thesis investigated psychosocial factors in children and adolescents with chronic musculoskeletal pain, most of the factors belonged to the psychological domain including emotional functioning and cognition, and therefore, lacking social and environmental domains. The complex transactional processes between the patient and their environment may ultimately influence the child's overall response to pain. Although it was not measured in the work of this thesis, the quality of the interview and/or potential extensive and supportive interactions with the study participants before or after recruitment into the studies may have unintended placebo effects during the assessment [257, 258]. Moreover, the gender and bias of the research assistant involved in the assessment of the participants may also have played an influential role in their responses. A recent study investigating caregiver-child interactions have observed that professional male and female caregivers showed the same levels of attention, and sensitivity toward very young boys and girls [259]. Despite all caregivers in their study were classified as feminine or androgynous with the Bem Sex Role Inventory, future investigation of the examiner's sex roles or bias is warranted in pediatric chronic pain research. Furthermore, reducing, or standardizing interactions with participants by using a computer-based training and explanation of procedures may decrease unintended placebo effects during the assessment.

Prior to the QST and neuroimaging assessment of all participants involved in the work of this thesis, the parents or legal guardians of the participants are asked to leave the study room and remain in the waiting area. This decision was made to decrease any parental influence on the child's perception or expectation responses to pain [260]. A study by Boerner et al. (2017) observed that sex-specific effects of parental exaggerated pain expression affected their children's own subsequent pain experience during a cold pressor task [261]. In the work of this thesis, there were some instances when the participant would ask that their parent or legal guardian to remain

in the room throughout the assessment due to high anxiety or other reasons. In these instances, the research assistant would instruct the parent or legal guardian to not interfere throughout the QST assessment and neuroimaging. Despite parental influence was not investigated in the work of this thesis, it is important to take it into consideration as family-based interventions are warranted in pediatric pain management and may focus on parents' protective and solicitous behaviors [46, 260, 261]. Moreover, a recent systematic review revealed moderate quality evidence that children with a family history of pain are at higher risk of experiencing MSK pain [262, 263]. However, a limitation of most studies investigating parent-child interactions is the predominance of mother-daughter dyads in study samples [208, 264-266]. A majority of the cohorts investigated in the work of this thesis were female. Future work investigating the influence of parents or a legal guardian on the QST or neuroimaging results of youth is warranted to further understand sex-specific parent-child pain associations and to provide appropriate family-based interventions.

4.5.2 Limitations of cross-sectional studies

Like all measures used in the work of this thesis, the novel analyses and identification of profiles need to undergo several steps to ensure their validity and meaningfulness. A major limitation of the studies presented in this thesis is the cross-sectional nature of these studies. It is unknown whether the profiles identified in the first three studies presented in this thesis would be reproduced if all participants underwent the same assessment at a standardized future time point. Studies evaluating the reliability of QST measures have shown good-to-excellent reliability for static QST, but poor-to-good reliability for dynamic QST (CPM and TSP) at different time intervals [267-269]. Moreover, a study by Ferland et al. observed difference between testing centers for multiple QST parameters assessed, despite a robust training session regarding the test procedures was conducted in each testing center [270]. Standardization of QST may be more

difficult when the experimenter is responsible for the stimulus, such as dynamic mechanical allodynia, vibration detection threshold and pressure pain threshold. Other variability interfering with the reliability of QST results could be attributed to the multi-examiner effect. As for the psychometrics of the psychosocial factors included in the assessment conducted in the work of this thesis, as mentioned in the studies of this thesis, most questionnaires were validated in a pediatric population and showed good reliability. However, it is unknown whether patients in the "high pain dysfunctional" or "high somatic symptoms" psychosocial cluster would report lower scores for the questionnaires at a follow-up assessment which may be explained by the phenomenon of "regression to the mean" [271]. This implies that repeated measures vary from one timepoint to the next due to random error, and extreme scores tend to approach the mean at subsequent timepoints. Nevertheless, more emphasis on standardization of questionnaires or stimuli administered, instructions to the subjects, and testing algorithms are mandatory to improve the quality of future studies including multiple elements contributing to chronic pain to identify psychosocial, somatosensory or pain modulatory profiles in patients.

4.5.3 Choice of multivariate data analysis

Hierarchical clustering method with k-means consolidation was conducted to identify different subgroups of profiles of patients in the first three articles of this thesis. This methodology was conducted to investigate interrelationships between patients based on specific variables in order to identify relatively homogenous subgroups by minimizing within-cluster variability but maximizing between-cluster variability [205, 207, 272]. Multiple other robust analyses have been previously conducted in different chronic pain populations, such as latent class analysis [246], semi-supervised clustering method [244, 245], or two-step cluster analysis [273, 274]. These choices are based on the objectives of the study, the variables investigated, or the outcome

discussed by the researchers. The hierarchical clustering method used in the work of this thesis was simple as a bottom-up approach which starts by finding similarities between cases. The latent class analysis, is a top-down probabilistic model for clustering that which starts by describing distribution of the data [272]. Since the goal for each method is generally the same (i.e., to identify homogenous groups within a larger population), and there is no consensus pertaining to the superiority of one method, and we hypothesize that latent class analyses would have produced qualitatively similar results.

CHAPTER 5 CONCLUSION

Effective assessment and communication about pain is associated with better pain management. Therefore, there is a need for a person-centered approach to the assessment of pain in youth. Detailed profiling of patients can inform individualized therapy and stratification for strategic therapeutic trials. The use of self-reported questionnaires, static and dynamic QST, and electroencephalography has allowed us to meet our research objective to better understand chronic pain in youth to improve the clinical assessment of pain processes in pediatric patients with chronic MSK pain Screening with self-reported questionnaires, and static and dynamic QST facilitate phenotyping of children and adolescents with chronic MSK pain in the clinical context. The combination may allow recognition of different subgroups or profiles of patients with chronic MSK pain with distinct pain mechanisms that can be targeted and may ultimately contribute to personalized therapy. A dry EEG headset revealed differential changes in brain activity during rest and tonic painful stimuli, mimicking clinical pain, in youth with chronic MSK pain and age-matched healthy controls. Our findings suggest that these tools can be used within the time constraints of clinical routines to further improve pediatric pain management. Moreover, our findings provide opportunities for future work to conduct similar projects on youth with other chronic pain conditions.

Pain assessment is a core component of effective communication about pain. The adequate assessment of pain offers a first step to better understand pain and improve the management of it. Pain assessment in youth is an inferential process in which all available and valuable information should be considered.

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