McGill University

Montreal

Pilot study: Validity of the Analgesia Nociception Index for the evaluation of children and adolescents with Chronic Pain conditions.

A comparison with the Quantitative sensory testing and Conditioned pain modulation paradigm

Nada Mohamed

Experimental Medicine

McGill University

June 2024

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Sciences.

Table of Contents

List of figures

Abbreviations:

- ANI : Analgésia Nociception Index
- CPC-MCH: Complex Pain Center at the Montreal Children's Hospital
- CPM: Conditioned Pain Modulation
- DFNS: (Deutscher Forschungsverbund Neuropathischer Schmerz) German Research Network on Neuropathic Pain
- DN4 : Douleur Neuropathique 4
- FDI: Functional Disability Inventory
- FLACC: Face, Leg, Activity and consolability
- HRV: Heart Rate Variability
- PAG: Periaqueductal gray
- PB: Parabrachial nucleus
- PSQI: Pittsburgh Sleep Quality Index
- QST : Quantitative sensory testing
- RCADS: Revised Child Anxiety and Depression Scale
- PS: Psychosocial

ABSTRACT

There is a need for an unbiased and practical pain assessment instrument that can be used at the bedside for adolescents and children with chronic pain, without being influenced by external factors.

The currently used methods either Numerical rating Pain scale or Visual Analog scales may be impractical in sedated patients and in young individuals with learning issues and cognitive limitations. This requires the utilization of objective pain monitoring.

The objective of this pilot study was to assess the validity of the Physio Doloris® analgesia. The study involved a comparison of Pain intensity (NRS), psychosocial phenotypes , quantitative sensory (QST) , and conditional pain modulation (CPM) with (Analgesia Nociception Index (ANI)).

A total of one hundred and six individuals recruited at the Complex Pain Center. Pain intensity scores and ANI values were measured concurrently during periods of rest. 62 patients of the 106 enrolled were continuously measured throughout the administration of QST and CPM testing. The relationship between indices was established, with a particular value of the ANI being associated with a pain intensity (NRS). The patients were divided into two categories based on their Analgesia Nociception Index at rest, using a threshold of 85.

Results: Before any stimulation, alert patients at rest exhibited ANI values with an average of 83.7 and a standard deviation of 12.4. There was a weak negative correlation between Numerical Rating scores and Analgesia Nociception Index values at rest. Applying stimuli led to a reduction in ANI values, but did not yield a specific differentiation among chronic pain mechanisms such as peripheral sensitization, central sensitization, and ineffective conditional pain modulation. There was no negative relationship between ANI and self-rated pain during the Conditional pain modulation. The presence of a psychosocial active diagnosis during the initial consultation was associated with a reduction of the Analgesia Nociception Index values.

Conclusion: The Analgesia Nociception Index demonstrates a negative relationship with psychosocial comorbidities, such as anxiety and depression. Further investigation is necessary to verify the results of this preliminary study and to analyze the fluctuations in the Analgesia Nociception Index during subsequent visits, as well as to investigate the effects of treatments like nerve blocks on the Analgesia Nociception Index values in pediatric patients with chronic pain conditions.

ABRÉGÉ

Il est nécessaire de disposer d'un instrument d'évaluation de la douleur impartial et pratique pouvant être utilisé au chevet des adolescents et des enfants souffrant de douleur chronique, sans être influencé par des facteurs externes.

Les méthodes actuellement utilisées, telles que l'échelle numérique d'évaluation de la douleur (NRS) ou les échelles visuelles analogiques, peuvent être inadaptées chez les patients sédatés et chez les jeunes présentant des troubles d'apprentissage ou des limitations cognitives. Cela nécessite l'utilisation d'un dispositif objectif de surveillance de la douleur.

L'objectif de cette étude pilote était d'évaluer la validité de l'appareil Physio Doloris pour l'analgésie. L'étude a consisté à comparer l'intensité de la douleur (NRS), les phénotypes psychosociaux, la sensibilité sensorielle quantitative (QST) et la modulation conditionnelle de la douleur (CPM) avec l'indice Analgésia Nociception Index (ANI).

Un total de 106 individus a été recruté au Complex Pain Center. Les scores d'intensité de la douleur et les valeurs de l'ANI ont été mesurés simultanément pendant les périodes de repos. 62 patients parmi les 106 recrutés ont été mesurés en continu lors des tests de QST et CPM. La relation entre les indices a été établie, une valeur particulière de l'ANI étant associée à une intensité de douleur

(NRS). Les patients ont été divisés en deux catégories selon leur indice ANI au repos, en utilisant un seuil de 85.

Résultats : Avant toute stimulation, les patients conscients au repos présentaient des valeurs d'ANI avec une moyenne de 83,7 et un écart type de 12,4. Une faible corrélation négative a été observée entre les scores NRS et les valeurs ANI au repos. L'application de stimuli a entraîné une diminution des valeurs ANI, mais n'a pas permis de différencier spécifiquement les mécanismes de douleur chronique tels que la sensibilisation périphérique, la sensibilisation centrale et la modulation conditionnelle inefficace de la douleur.

Il n'y avait pas de relation négative entre l'ANI et la douleur auto-évaluée pendant la modulation conditionnelle de la douleur. La présence d'un diagnostic psychosocial actif lors de la consultation initiale a significativement réduit l'indice ANI.

Conclusion : L'indice ANI montre une relation négative avec les comorbidités psychosociales, telles que l'anxiété et la dépression. Des recherches supplémentaires sont nécessaires pour vérifier les résultats de cette étude préliminaire, analyser les fluctuations de l'indice ANI lors des consultations ultérieures et examiner les effets des blocs nerveux sur l'indice ANI.

ACKNOWLEDGEMENTS

I would like to express my gratitude to the members of my thesis committee for their effort, time, and valuable insights: Dr. Sabrina Carrié, Dr. Jonathan Hudon, Dr. Marc Martel, and my academic advisor, Dr. Larry Lands. I would also like to thank Dr. Thomas Engelhardt for his personal support and assistance with my research project.

To my supervisor, mentor, and role model, Dr. Pablo M. Ingelmo, thank you for your unwavering support, for believing in me, and for your dedication to providing scientific feedback throughout this project. I am grateful for the opportunity to be part of such an exceptional team, and it has been an honor to work alongside you and the Complex Pain Center team. I know that I have much more to learn from you.

I also extend my thanks to Dr. Don Daniel Ocay for teaching me assessment techniques, for your strong work ethic, and for our engaging discussions about Quantitative Sensory Testing (QST) and Conditioned Pain Modulation (CPM). You have significantly helped me develop my testing techniques and understand the scientific importance of each test, as well as our limitations.

Thank you to my wonderful family for your daily support and for asking the right questions at the right times. Words cannot adequately express how much you have assisted me in achieving my goals. I am also grateful to Maria Danielle, Nathalie Comtois, and Rebecca Pitt for our health walks

and indulgent desserts, for keeping me grounded, and for your excellent ongoing scientific feedback on Chronic Pain, as well as your endless patience in scheduling patients for the project.

I would like to thank Dr. Marie Vigoroux and Dr. Mona Salah for being valuable friends during my journey and for their scientific and spiritual support throughout this process.

Finally, I want to express my appreciation once again to my supervisor, Dr. Ingelmo, for the opportunity to work within the Alan Edwards Complex Pain Center research group on this fascinating project, which has ignited my passion for pursuing further research in Chronic Pain.

Merci à Tous. Thank you all. Gracias a to-dos,

CONTRIBUTION OF AUTHORS

Nada Mohamed, the candidate contributed to the creation of the full content of this thesis. The candidate's supervisor, Dr Pablo Ingelmo, approved the entire work.

The ANI research protocol was developed by the Complex Pain Center at the Montreal Children's Hospital with the contribution of Dr Pablo Ingelmo, Dr Sabrina Carrié, and Courtney Wood. Marie Linda has conducted some of the ANI sessions.

Nada Mohamed was responsible for the ANI, QST, CPM evaluations, data collection, REB submission, Data analysis, writing and any other steps required for the completion of the research study and submission of the thesis as per McGill University and Experimental Medicine requirements.

Dr Sabrina Carrié, Alice Bruneau along with Dr Pablo Ingelmo director of the CCP -have contributed to the design and scientific content.

CHAPTER 1: INTRODUCTION

Twenty percent to thirty-five percent of young people worldwide deal with chronic pain[2]. It is crucial to treat children's chronic pain for several reasons. It reduces the likelihood of transitioning to adulthood with pain and psychological disorders while simultaneously improving the quality of life [3].

One set of non-invasive methods for evaluating Nociception is the Analgesia Nociception Index (ANI), which measures parasympathetic tone with heart-rate variability (HRV)[4]. Because it is mostly used at the bedside, ANI is an interesting tool for testing nociceptive stimulation during general anesthesia work. Reduced nociception , increased parasympathetic modulation and HRV are all indicators of a higher ANI score (which ranges from 0 to 100). Lower scores indicated that both sympathetic control and heart rate variability (HRV) are related to an increase in nociception. The latter's much-increased sensitivity to nociception is a key distinction between ANI and more traditional measurements [5,6]. With its shown efficacy in reducing sensitivity to nociceptive stimuli [7,8],[9] ANI is a useful tool in pediatric surgical settings, and its efficacy is further enhanced following opioid treatment [10]. There is an inverse relationship between the Numerical Rating Scale (NRS) and ANI, according to studies done on individuals following surgeries [11] . Higher NRS scores, indicative of greater pain intensity, correspond with lower ANI values due to heightened autonomic response to pain. Conversely, lower NRS scores are associated with higher ANI values, reflecting reduced pain perception and improved autonomic stability. This inverse relationship emphasizes ANI's utility as an objective marker of autonomic nervous system response to pain and its potential application in guiding clinical pain management[5].

Even with all these improvements, there has not been enough research on how well ANI works as a nociceptive evaluation tool for children and adolescents with chronic pain. Because their

resting HRV and HRV response to nociceptive stimuli are lower than those of without chronic pain, this cohort is interesting to study [12,13]. Filling this knowledge gap will allow us to learn more about chronic pain in children and how to employ ANI more effectively in this setting. This group may benefit from an ANI-based objective assessment of therapy success dependent on parasympathetic tone (and restoration thereof). For quick and easy evaluations and follow-ups in routine practice, more and more physicians are using ANI, an objective nociception measure in patients under general anesthesia or postoperatively.

OBJECTIVES & RATIONALE

This study seeks to explore the potential of the ANI as an objective measure of pain intensity in pediatric patients with chronic pain. The study specifically addresses the following questions:

1. **Baseline ANI use in chronic pain patients without stimulus**: Is the baseline Analgesia Nociception Index (ANI) different in patients with chronic pain conditions?

2. **Correlation between ANI values and pain intensity (NRS):** What is the relationship between ANI readings and self-reported pain intensity, as measured by the Numerical Rating Scale (NRS), in pediatric patients with chronic pain?

3. **Impact of controlled stimuli on ANI values (QST/CPM):** How do ANI values change when controlled non-surgical stimuli is used such as during the Quantitative Sensory Testing (QST) and Conditioned Pain Modulation (CPM), applied in pediatric patients with chronic pain?

4. **Differences in ANI values across psychosocial phenotypes**: Do ANI values vary between different psychosocial phenotypes in children with chronic pain?

   The study hypothesizes several key relationships regarding the Analgesia Nociception Index (ANI) in children with chronic pain. First, baseline ANI values are expected to differ from the standard value of 100, reflecting altered nociceptive regulation in this population. Additionally, a negative correlation between ANI and Numerical Rating Scale (NRS) scores is anticipated, with lower ANI values associated with higher self-reported pain intensity. It is also proposed that ANI will be responsive to controlled stimuli, such as during Quantitative Sensory Testing (QST) or Conditioned Pain Modulation (CPM), indicating it is potential as a

dynamic tool for measuring changes in nociceptive response. Furthermore, different psychosocial profiles are expected to result in varying baseline ANI values, suggesting that psychosocial factors modulate nociception in pediatric chronic pain patients. Finally, ANI is predicted to be sensitive to differences in psychosocial phenotypes associated with nociceptive responses capturing the interplay between psychological, social, and physiological dimensions of pain.

1

CHAPTER TWO:2. LITERATURE REVIEW:

2.1 EXPERIENCE OF CHRONIC PAIN

About 1 in every 5 children and adolescents report persistent or recurrent chronic pain[14], often persisting into adulthood. It is a complex and challenging health issue impacting daily lives, emotional well-being, and overall quality of life [11]. Chronic pain not only affects physical health but also has substantial psychosocial implications, including increased rates of anxiety, depression, and impaired social functioning. Additionally, it creates a financial burden on families, involving healthcare costs and loss of wages for medical appointments [15].

In 2017, the International Association for the Study of Pain (IASP) introduced a new category of pain, nociplastic pain, alongside nociceptive and neuropathic pain. Nociplastic pain is characterized 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. Recently, the IASP Terminology Task Force (TTF) established clinically useful criteria for nociplastic pain. Chronic nociplastic pain is defined as pain that lasts for more than three months, has a regional rather than discrete distribution, is not entirely explained by nociceptive or neuropathic pain mechanisms, and displays 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 comorbidities (such as sleep disturbance and cognitive problems) strengthens the probability of nociplastic pain. These criteria can be assessed through validated self-reported questionnaires and quantitative sensory testing.[16],[17]. Research on nociplastic pain has increasingly employed quantitative sensory testing (QST) and conditioned pain modulation (CPM) tests to assess altered nociceptive processing, with the aim of understanding mechanisms like peripheral

sensitization, central sensitization, and descending inhibitory pathways. These methods involve multiple stimuli to evaluate changes in pain perception and modulation, helping to discern whether alterations are driven by heightened peripheral response, maladaptive central processing, or impairments in endogenous pain inhibition. In many cases, these mechanisms may overlap, contributing to the complexity and variability of nociplastic pain presentations. Examples of chronic pain conditions that meet the criteria for nociplastic pain include fibromyalgia, complex regional pain syndrome, and irritable bowel syndrome. These conditions are also observed in pediatric populations, and studies have demonstrated altered nociceptive processing and the presence of comorbidities in youth. However, describing nociplastic pain in pediatrics and investigating whether the clinical criteria reflect what is observed in the pediatric population remain areas of limited knowledge.

The multifactorial nature of chronic pain in this age group involves biological, psychological, and social factors. Commonly associated conditions include migraines and musculoskeletal disorders. Psychosocial factors, including parental influences and socio-economic status, also play a significant role [18].

Accurate assessment and diagnosis of chronic pain in children pose unique challenges due to developmental differences and varying expressions of pain. The use of standardized tools, such as the Pediatric Pain Questionnaire, proves effective in capturing diverse aspects of pain experiences in this population. Multidimensional assessments considering both physical and psychosocial factors are essential for a comprehensive understanding [19].

Effective management requires a **multidisciplinary** approach. Pharmacological interventions and non-pharmacological approaches such as cognitive-behavioral therapy, physical therapy, and mindfulness-based approaches show promise in improving outcomes [19].

2.2 Basic Understanding of Chronic Pain

We as humans were granted mechanisms of pain plasticity to facilitate healing and provide mechanisms for protection. However, persistence in pain plasticity and its chronicity can become a condition by itself. Three mechanisms of Chronicity of pain are currently known: Peripheral sensitization, Central sensitization, and inefficient descending inhibitory pathway [20]

Peripheral Sensitization refers to a phenomenon in which the peripheral nervous system becomes hypersensitive to stimuli, leading to an exaggerated and prolonged response to painful or noxious stimuli. This process plays a significant role in the development and maintenance of chronic pain conditions.[20–22]

In chronic pain, persistent or repeated injury, inflammation, or damage to tissues can trigger a cascade of events that contribute to peripheral sensitization.

Peripheral sensitization in patients involves several key components contributing to the chronicity of pain. Nociceptor activation plays a pivotal role. These specialized nerve endings detect noxious stimuli, such as mechanical pressure, extreme temperatures, or inflammatory chemicals. In chronic pain, nociceptors can become easily activated, lowering the threshold for pain signaling.[21]

Additionally, the release of inflammatory mediators exacerbates the situation. Tissue injury or inflammation triggers the release of substances like prostaglandins, cytokines, and growth factors. These chemicals sensitize nociceptors, heightening their responsiveness to stimuli and amplifying pain sensitivity.

Consequently, this heightened activity of nociceptors and the presence of inflammatory mediators induce a state of peripheral sensitization. Even mild or non-painful stimuli can evoke a stronger and prolonged pain response. Moreover, this sensitization can extend beyond the initial site of injury, affecting neighboring tissues.[23]

Furthermore, chronic pain conditions entail neuroplastic changes in peripheral nerves. These alterations involve structural and functional modifications in neurons, rendering them more excitable and responsive. Ultimately, the increased sensitivity of peripheral nerves perpetuates the cycle of chronic pain.

Central sensitization is another crucial concept in understanding chronic pain is central sensitization which involves changes within the central nervous system (CNS), particularly in the spinal cord and brain, that result in an amplification of pain signals [21]. Prolonged exposure to pain or repetitive nociceptive stimuli can lead to an increased excitability of neurons in the spinal cord and brain. This heightened excitability is a result of prolonged stimulation, which alters the functioning of neurons in pain pathways.

Furthermore, neurotransmitter release within the central nervous system contributes significantly to the transmission and amplification of pain signals. Substances such as glutamate and substance P play crucial roles in this process, enhancing the perception of pain.

Long-Term Potentiation (LTP) is another critical factor in central sensitization. This phenomenon involves the strengthening of synaptic connections between neurons following repeated stimulation. In the context of pain pathways, LTP leads to a sustained increase in the transmission of pain signals, contributing to chronic pain.[22]

Similar to peripheral sensitization, central sensitization involves neuroplastic changes within the central nervous system. These alterations encompass structural and functional modifications in neurons, as well as changes in connectivity between different brain regions associated with pain processing.[24]

Moreover, central sensitization can result in widespread pain sensitization, where non-painful stimuli become more intense and painful. This generalized hypersensitivity to pain extends beyond the initial injury site, contributing significantly to the experience of chronic pain. [25]

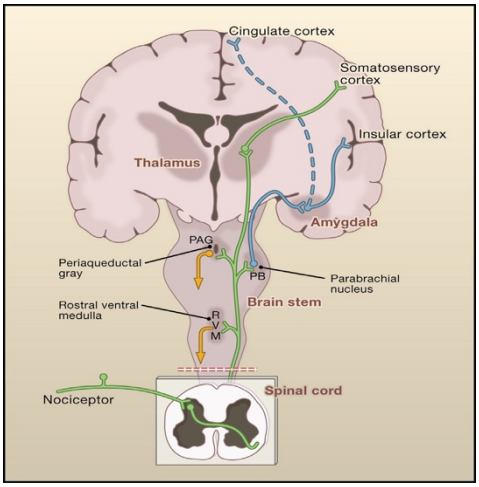

Figure 1 Anatomy of pain pathways (©Buxbaum et al. 2009)

Descending inhibitory pathways are an essential component of the body's pain modulation system. These pathways involve the release of neurotransmitters that inhibit or modulate pain signals at various levels of the nervous system. Dysfunction in descending inhibitory pathways can contribute to the development and maintenance of chronic pain. Multiple mechanisms contribute to the modulation of pain signals through descending inhibitory pathways. [26]

Descending inhibitory pathways originate from higher brain centers, such as the periaqueductal gray (PAG) in the midbrain and the rostral ventromedial medulla (RVM). These regions play crucial roles in modulating pain signals, particularly in response to stress, fear, or pain.[27]

Moreover, these pathways utilize endogenous opioids, such as endorphins and enkephalins, as neurotransmitters. Endogenous opioids act on receptors in the spinal cord and peripheral nerves,

inhibiting the transmission of pain signals. Consequently, activating these pathways can effectively reduce the intensity of pain perception.[17,27]

Additionally, serotonin (5-HT) plays a significant role in descending inhibitory pathways. Serotonergic neurons originating in the brainstem release serotonin, which then activates inhibitory receptors (5-HT receptors) in the spinal cord. This activation suppresses the transmission of pain signals and modulates pain sensitivity.[28]

Norepinephrine, released by noradrenergic pathways, also contributes to pain signal modulation. Norepinephrine acts on receptors in the spinal cord, inhibiting the release of pain neurotransmitters. Dysfunction in these pathways has been implicated in various chronic pain conditions.[26,28]

Furthermore, the endocannabinoid system, comprising endogenous cannabinoids (endocannabinoids) and their receptors, plays a role in descending inhibition. Activation of cannabinoid receptors can reduce the release of pain neurotransmitters in the spinal cord, providing analgesic effects.[26]Dysfunction in descending inhibitory pathways is associated with chronic pain conditions. Understanding these mechanisms is crucial for developing more tailored and individualized treatment plans.[28]

2.3 Quantitative Sensory Testing and Conditional Pain MODULATION TESTS (QST&CPM):

2.3.1 Quantitative sensory testing and Conditional pain MODULATION:

QST and CPM evaluations can suggest which of the three mechanisms may be associated with chronic pain conditions in individual patients. Peripheral sensitization can be suggested using QST if a patient reported increased sensitivity when applying pressure to deep tissues using a blunt pressure algometer on deeper tissues[29]. It can also be investigated using thermal pain thresholds, where a lower heat pain threshold is a sign of peripheral sensitization[30]. Both techniques assess Aδ-fibers and C-fibers functions. Values obtained experimentally can be compared to a baseline value in the same subject of an experimental protocol, or compared to reference values available in the healthy population corrected for sex and age, and with consideration to the test site.

Different QST techniques can be used to assess the presence of central sensitization. The German Research Network on Neuropathic Pain (DFNS) suggests using mechanical dynamic non-nociceptive stimulation to assess for the presence of allodynia, a purely central sensitization manifestation. Allodynia, described as pain in response to non-nociceptive stimuli, is a phenomenon modulated by Aß-fibers which can be assessed with the help of a brush or cotton swab with a brushing motion on the skin. Von Frey filaments allow for testing of mechanical detection threshold, a modality involving sensory Aß- fibers. Mechanical pain may be assessed through pinprick stimulations with the help of various tools such as the needle-like stimulators and will evaluate the function of Aδ-fibers and C-fibers (fast, sharp pain and dull, longer pain).

Central hyperalgesia can be assessed through the use of mechanical pain thresholds and repeated pinprick stimulations.

Repeated pinprick stimulations can also evaluate the presence of central sensitization when there is presence of a significant increase in pain sensation after multiple stimulations repeated at a rate of 1/s. The DFNS also uses mechanical detection threshold, vibration detection threshold and thermal detection thresholds to assess any gain or loss of function that would be an indicator of Aβ-fiber deafferentation[31]

As described earlier, the CPM paradigm evaluates the body's endogenous capacity for intrinsic analgesia. An inefficient or suboptimal result during the CPM task may indicate that the subject has an impaired or deficient descending endogenous pain inhibitory control, mediated by 5-HT and NE.[32]

There have been several studies with QST in healthy children and adolescents describing differences across age and gender using various QST modalities[32–34]. There have been other QST studies investigating physical and psychological predictors of pain sensitivity by comparing healthy children with children suffering from various chronic pain conditions, and suggesting an underlying neurophysiological pain mechanism[35–37]. However, to date, there is no published data evaluating the clinical use of an extensive QST and CPM protocol in pediatric chronic pain interdisciplinary clinics. Indeed, the transfer of QST and CPM to a clinical application has not yet been made in paediatric population.

2.3.2. DIFFERENTIATING PAIN MECHANISM IDENTIFIED BY QST AND CPM

Children experiencing chronic pain require a comprehensive evaluation of their pain. Quantitative Sensory Testing (QST) is a valuable tool for objectively measuring and characterizing sensory abnormalities associated with various pain conditions [37]. It aids in suggesting underlying mechanisms, distinguishing between neuropathic and nociceptive pain, and objectively measuring changes in sensory function following interventions.

Quantitative Sensory Testing (QST) and Conditioned Pain Modulation (CPM) are two valuable methods used to assess and differentiate between various mechanisms of pain, including peripheral sensitization, central sensitization, and inefficient descending inhibitory pathways.[38]

QST involves the systematic measurement of responses to standardized sensory stimuli, providing a comprehensive assessment of sensory processing and pain perception.[38,39]

"Peripheral Sensitization" can be identified by detecting heightened sensitivity to peripheral stimuli, such as mechanical pressure using Algometer on deeper tissues. Increased pain sensitivity and reduced pain thresholds at pain site are indicative of peripheral sensitization as well. It can also be investigated using thermal pain thresholds, where a lower heat pain threshold is a sign of peripheral sensitization[29]. Both techniques assess Aδ-fibers and C-fibers functions. Values obtained experimentally can be compared to a baseline value in the same subject of an experimental protocol, or compared to reference values available in the healthy population corrected for sex and age, and with consideration to the test site[38].

QST protocol can reveal widespread alterations in sensory processing beyond the injury site, reflecting "**Central sensitization**". Increased pain sensitivity in regions remote from the initial injury measured by tests for deep tissue sensitivity(using Algometer) or dynamic mechanical allodynia (using sensory brush) detected in sites other than the primary pain site suggests central sensitization involvement [38]. Various quantitative sensory testing (QST) procedures can be employed to evaluate the existence of central sensitization. The DFNS recommends utilizing mechanical dynamic non-nociceptive stimulation as a means of evaluating the existence of allodynia, which is a manifestation only related to central sensitization[31]. Allodynia refers to the experience of pain in reaction to stimuli that are not normally painful. This phenomenon is influenced by Aß-fibers and can be evaluated by gently touching the skin with a brush or cotton swab. Von Frey filaments enable the assessment of the mechanical detection threshold, which is a method that involves sensory Aß- fibers. Mechanical pain can be evaluated by using pinprick stimulations with equipment like needle-like stimulators. This assessment helps determine the functioning of Aδ-fibers and C-fibers, which are responsible for quick, intense pain and dull, longer-lasting pain, respectively. Central hyperalgesia can be evaluated by measuring mechanical pain thresholds and administering repeated pinprick stimulations. Similar to the pain pressure threshold, the mechanical pain threshold can be measured and compared to a reference value in the same individual.

When conducting experiments, it is important to follow a certain set of instructions. Additionally, it is crucial to compare the results to established values from a healthy population, taking into account factors such as sex, age, and the location of the test. Repeated pinprick stimulations can be used to assess the presence of central sensitization by seeing a substantial rise in pain feeling

following multiple stimulations at a rate of 1 per second. The DFNS employs mechanical detection threshold, vibration detection threshold, and thermal detection thresholds to evaluate any changes in function that may indicate Aβ-fiber deafferentation[29,31,36]

Conditional Pain Modulation known as ''CPM'' can also assess the efficiency of endogenous pain modulation by measuring the change in pain perception during the application of a conditioning stimulus (e.g., cold pressor test). Inefficient Descending Inhibitory Pathways are indicated by reduced or absent CPM responses which may indicate dysfunction in descending inhibitory pathways. Inefficient pain modulation reflects a diminished ability of the central nervous system to inhibit pain signals [33].The test is done by comparing the decrease in pain levels before and after conditional inhibition (cold bath) and calculating the efficacy of CPM.

Several investigations have been conducted on healthy children and adolescents using QST, which have identified differences in age and gender using different QST methods[40,41]Other QST research have examined physical and psychological factors that can predict pain sensitivity[40]. These studies have compared healthy children with children who have different chronic pain disorders, and have proposed a neurophysiological pain mechanism as a possible explanation. Currently, there is no available published evidence that assesses the application of a comprehensive Quantitative Sensory Testing (QST) and Conditioned Pain Modulation (CPM) strategy in a pediatric chronic pain interdisciplinary clinic. Currently, the implementation of QST and CPM in a clinical setting for pediatric patients has not been implemented yet.

In summary, QST is currently used to objectively identify sensory abnormalities associated with peripheral and central sensitization, while CPM provides insights into the efficiency of descending

inhibitory pathways. Integrating the mentioned assessments allows clinicians and researchers to gain a more nuanced understanding of the underlying mechanisms contributing to chronic pain.[42] However, like any other methodology, QST has its limitations. These include the impact of psychological variables on outcomes, the absence of standardized protocols, and possible ethnic and cultural differences in pain perception. Additionally, administering tests to non-verbal patients, those under the age of eight, and other complex populations (such as individuals with severe anxiety or ADHD) can present challenges. As a result, researchers are continuously working to improve assessment techniques tailored to children experiencing chronic pain.[43]

2.4 Exploring the Connection between Chronic Pain and Heart Rate Variability in Pediatric Populations

Chronic pain in children and adolescents is a complex and multifaceted phenomenon that not only affects their physical well-being but also has implications for their autonomic nervous system (ANS) functioning [13]. One of the key indicators of ANS activity is heart rate variability (HRV) sheds light on how alterations in autonomic regulation may contribute to the pain experience.

HRV, the variation in the time interval between consecutive heartbeats, reflects the dynamic interplay between the sympathetic and parasympathetic branches of the autonomic nervous system [10,44]. Higher HRV is generally associated with better adaptive capacity, while reduced HRV may indicate increased stress or compromised regulatory mechanisms.[10]

Pain stimuli research has begun to discover a complex interplay between chronic pain and HRV in the pediatric population[45,46] . Studies have suggested that children and adolescents with chronic pain conditions may exhibit alterations in HRV parameters, indicating disruptions in autonomic balance[47]. Especially in chronic pain conditions, where pain can disrupt autonomic nervous system (ANS) function, and in turn, autonomic dysregulation can amplify pain perception. Heart rate variability (HRV), a measure of the variation in time between heartbeats, reflects the balance between sympathetic (fight-or-flight) and parasympathetic (rest-and-digest) activity within the ANS.

Chronic pain, such as that seen in pediatric populations, often involves increased sympathetic activity (leading to stress-like responses) and reduced parasympathetic activity, contributing to a lower HRV.[47]

A lower HRV in these patients is associated with a heightened sensitivity to pain, likely because the body remains in a state of sympathetic dominance, making it more reactive to. This dysregulation can perpetuate pain by creating a feedback loop where autonomic imbalances fuel pain sensitivity, which then further disrupts autonomic function.

HRV's role as a marker in this context is significant for both assessment and potential treatment. Tracking HRV may help clinicians identify pain-related autonomic dysfunction early and monitor responses to interventions. Therapeutically, interventions that increase HRV, such as biofeedback, relaxation techniques, or physical exercise, may help rebalance the autonomic nervous system, reducing pain sensitivity and improving overall quality of life in pediatric chronic pain patients. [47].

Chronic pain conditions, such as juvenile idiopathic arthritis, migraines, or musculoskeletal disorders, can contribute to alterations in autonomic regulation, potentially reflected in HRV patterns . These conditions tend to increase sympathetic (stress-related) activity and decrease parasympathetic (calming) activity, leading to a lower HRV, which reflects impaired autonomic balance. Dysfunctional autonomic regulation can then perpetuate pain by amplifying sensitivity to pain stimuli and reducing the body's natural capacity for pain inhibition.

This creates a feedback loop where persistent pain exacerbates autonomic dysregulation, and this dysregulation, in turn, heightens pain perception. Such a cycle can sustain or worsen chronic pain conditions, making it increasingly challenging to manage symptoms. Understanding this relationship

emphasizes the importance of assessing HRV in chronic pain patients, as it may provide insights into the extent of autonomic involvement in their pain experience and guide potential therapeutic interventions aimed at restoring autonomic balance to help break the pain-dysregulation cycle. Dysfunctional autonomic regulation may perpetuate pain states, creating a cycle where pain exacerbates autonomic dysregulation, and vice versa.[12]

Several mechanisms may underlie the observed alterations in HRV in children and adolescents with chronic pain. Persistent pain experiences can lead to increased sympathetic arousal and reduced parasympathetic activity, disrupting the delicate balance of the autonomic nervous system. Additionally, the psychological and emotional aspects of chronic pain may contribute to altering HRV, reflecting the psychophysiological impact of prolonged pain experiences [48].

Understanding the intricate relationship between chronic pain and HRV in children and adolescents holds potential clinical significance. Monitoring HRV could serve as an adjunctive tool for assessing pain severity and treatment efficacy. Additionally, interventions targeting autonomic dysregulation, such as biofeedback or mindfulness-based approaches, may be explored to complement traditional pain management strategies[49].

In conclusion, the intricate interplay between chronic pain and heart rate variability in pediatric populations is an evolving area of research with potential clinical implications. Continued investigation into the bidirectional relationship, potential mechanisms, and the use of HRV as an objective marker in pediatric chronic pain could contribute to a more comprehensive understanding of these conditions and inform novel therapeutic approaches. The integration of HRV assessment

into the pediatric chronic pain paradigm represents a promising avenue for advancing both research and clinical care in this challenging domain.

2.5 Understanding the method of calculation of the Analgesia Nociception Index.

Calculating analgesia and nociception involves various methods, with one common approach being the use of mathematical formulas to quantify these phenomena.

ANI, based on Heart Rate Variability (HRV) analysis, measures the effect of Respiratory Sinus Arrhythmia (RSA) on Heart Rate through the parasympathetic reflex loop.
The ANI monitor collects signals with specific ECG electrodes, positioned appropriately on the chest or back to ensure correct signal acquisition. RSA, present in mammals including humans, involves bronchiolar stretch communication to the vagus node in the brain stem, leading to a transient increase in parasympathetic tone and consequent heart rate increase. ANI technology measures RSA, displaying and quantifying it as a normalized measure.

Furthermore, ANI computation involves R-wave detection, automatic correction of ectopic beats, mean RR subtraction after band pass filtering, and normalization to yield a RR series centered on 0. This process facilitates the identification of RR shortenings related to inspiratory cycles.

The technology utilizes an innovative computing process to collect frequencies from 0.15 to 0.4 Hz, isolating a pure signal related to parasympathetic activity from other frequency ranges influenced

by different factors and activities. In order to accurately analyze the data from monitoring devices, it is crucial to have a clear understanding of the underlying methodology and any factors that may influence the results. This section delineates the fundamental principles of ANI/HFVI.

The electrocardiogram (ECG) displays periodic changes in the interval between R-R waves, which are caused by the influence of the autonomic nervous system.

The phenomenon being referred to is known as heart rate variability (HRV), which has been the subject of research for over 50 years[50] .

Heart rate variability (HRV) can be shown by graphing the time series of the R-R interval from the electrocardiogram (ECG). When conducting spectral analysis on the periodic fluctuations in HRV, HRV may be divided into two components. The first component, known as high frequency (HF), exhibits a peak in the frequency range of 0.15-0.4 (or 0.5) Hz. The second component, known as low frequency (LF), exhibits a peak in the frequency range of 0.04-0.15 Hz 12. The high-frequency (HF) component of the signal reflects respiratory sinus arrhythmia. It is well-established that the efferent vagal activity plays a significant role in contributing to the HF component.

ANI utilizes heart rate variability (HRV) to evaluate the relative activity of the parasympathetic nervous system. It detects R waves using a digitized electrocardiogram (ECG) with a frequency of 250 Hz. The R-R samples that were acquired are separated into moving windows of 64 seconds and then normalized using the approach described in reference [51].

To begin, compute the mean by using the following variables: M for the mean value, n for the number of samples in the window, and RRi for each R-R sample value.

To determine the norm value (N), the machine uses the following formula: $N = \sqrt{(\Sigma(RRi - M)^2 / n)}$, where RRi represents each R-R sample value and M is the mean value. The norm value is calculated based on the number of samples in the window (n).

Next, dividing each R–R sample obtained by the norm value (N), where RRi represents each R–R sample value, M represents the mean value, and N represents the norm value.

The R-R series, which has been mean-centered and normalized, is automatically filtered using a fast wavelet transform.

This computation of the R-R series results in the extraction of only the high-frequency (HF) component in real time [52].

The R-R series undergoes alterations in response to variations in parasympathetic tone during breathing. Reducing parasympathetic tone diminishes the impact of respiratory alterations. The ANI algorithm partitions the 64-second moving window into four 16-second sub-windows and proceeds to evaluate each sub-window individually. In order to mitigate the impact of fluctuations in respiratory rate, the peaks and valleys of the data are connected, and the regions between the lowest and highest points (referred to as the area under the curve, or AUC) are examined. The amplitude of the normalized and filtered R-R series varies between 0 and 0.2 normalized units[45,53] .

The minimum Area Under the Curve (AUC) in each sub-window is defined as AUC min, while the total AUC is defined as AUC total. The greatest feasible value for AUC total is 0.2 normalized units multiplied by 64 seconds, which equals 12.8 seconds. ANI computes the percentage of the AUC total by using a formula that yields a value ranging from 0 to 100.

The values of α and β in the above formula are determined empirically using a general anesthesia

Dataset [54], with α set to 5.1 and β set to 1.2. The monitor continuously displays the average ANI for 2 and 4 minutes.

$$\mathrm{ANI} = 100 \times \frac{(\alpha \times \mathrm{AUC}_{\mathrm{min}} + \beta)}{12.8}$$

The ANI system also incorporates a green gridded surface to continuously measure the importance of RSA in a patient. This measurement, automatically derived by detecting upper and lower envelopes of the RR series, correlates directly with the amount of parasympathetic tone present. The normalization process enables an index between 0 and 100, obtained by dividing the measured surface by 12.8. This index, updated every second, provides insights into the patient's reactions to nociception induced by surgical activity, crucial for effective pain management strategies[1,52].

A waterproof adhesive covering electrodes prevents signal loss due to excessive moisture. After calibration, the ANI number appears in yellow on the monitor and varies with reactions. Even small changes in ANI can be observed after mild stimulations like the application of cold iodine or electric stimulation. In addition to the yellow ANI index (ANIi), the monitor displays an orange value for ANIm, resulting from a 2-minute averaging of ANIi signal and useful for titrating analgesia. ANIm indicates analgesia effects, while ANIi shows patient reactions to nociception induced by surgical activity.

2.6 The Role of Analgesia Nociception Index in Enhancing Pediatric Pain Management.

Previous studies in children have demonstrated that ANI measurement determined specifically ANIi and DeltaANI, possess substantial diagnostic utility in identifying surgical noxious stimulation in children[8,55,56]. All ANI parameters demonstrated satisfactory accuracy in detecting surgical unpleasant stimuli, predict patient outcomes in terms of pain experience after a specific treatment. ANI also aids in distinguishing the underlying source of hemodynamic alterations. During surgery, elevated blood pressure may arise because of prolonged tourniquet application or insufficient analgesia. In this context, the use of ANI can be beneficial in distinguishing between hypertension and pain, as well as in determining the most suitable medications for their management .[57]

The ANI values can vary between 0 and 100. A value of 0 indicates severe nociception and highly inadequate analgesia, while a value of 100 suggests the entire lack of nociception and the presence of opulent analgesia. Values below 50 indicate a high level of nociception, which suggest the need for analgesics. Values between 50 and 70 suggest an acceptable level of nociceptive stimulus and an optimal state of analgesia. Values above 70 indicate a minimal level of nociception, which requires a reduction in the dose of analgesia [1]

Several research examined the use of the ANI as a tool for evaluating postoperative pain in pediatric population, pain assessment in ICU setting and impact of using ANI in reducing opioid consumption [59]. Analgesia Nociception index (ANI) have shown strong efficacy in predicting immediate postoperative pain, which can help clinicians optimize acute pain management. The evaluation of ANI in the immediate period preceding extubating during inhalation remifentanil anesthesia showed a strong correlation with the degree of pain upon arrival in the PACU[58]In awake patients, ANI can be used to monitor the efficacy of analgesic interventions. For example, ANI has been used to assess the adequacy of epidural analgesia during labor and the effectiveness of regional anesthesia in various surgical procedures. By providing real-time feedback on the balance between nociception and analgesia[60–63].

In awake adult volunteers ANI vs self-report was tested in different settings, with experimental painful stimulus and there was a weak correlation between subjective pain scales and the Analgesia and Nociception Index, suggesting that a part of pain self-report is explained by nociception assessed through ANI. [64]

In chronic pain conditions, ANI may provide an objective measure of pain intensity, although its use in this context is less well-established and there was no literature found to the best of our knowledge examining the ANI usage in chronic pain awake pediatric population either with stimulus or without[60,61,65,66].

In pediatric care, the accurate assessment and management of pain remain critical, necessitating reliable tools to monitor nociception. The Analgesia Nociception Index (ANI) has emerged as a potential solution, utilizing heart rate variability to gauge nociceptive responses objectively specifically in the pediatric population, where verbal communication is often limited[8].

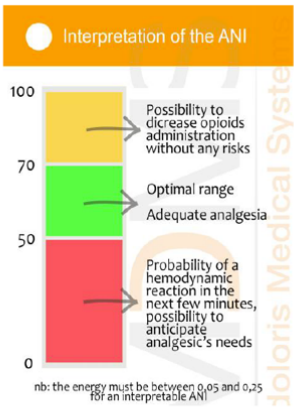

Figure 2, Interpretation of ANI as per manufacturer [1]

ANI enables an objective evaluation of nociception, minimizing reliance on subjective measures and ensuring a more precise understanding of pediatric pain experiences [7,67]. The continuous monitoring capacity of ANI allows for early detection of pain, facilitating timely interventions and preventing the escalation of discomfort in pediatric patients[56] . It supports individualized analgesic management by offering real-time nociception data, crucial for addressing the variability in pain sensitivity among pediatric patients [10,68]. By guiding healthcare providers to administer analgesics selectively, ANI may contribute to a reduction in opioid exposure, aligning with current efforts to minimize unnecessary medication in pediatrics [69]. While ANI exhibits promise across age groups, understanding age-related variability remains crucial. Ongoing research is required to validate its efficacy in neonates,

infants, and older children. ANI should complement rather than replace clinical judgment, emphasizing the importance of interpreting data in the broader clinical context [56]. Successful ANI implementation necessitates training healthcare providers in its use and interpretation, addressing potential challenges associated with unfamiliarity [63]

The integration of Analgesia Nociception Index in pediatric pain management marks a significant stride, providing an objective lens into nociception levels. Its continuous monitoring capabilities, early pain detection, and support for individualized analgesic interventions render ANI a valuable tool in elevating the care of pediatric patients. As research continues to refine its applications and address challenges, ANI holds considerable promise for enhancing the precision and efficacy of pain management in the pediatric population.

Fig 3 : screenshot from ANI device used in the lab .

CHAPTER 3:

METHODOLOGY:

Study design

The study was designed as a prospective longitudinal observational study. All patients enrolled in the study received standard of care in the interdisciplinary outpatient program of the Edwards Family Interdisciplinary Center for Complex Pain. This includes an interdisciplinary evaluation, a set of questionnaires, and quantitative sensory testing/conditioned pain modulation (QST/CPM) evaluation protocols. (See below). In addition to the standard of care, we added ANI using ANI mdoloris V2™ as part of the study to assess if ANI values correlate with the other measures measured in the interdisciplinary program.

Procedure:

Interdisciplinary evaluation

The interdisciplinary outpatient program of the Edwards Family Interdisciplinary Center for Complex Pain focuses on optimizing physical and psychological function, normalizing sleep and social function, and increasing levels of activity, while assisting with the management of the pain. The core team at each evaluation includes a nurse, psychologist, social worker, physiotherapist, a clinical fellow and a pain physician.

During an interdisciplinary face-to-face interview, we evaluate the intensity, duration and frequency of the pain over the previous month using the numerical rating scale (NRS) ranging from 0 (no pain at all) to 10 (worst pain imaginable).

After the interdisciplinary interview which includes pain assessment, the patient undergoes a physical examination (clinical fellow, physician and physiotherapist) that includes a detailed neurological exam with particular attention to changes in sensations. The clinicians report the presence and distribution of hyperalgesia, allodynia, Hypoesthesia, and any other specific finding relevant changes on the standard neurological exam.

Patient and parent perspectives on psychosocial outcomes were collected through various assessment tools. Patients completed the Functional Disability Inventory (FDI) questionnaire is completed by patients, in which the total score is summed to detect different levels of disability [70], Revised Child Anxiety and Depression Scale (RCADS) questionnaire[71], and Pittsburgh Sleep Quality Index (PSQI) completed by patients to assess sleep quality[72].

The RCADS includes subscales for separation anxiety disorder, generalized anxiety disorder, panic disorder, social phobia, obsessive-compulsive disorder, and low mood (major depressive disorder). The Douleur Neuropathique 4 (DN4) questionnaire[73] to identify if pain had a neuropathic component was completed by both patients and their physicians. Patients also completed the Pain Catastrophizing Scale for Children (PCS-C)[74] to assess negative thoughts or feelings during pain experiences.

Parents contributed to the assessment through the completion of the Impact on Family Scale (IOFS), which measures the burden on families in the pediatric care context.A higher score indicates a greater negative impact on social and familial systems due to a chronic childhood illness. Additionally, parents completed the Pain Catastrophizing Scale for Parents (PCS-P) to evaluate their negative thoughts or feelings while their child is in pain

QST/CPM evaluation protocol

Since 2016, as part of the standard evaluation in the Edwards Family Interdisciplinary Center for Complex Pain, a comprehensive QST protocol is used to assess mechanisms of pain as well; a CPM protocol is also used to evaluate the endogenous descending pain inhibitory control of patients before the initiation of a treatment. The evaluation take place before the initial evaluation at the Center for complex Pain and is used to personalize the pharmacological treatment.

The full evaluation is termed QST/CPM evaluation but may be abbreviated to "QST" only for short in the tables/figures. The QST protocol was based on previous comprehensive studies [36] and includes assessments of mechanical detection threshold, vibration detection threshold, dynamic mechanical allodynia, pain pressure threshold, heat pain threshold, and mechanical pain summation. Results were evaluated and compared to reference values from the literature when available, with respect to protocol and test sites. The endogenous descending pain inhibitory pathway is evaluated using a CPM paradigm of tonic thermal stimulations [31].

The pain pressure threshold (PPT) is measured using a pressure algometer (Jtech). If the PPT is significantly below the lower bound of the 95% CI of the reference values at a control site [36] or

significantly lower (difference of at least 30%) compared to a same-subject's contralateral site in the instance of unilateral pain, deep-tissue pressure pain sensitivity is reported. A high pain sensitivity indicates enhanced mechanical sensitivity.[36]

The presence of dynamic mechanical allodynia is reported using a standardized brush (Somedic SENSELab – Brush-05). Allodynia is defined by the International Association on the Study of Pain IASP as "pain due to a stimulus that does not normally provoke pain" [75]. On a mechanistic level, allodynia is proposed as a lack of inhibition of excitatory crosstalk between sensory modalities (touch and pain) by interneurons in the spinal dorsal horn. In other words, there is a failure to separate the input from Aβ-fibers (touch) and nociceptive-specific neurons [76]

The presence of temporal summation is evaluated thermally. Thermal temporal summation is measured during a constant heat stimulus over a period of 2 minutes at a pre-determined temperature self-reported to cause ≥5/10 pain and interpreted as the difference in pain intensity between the numerical rating score at 60s and at 120s of the test. For temporal summation tests, a significant increase of >2/10 in pain rating is considered a positive result based on IMMPACT recommendations for clinically important differences in pain intensity[77] .

All thermal testing is performed using the Medoc Qsense apparatus and a computerized visual analogue scale (CoVAS). Mechanistically, temporal summation, also called wind-up, may reflect an increase in the excitatory postsynaptic potentials in response to repeated C-fiber stimulation [24,34]. Studies suggest that temporal summation is stronger in individuals with primary chronic pain (including chronic widespread pain) compared to normal controls [24,34].

Mechanical detection threshold is investigated using Von Frey Filaments and compared to reference values[41] . This measure is used as additional information regarding the integrity of the Aβ-fibers as complimentary information to suggest the possibility of deafferentation pain.

CPM:

The endogenous descending pain inhibitory pathway control is quantitatively evaluated using the conditioned pain modulation (CPM) paradigm developed by Marchand and colleagues [33] and simplified to be used in younger patients.

The paradigm consists in the difference in continuous pain rating during two tonic thermal heat pain stimulations on the right forearm separated by a cold-water conditioning stimulus consisting of a left forearm immersion of 2 minutes at 12°C. The thermal heat component is performed using the Medoc Qsense and a computerized visual analogue scale (CoVAS). The two-minute painful thermal stimulation temperature is predetermined as the temperature at which the patient experienced a self-reported pain of ≥5/10. The efficacy of the CPM test is categorized as efficient, suboptimal or inefficient. An efficient CPM score corresponded to a pain reduction of 30% or more, whereas an inefficient CPM score corresponded to a pain reduction of less than 10%. [33,78]. The numerical value is also reported. The suboptimal CPM category is included as a conservative buffer to allow for a margin of error of 20% [23, 34], an inefficient CPM result is suggested to reflect an incapacity to trigger a proper endogenous pain inhibition [32]. (Fig.4)

Figure 4: showing the QST /CPM tests involved in the Assessment .PPT test presents the pressure test done with Algometer at pain site and control site , CPM1 presents the 2 min thermode test before cold bath , CPM2 presents the cold bath where arm is inserted up to elbow for 2 min , CPM3 represents the 2 min thermode test after cold bath

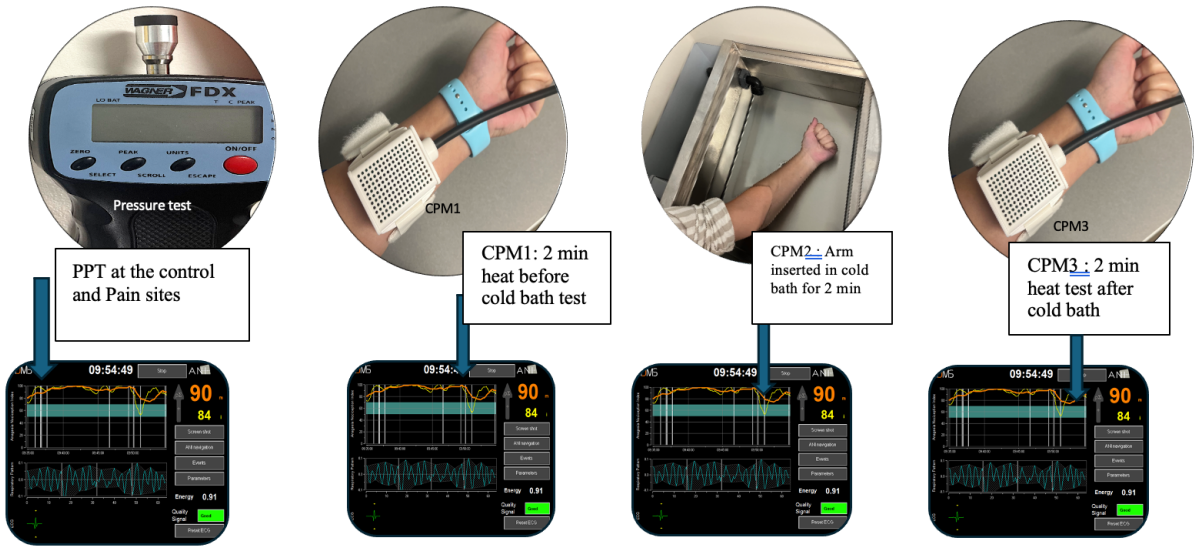

FIGURE 3: TESTS USED DURING QST CPM AND CORRESPONDING EVENT ON ANALGESIA NOCICEPTION INDEX

ANI

The ANI device and the pads required to obtain ANI values for this study has been made available to the department of anesthesia and the Edwards Family Interdisciplinary Centre for Complex Pain for the purpose of this research. As part of the study, ANI values were recorded at different test points. ANI values were collected at the appointment for the QST/CPM protocol. These ANI values will the pre-treatment ANI values and this were correlated with the NRS scores at the initial evaluation. The pre-treatment ANI values were also correlated with the impact of chronic pain conditions on physical function, psychological function and social function (PSQI, FDI, and RCADS).

TEST POINTS	TEST	DURATION OF TEST	ANI
QST TESTS			Measured at the start of each test (ANI i) and end of each Test. We then tabulated the ANI max and min during each test and calculated Delta ANI Ani max – Ani min= Delta Ani per test (Fig. 6)
T1	PPT-C: Pressure pain threshold at control site	1-2 min	
T2	PPT-P: Pressure pain threshold at pain site	1-2 min	
CPM TEST			
T3	CPM1: Pre-conditioning Heat test / Temporal summation of pain	2 min	
T4	CPM2: Cold bath	2 min	
T5	CPM3: Post conditioning heat test	2min	

Table 1 showing the test points and their corresponding tests, durations and the ANI calculation

.

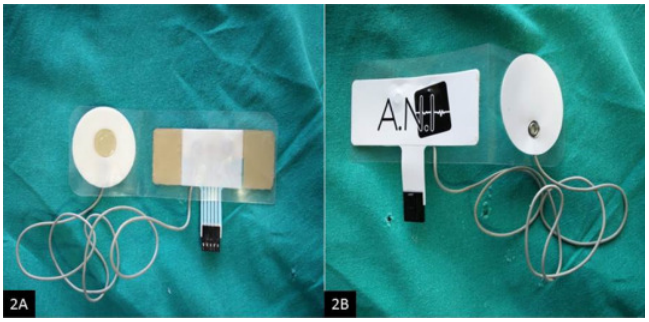

Figure 5:ANI sensor. 2A shows the patient side and 2B shows the free surface[79]

.

Figure 6: THE display screen of the ANI monitor, showing the events identified for each test, to measure delta ANI during the tests

Study population

All patients referred to the Edwards Family Interdisciplinary Center for Complex Pain of the Montreal Children's Hospital Potential patients were invited to participate. At the appointment for the QST, patient was approached by myself to participate in the study and to confirm eligibility criteria prior to receiving signed consent.

Inclusion criteria

Patients must fulfill the following criteria:

- Be between 9-17 years old
- Experiencing chronic pain defined by: persistent or recurrent pain at least once a week for at least three months in their electronic medical charts or by reference of the patient's physician.

Exclusion criteria

- Taking medications known to affect the sympathetic or parasympathetic nervous systems such as cholinomimetics (e.g., pilocarpine), anticholinergics (e.g., ipratropium), sympathomimetic (e.g., salbutamol), and adrenergic antagonists (e.g., propranolol).

- Cardiac or neurological conditions will also be excluded, including patients with arrhythmias, heart block, postural orthostatic tachycardia syndrome, Guillain-Barre syndrome, or spinal cord injury
- Cancer diagnosis
- Conditions that may interfere with the ability to understand instructions or complete measures including: cognitive, or developmental delay, as well as patients who do not speak English or French
- Not candidate for QST/CPM testing (patients were excluded from the test if they were younger than 8 years of age, had difficulty in understanding the tests due to underlying conditions, at time of testing had an injury in upper limbs that prevents the testing e.g. cast)

The evaluation includes the following:

Questionnaires: 45 minutes, through the Atlas Platform or using a PDF format. Were be done by patients at home as part of the usual center protocol.

QST/CPM evaluation: 40 minutes at the Center for Innovative Medicine (CIM)

-ANI: At the CIM on the same day of the QST/CPM

Description of data being retrieved

The current pain was reported using the numerical rating scale (NRS) ranging from 0 (no pain at all) to 10 (worst pain imaginable).

Pittsburgh Sleep Quality Index [72] (PSQI) consists of 19 self-rated items under 7 different components. Each question is rated from "very good" which is a score of 0 to "very bad" which a score of 3 is. A score of 0 indicates no difficulty and 21 indicates severe difficulty in all areas.

Functional Disability Inventory [15] (FDI) is a series of 15 questions that the patient self-rates. The score for each question ranges from 0 (no trouble with the activity) to 4 (impossible to do the activity).

Revised Child Anxiety and Depression Scale [71,73] (RCADS) is a 47 item self-report questionnaire with subscales for separation anxiety disorder, social phobia, generalized anxiety disorder, panic disorder, obsessive compulsive disorder and major depressive disorder. Items are on a scale from 0 ("never") to 4 ("always").

Douleur Neuropathique 4 (DN4)[73] questionnaire to assess for the presence of neuropathic pain with a series of ten questions. Scores of equal to or greater than 4 indicate that the pain experienced by the patient is likely neuropathic.

Physical examination (clinical fellow, physician and physiotherapist) that includes a detailed neurological exam with particular attention to changes in sensations. The clinicians report the

presence and distribution of hyperalgesia, allodynia, dysesthesia, loss of sensation, and any other specific finding relevant changes on the standard neurological exam.

ANI scores range from 0-100. This score indicates heart-rate variability and provides an assessment of parasympathetic tone and nociception. A high score indicates low nociception and a low score indicates high nociception.

QST/CPM as described above to measure the mechanical detection threshold, vibration detection threshold, dynamic mechanical allodynia, pain pressure threshold, heat pain threshold, and mechanical pain summation. Depending on the results, patients were categorized as having or not the presence of peripheral sensitization or central sensitization. The efficacy of the CPM test is categorized as efficient, suboptimal or inefficient.

The purpose was assess the variations in the ANI across different phases of the QST and CPM sessions. The aim was to determine how the ANI fluctuates in response to specific pain stimuli and pressure tests.

During the QST & CPM sessions, the changes in delta ANI were evaluated across various tests each test was stamped on the ANI machine as an event. The events were stamped when they started and when they ended the maximum ANI at each test and minimum ANI were recorded during the event /test. Delta ANI was calculated as the difference between ANI max and ANI min in each event.

Data for QST/CPM as well as ANI values were collected in redcap. The data of the questionnaires was retrieved from the Atlas/telehealth platform or the patient chart (OACIS)

Data Analysis

Descriptive statistics

Data of patients including age, gender, type of pain condition and parameters recorded at physical examination (weight, height, and vital parameters) were presented as recorded on the patient chart. Categorical variables were presented as a frequency distribution.

We primarily used Pearson's correlation coefficient to investigate the relationship between various pain assessment measures and the Autonomic Nervous Index (ANI) at rest for values . The p-value associated with each correlation coefficient was also calculated to determine the statistical significance of the observed correlations. The datasets were cleaned to remove any or infinite values to ensure the accuracy of the statistical tests.

Normality tests were first conducted to determine the distribution of each data set. To analyze the variables over tests (T1 vs T2), categorical variables, such as Global Impression of Change, Reduction in Pain Intensity, Functional Disability Inventory, and Quantitative Sensory Testing (QST/CPM), were evaluated using the Chi-square test or Fisher's exact test. These tests are suitable for identifying significant differences in categorical data between baseline.

On the other hand, continuous variables, including the Numerical Rating Scale (NRS), Revised Child Anxiety and Depression Scale, Pittsburgh Sleep Quality Index (PSQI), Role Functioning

(number of school days missed), Douleur Neuropathique 4 (DN4), and ANI scores (0-100), were analyzed using the t-test or Mann-Whitney/Wilcoxon test, depending on data normality. These tests allow for mean comparisons and help analyze differences in pain intensity, emotional symptoms, sleep quality, functionality, and the presence of neuropathic pain at various treatment stages.

RESULTS:

Participants

We conducted the recruitment for this study from May 2022 to September 2023. A total of 120 potential patients were approached, of whom 117 consented to participate. Ultimately, 110 patients were included in our analysis. The details of the recruitment process are illustrated in the PRIMSA Flow Chart below. Among the 110 patients included in the study, 86% were female, with a mean age of 14 years (SD = 2.4), ranging from 8 to 17 years. These patients were referred to the Center for complex pain (CCP) with a diagnosis of chronic pain conditions.

Notably, seven patients were unable to complete the testing; specifically, two patients reported that the tests were too painful, while five patients missed their testing appointments. All participants had experienced pain for more than three months. The distribution of pain presentations among the patients indicated that 20% were referred for headaches, 15% reported pain in the upper limbs, and 30% in the lower limbs. Additionally, 20% of the patients experienced back pain, while 15% reported abdominal pain.

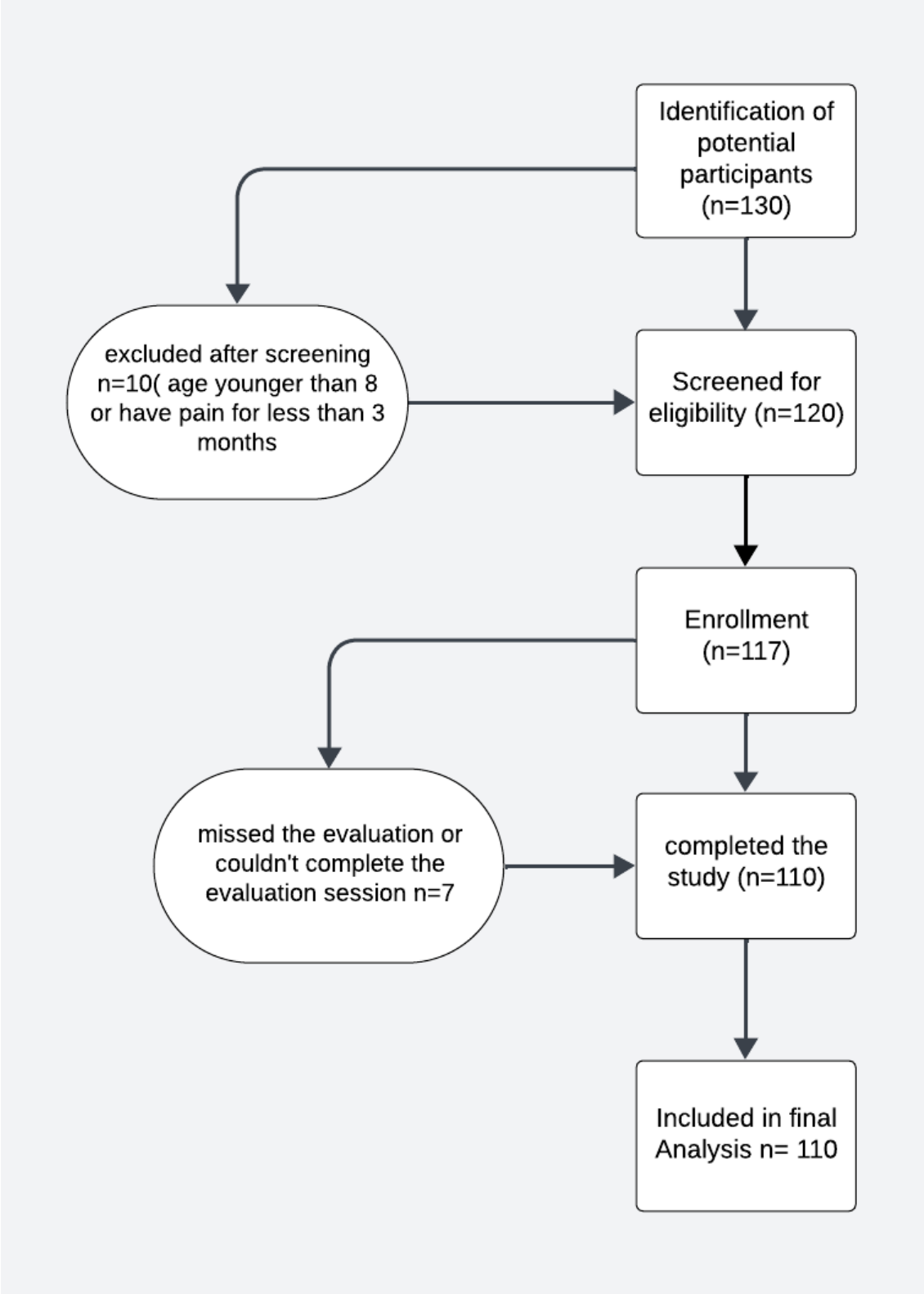

Figure 7: Flow Chart showing the number of patients during the study.

Average ANI distribution in the population at rest:

We analyzed the distribution of Analgesia Nociception Index (ANI) values at rest, which revealed varying values of autonomic nervous system activity among the patients.

Fifty six patients (50.9%) had ANI values > 85 .Thirty eight participants (34.5%)had ANI values between 85 and 70 (n=38), Fourteen patients (12.7%) had ANI values between 70 and 50 which may suggest moderate levels of nociceptive activation or stress. Only two patients presented ANI values below 50 indicating significant nociceptive activation. Notably, both were undergoing an acute inflammatory condition on the day of testing—one exhibited gastrointestinal symptom, and the other presented with flu-like symptoms.

Overall, the distribution is notably skewed towards higher ANI scores, with 94 out of 110 (85.4%) patients having ANI scores above 70, which is widely recognized in the literature as the threshold for adequate analgesia during stimulation. (see Figure 8,9).

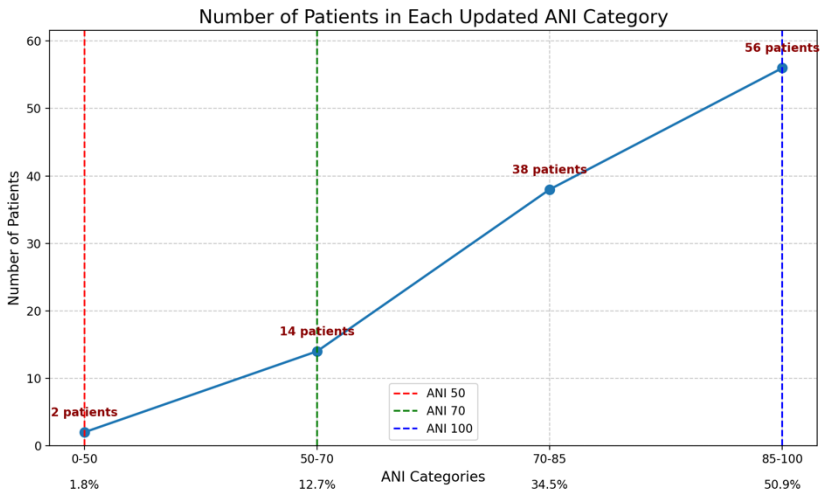

FIGURE 8: LINE GRAPH SHOWING NUMBER OF PATIENTS AT REST AND THEIR CORRESPONDING ANI MEAN VALUES

This distribution aligns with our earlier descriptive analysis, confirming that most patients in this dataset have relatively high ANI values at rest and that this population might not be best presented with the previously determined cut-off for the device in a surgical setting .(Figure 8,9)

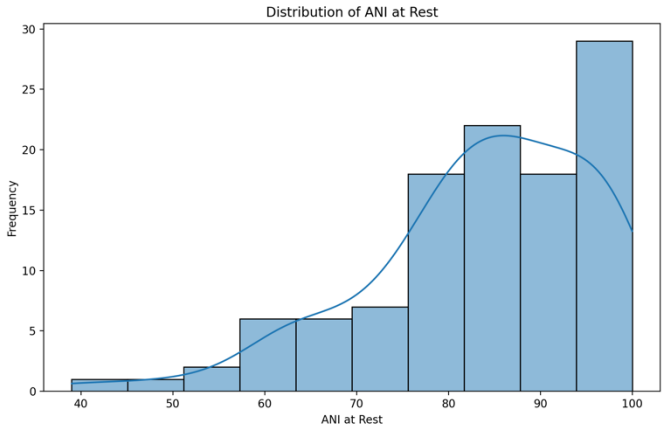

FIGURE 9: SHOWING THE DISTRIBUTION OF ANI AT REST

ANI And Numerical Rating scores (NRS):

We analyzed the pain intensity reported by patients using a numerical rating scale(NRS 0-10) and the corresponding average ANI values for each category ranges: 0-50, 50-70, 70-85, and 85-100

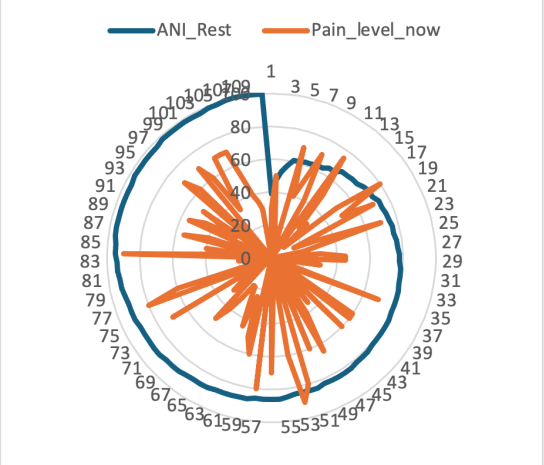

Figure 10: Showing average Pain levels measured using numerical rating scale (NRS) and their corresponding ANI values

In the 50-70 ANI group showing an average NRS of 3,5 ± 2,5 (n=14), and the 70-85 ANI group score of NRS 3,4 ± 2,9 (n=38). Patients in the highest ANI range (85-100), reported an average of 3,4 ± 2,7. The highest average pain intensity scores was found in the 0-50 ANI group (4,0 ± 1,4), though this group had the smallest sample size with only 2 patients.

We calculated the correlation between ANI values at rest and pain scores at rest. The Pearson correlation coefficient was -0.013 [95%CI 0.200 to 0.174. This correlation coefficient is very low, indicating that there is no meaningful relationship between the ANI values at rest and the pain intensity scores at rest in this sample (Figure 10)

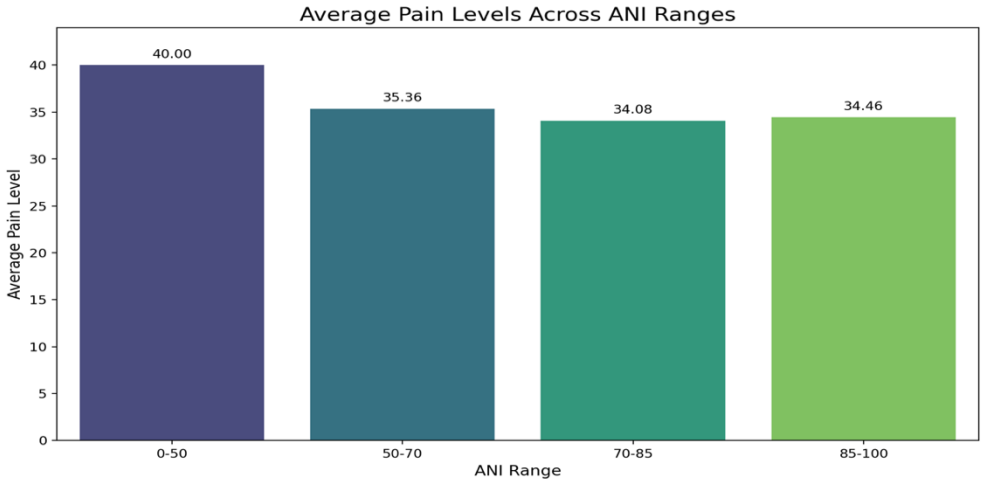

FIGURE 11: BAR GRAPH SHOWING AVERAGE ANI IN EACH CATEGORY AND CORRESPONDING AVERAGE PAIN LEVEL(NRS)

We observed that 53 patients (48%) had mean (ANI) scores at rest below 85 points, with an average score of 73.7 (SD = 10.1). During the initial four minutes of the session, these patients reported an average pain intensity, as measured by the Numeric Rating Scale (NRS), of 3.5 (SD = 1.014). (Figure 11)

In contrast, the 57(52%) patients exhibiting ANI values above 85 (mean = 93, SD = 4.76) demonstrated a mean NRS score of 3.3 (SD = 0.091). A t-test comparing pain intensity between the two groups yielded a statistic of 3.337 (p = 0.0016), suggesting a potentially meaningful threshold for ANI values around 80-85 within this population.

. The t-test results support a significant difference in pain levels between the two groups (t = 3.337, p = 0.0016), highlighting a potentially cut-off around the average ANI value of 80-85 in this population (see Figure 12).

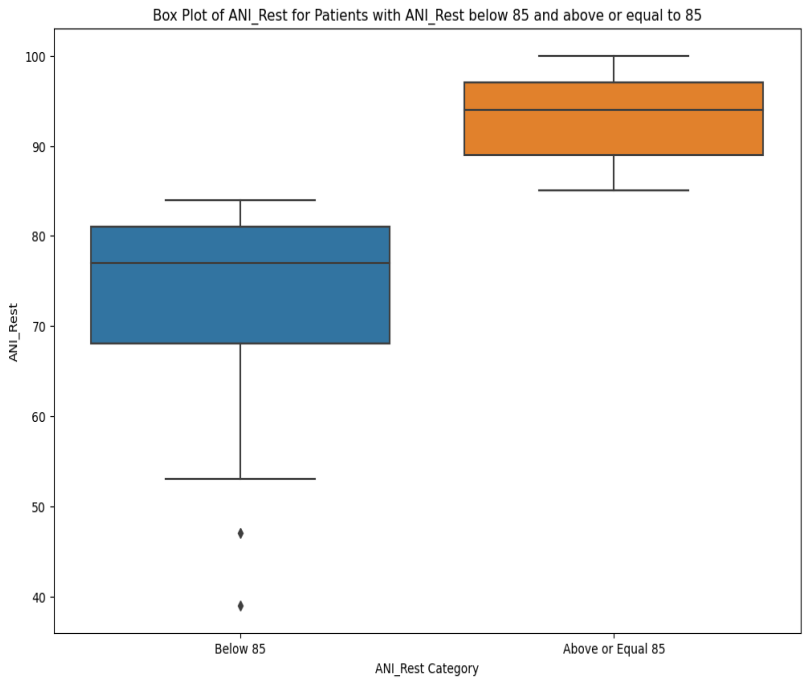

FIGURE 12 BOX PLOT COMPARING ANI LEVELS AT REST AND AVERAGE IN LOW AND HIGH ANI GROUPS BASED ON THEIR AVERAGE ANI AT REST.

Comparison of Mean Maximum ANI Values Across Different Tests

Because we were not able to find a correlation between pain intensity and the ANI values, we hypothesized that ANI may sensor the nociceptive response of non-harmful stimulus applied during the QST

We compared the mean maximum Analgesia Nociception Index (ANI) values obtained from various tests utilizing controlled, non-harmful, and non-surgical stimuli. We decided to conducted a comparison of the mean maximum Analgesia Nociception Index (ANI) values obtained during various tests that applied controlled, non-harmful, and non-surgical stimuli. The evaluation session involved recording each event as monitored by the ANI machine during the quantitative sensory testing (QST) and conditioning pain modulation (CPM) tests. We analysed mean ANI values during five distinct tests . (see Table 2)

TABLE 2 SHOWS THE TESTS DONE DURING THE QST CPM SESSION AND THEIR DURATIONS

TEST		DURATION
T1	PPT-C: Pressure pain threshold at control site	1-2 min
T2	PPT-P: Pressure pain threshold at pain site	1-2 min
	CPM TEST	
T3	CPM1: Pre-conditioning Heat test / Temporal summation of pain	2 min
T4	CPM2: Cold bath	2 min
T5	CPM3: Post conditioning heat test	2min

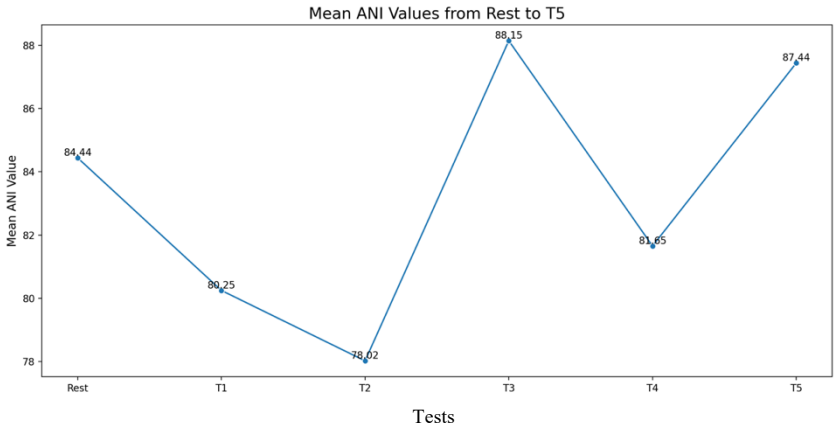

FIGURE 13: LINE GRAPH SHOWING CHANGES IN AVERAGE ANI MEASURED AT EACH TEST

Mean ANI Values Analysis by Group

We compared the changes of any values during non-harmful stimulus in patients with ANI at rest scores below 85 and those with ANI scores at rest equal to or above 85. Our observations indicate that the group with ANI scores below 85 exhibits lower and more stable mean ANI values over time. In contrast, the group with ANI scores equal to or above 85 demonstrates greater fluctuations and consistently higher values that exceed the reference line of 85. This reference line, highlighted in red (Figure 14), underscores the threshold of 85 as a potential new cutoff during assessments involving non-surgical stimuli .

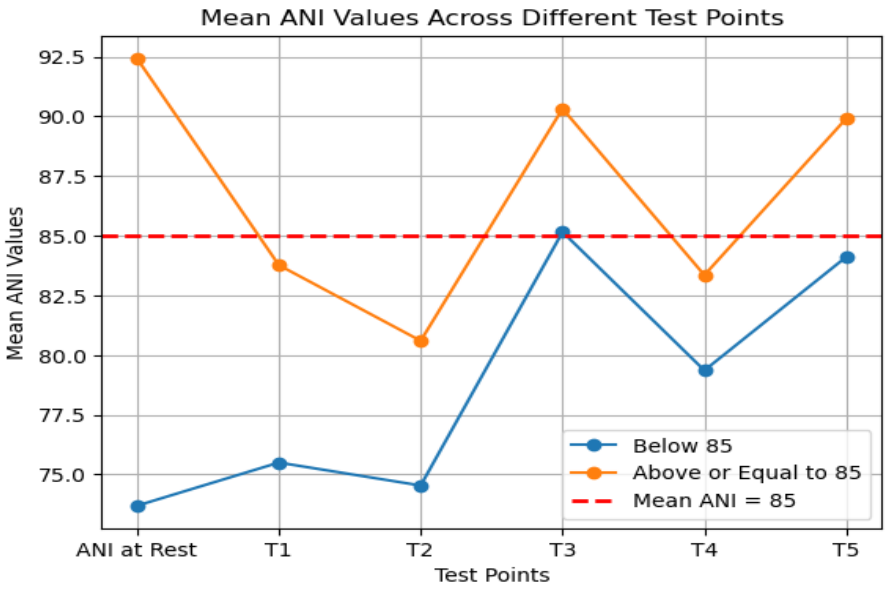

FIGURE 14: SHOWING THE CHANGES IN ANI MEAN VALUES WITH TIME DURING DIFFERENT TESTS DONE IN THE QST & CPM SESSION.

.

Secondly, we performed a t-test to compare the means between two groups (see Table 2). The results indicated a significant difference between the groups with different tests (PPT pain site, PPT control site , CPM1 , CPM2,CPM3) both of which exhibited a medium to large effect size (Cohen's d > 0.5).

Analgesia Nociception Index and Pain Phenotypes

We analyzed the distribution of pain phenotypes based on quantitative sensory testing (QST) within our patient population. We analyzed the ANI response in patients with Peripheral, central and inefficient CPM. Peripheral sensitization emerged as the most prevalent phenotype, affecting 87 individuals. In comparison, central sensitization was observed in 45 patients, while inefficient conditioned pain modulation (CPM) was present in 46 patients.

Importantly, we noted significant overlap among these phenotypes: 40 patients experienced both peripheral and central sensitization, and 20 patients exhibited all three conditions simultaneously.

The average ANI values remained relatively consistent across the different phenotypes, with patients experiencing peripheral sensitization showing an average ANI of 84.25, those with central sensitization having an average ANI of 84.04, and patients with inefficient CPM reporting an average ANI of 82.41.

Analysis of ANI at Rest and Peripheral Sensitization

We conducted a linear regression analysis to assess the relationship between 'ANI at rest' and 'Peripheral Sensitization' in a cohort of 106 patients. The aim was to determine whether resting ANI levels significantly associate with peripheral sensitization in this population.

The analysis yielded an R-squared value of 0.009, indicating that 'ANI at rest' can't explain variability in peripheral sensitization (see Table 2). Furthermore, the coefficient associated with 'ANI at rest' was found to be statistically insignificant, with a p-value of 0.325. This finding suggests that no significant relationship exists between these two variables within the studied sample (see Figure 15). Overall, these results indicate that resting ANI levels may not be a reliable predictor of peripheral sensitization in this patient group.

Table 2 :mean differences between group 1 (average ANI below 85) and group 2(equal or higher than 85) in each time point.					
	Mean Group 1 (ANIm > 85 at rest) n=33	Mean Group 2 (ANIm <85 or =85) n=26	Mean Difference	P-VAlue	Cohen d
ANi_rest	92.5	73.77	18.78	0	2.632
ANIm Pressure test Control	83.39	75.85	7.54	0.034	0.586
ANIm Pressure test at pain site	80.33	74.19	6.14	0.085	0.466
ANIm CPM1(2 min heat test Before Bath)	90.42	85.23	5.19	0.103	0.455
ANIm CPM2(2 min cold bath)	83.42	79.42	4	0.247	0.306
ANIm CPM3 (2 min heat after cold bath)	90.15	83.42	6.73	0.021	0.637

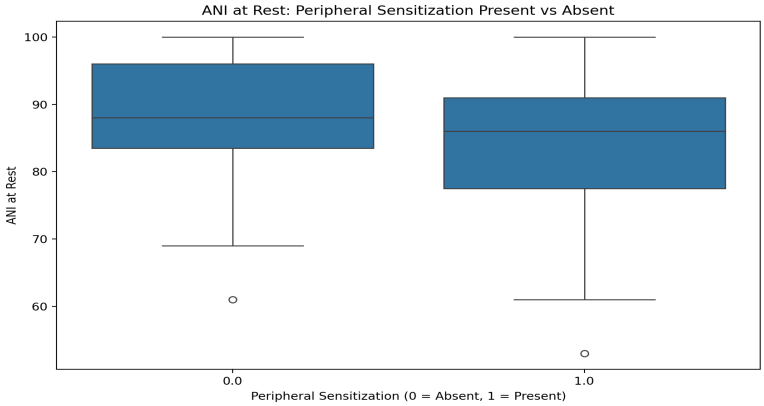

FIGURE 15: BOX PLOT SHOWING AVERAGE ANI AT REST IN PATIENTS WITH OR WITHOUT PERIPHERAL SENSITIZATION

Analysis of ANI at Rest in Patients with Central Sensitization

We conducted a linear regression analysis to evaluate the relationship between 'ANI at rest' and central sensitization (see Table 3). This analysis resulted in an R-squared value of 0.001, indicating that 'ANI at rest' can't explain variability in central sensitization

Table 3. Descriptive Statistics for ANI at Rest by Presence or Absence of Central Sensitization (CS)

Statistic	Central Sensitization Present	Central Sensitization Absent
Count	30.0	31.0
Mean	80.03	85.1
Std Dev	14.59	10.52
Min	39.0	62.0
25th Percentile	75.25	77.5
Median (50th Percentile)	82.5	86.0
75th Percentile	89.75	95.0
Max	99.0	100.0

Additionally, the p-value for the coefficient associated with 'ANI at rest' was 0.788, suggesting no statistically significant relationship exists between these two variables (see Figure 16). Interestingly, we observed that higher ANI at rest values were associated with lower values in Temporal Summation of Pain (TSP), with a correlation coefficient of -0.357. TSP was further analyzed in two groups: those with ANI scores above 85 and those with ANI scores below 85 (see Figure 17). A t-test yielded a statistic of -2.519 with a p-value of 0.015, indicating a statistically significant difference in ANI at rest between the two groups. These findings suggest that while ANI at rest may not be significantly associated with central sensitization overall, it does correlate with TSP, highlighting potential distinctions in pain perception among different ANI classifications in this population. We observed that higher ANI at rest values were associated with lower values

in Temporal Summation of Pain (TSP = -0.357). TSP was analyzed in two groups (group with ANI above 85 and group with ANI below 85) (**Figure 17),** T-test statistic of -2.519 with a p-value of 0.015, indicating that the difference in ANI at rest between the two groups is statistically significant .

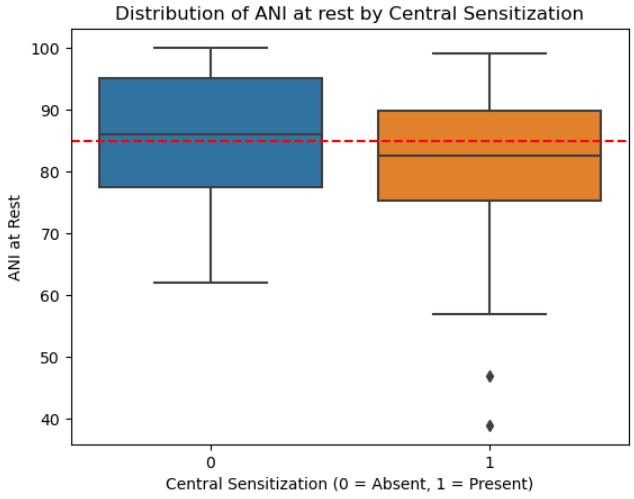

FIGURE 16 REPRESENTS THE DISTRIBUTION OF PATIENTS BY CENTRAL SENSITIZATION

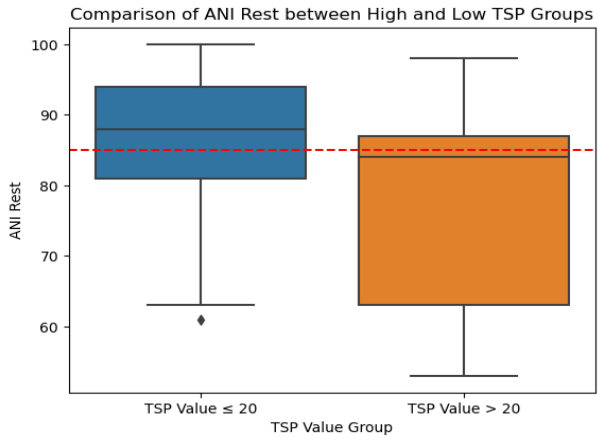

FIGURE 17. GRAPH SHOWS THE PATIENTS TEMPORAL SUMMATION OF PAIN (TSP) IN BOTH LOW AND HIGH ANI GROUPS

Distribution of ANI in patients with inefficient Conditional Pain Modulation.

The logistic regression model indicated a weak correlation between ANI at rest and inefficient conditioned pain modulation (CPM), with a coefficient close to zero. The R-squared value of the model was 0.0062, suggesting that ANI at rest accounts for only 0.62% of the variability in CPM inefficiency among the evaluated patients. The p-value for the coefficient was 0.422, further indicating that no significant correlation exists between these variables.

These findings imply that ANI at rest may not be used as a reliable tool for predicting CPM inefficiency in this population. (see Figure 18 & table 4).

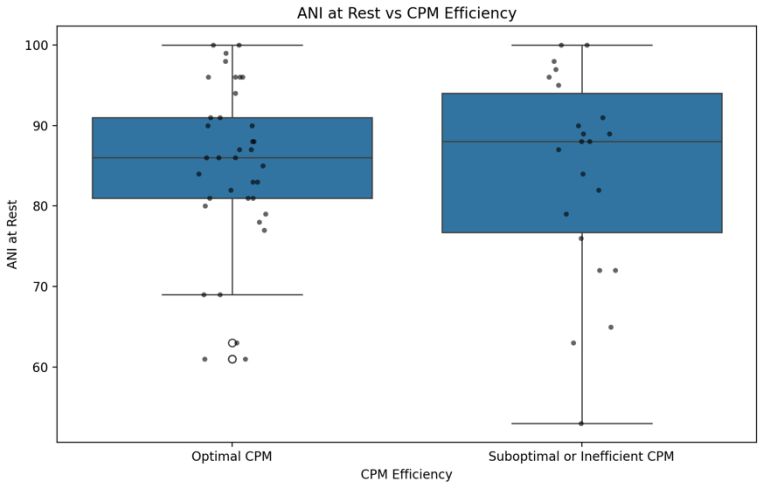

Figure 18: showing distribution of ANI mean at rest in patients according to CPM efficiency

.

Statistic	Optimal CPM	Suboptimal or Inefficient CPM
Count	37.00	22.00
Mean	84.92	84.27
Standard Deviation	10.43	12.84
Min	61.00	53.00
25%	81.00	76.75
50%	86.00	88.00
75%	91.00	94.00
Max	100.00	100.00

Title: Descriptive Analysis for ANI at Rest in Optimal and Suboptimal/Inefficient CPM

Table 4 showing the descriptive analysis for patients with optimal CPM and patients with inefficient CPM

Assessment of Variations in ANI During QST and CPM Sessions

The purpose of our analysis was to assess variations in the analgesia Nociception Index (ANI) across different phases of the quantitative sensory testing (QST) and conditioned pain modulation (CPM) sessions. Specifically, we aimed to determine how the ANI fluctuates in response to specific pain stimuli and pressure tests, which can yield valuable insights into the body's pain modulation mechanisms.

During the QST and CPM sessions, we evaluated changes in delta ANI across various tests, with each test marked as an event on the ANI machine. The events were monitored from their initiation to completion, recording both the maximum and minimum ANI values during each test. Delta ANI was subsequently calculated as the difference between the maximum and minimum ANI for each event.

-Delta CPM1 refers to the change in ANI during the pre-test phase of the CPM, specifically during a two-minute heat test preceding cold bath immersion. This phase was designed to measure the body's initial response to the heat stimulus, yielding an average delta ANI of 22.38 with a standard deviation of 9.833 (N=45).

Delta CPM2 captures the change in ANI during the cold bath immersion test, the second phase of the CPM testing module, intended to evaluate the body's response to a cold stimulus. The mean delta ANI for this phase was 19.13, with a standard deviation of 10.491 (N=45).

Delta CPM3 represents the change in ANI during the two-minute heat test following cold bath immersion, which aimed to assess the body's recovery and adaptation after exposure to the cold stimulus. This phase exhibited the largest mean change in ANI, at 29.27 with a standard deviation of 10.4 (N=45).

In addition to the CPM tests, we evaluated Delta ANI PPT P at pain site, which signifies the Pressure Pain Threshold (PPT) test at the pain site using an algometer. This test was designed to measure the body's sensitivity to pressure at a known pain site, yielding an average delta ANI of 5.16 with a standard deviation of 3.9.

Delta PPTC denotes the Pressure Pain Threshold test at a control site, serving as a comparison to assess the body's response to pressure at a non-painful site. The mean delta ANI for this

control test was recorded at 7.6, with a standard deviation of 0.499 (N=45) (see Figures 19 and 20).

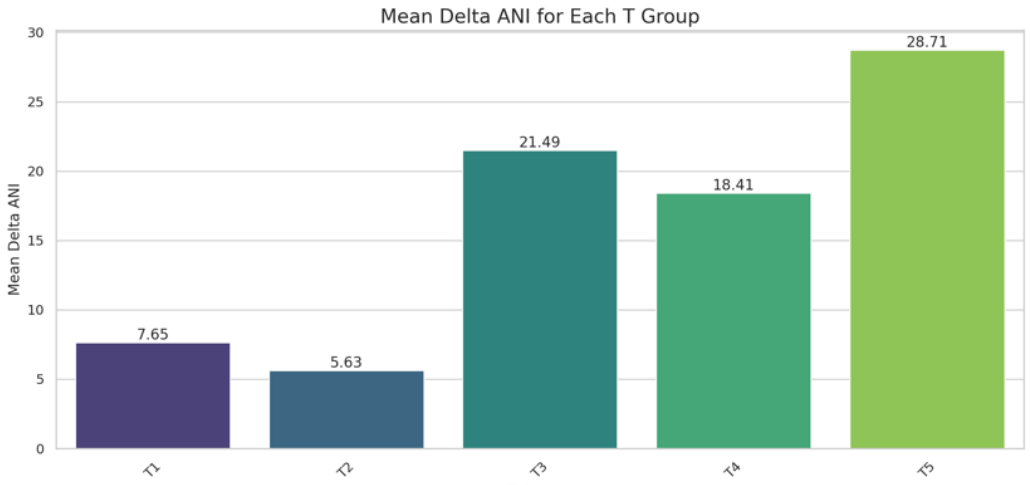

Figure 19: Delta ANI for Patients During QST and CPM Evaluation

Figure 19 illustrates the Delta ANI values for patients across the various tests performed during the QST and CPM evaluation. Each test is designated as follows:

T1 represents the Pressure Pain Threshold (PPT) test conducted at the control site.
-T2 denotes the PPT test executed at the pain site.
- T3 corresponds to the CPM1 test, which consists of a two-minute thermode test.
- T4 represents the cold bath immersion test.
- T5 signifies the two-minute thermode test conducted following the cold bath.

.

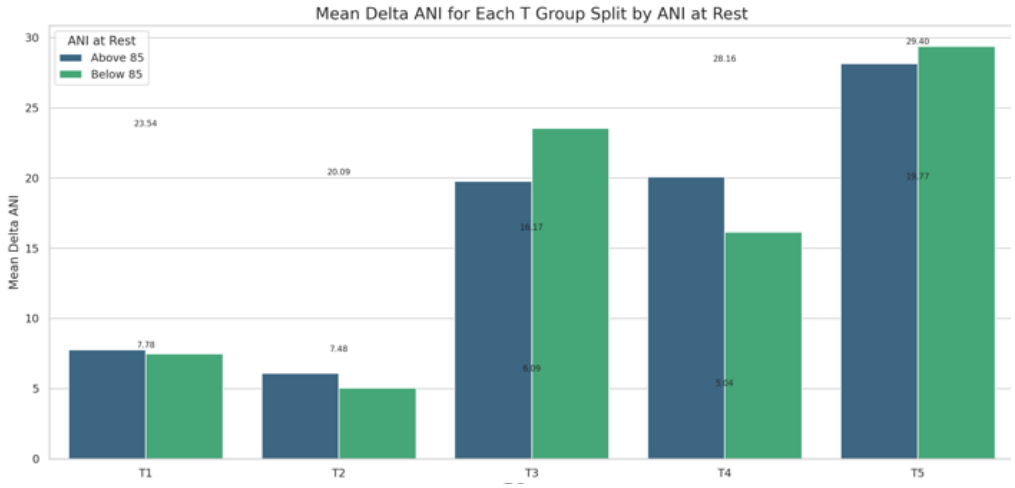

Figure 20: presents the delta ANI values for each test conducted during the session, categorized into two groups based on their ANI averages. The low ANI group, defined by average scores lower than 85, is represented by light green bars, while the high ANI group, with average scores equal to or above 85, is depicted with dark green bars.

.

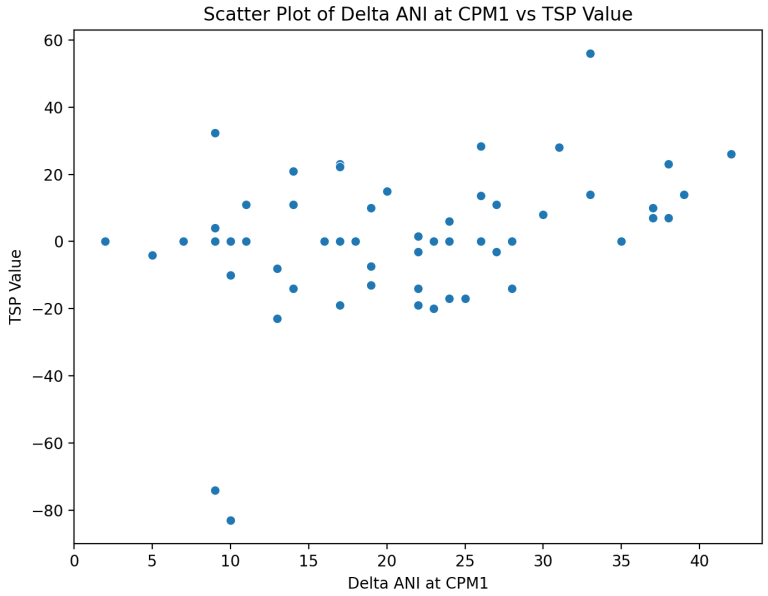

Figure 21. scatter plot showing the moderate positive correlation between Delta ANI during the CPM1 test and Temporal summation of pain value (TSP).

Based on the analysis of Delta ANI at CPM1 and the Temporal Summation of Pain (TSP) values, we observe a moderate positive correlation between these two variables (see Figure 21), with a correlation coefficient of approximately 0.373. This relationship indicates that as Delta ANI at CPM1 increases, there is a tendency for TSP values to also increase, suggesting some level of association, albeit not particularly strong.

The scatter plot visually reinforces this moderate positive trend, illustrating a general upward slope among the data points, although accompanied by considerable scatter. This correlation implies that patients exhibiting higher Delta ANI values during the Conditioned Pain Modulation (CPM) test at the first time point are likely to have elevated TSP values. However, the moderate strength of this correlation indicates that other factors are likely influencing TSP values, suggesting that the relationship is not deterministic.

ANI distribution and patient reported Questionnaires

We assessed the distribution of a positive psychosocial phenotype, defined by a positive history of psychosocial events or clinically significant scores on the Revised Child Anxiety and Depression Scale (RCADS) for conditions such as anxiety, depression, and PTSD, among all patients tested. The statistical analysis revealed a significant difference between the two groups of positive and Negative psychosocial phenotype, with patients exhibiting a positive psychosocial phenotype demonstrating lower mean and median ANI values (median = 81, mean = 79, SD = 12.7, n = 60) compared to those without a psychosocial phenotype (median = 91, mean = 89, SD = 9.4, n = 47).

A t-test produced a statistic of -4.5973 with a p-value of 0.0000, indicating a highly significant difference between the groups of positive Psychosocial phenotype and negative psychosocial phenotype. The effect size, as measured by Cohen's d, was -0.9111, signifying a large effect size. These statistical findings further emphasize the significant differences in ANI at rest values between the 2 groups of psychosocial phenotypes, with the psychosocial phenotype group consistently exhibiting lower ANI values and greater variability compared to the group without a psychosocial phenotype (see Table 4).

These results underscore the potential influence of psychosocial factors on pain perception and modulation.

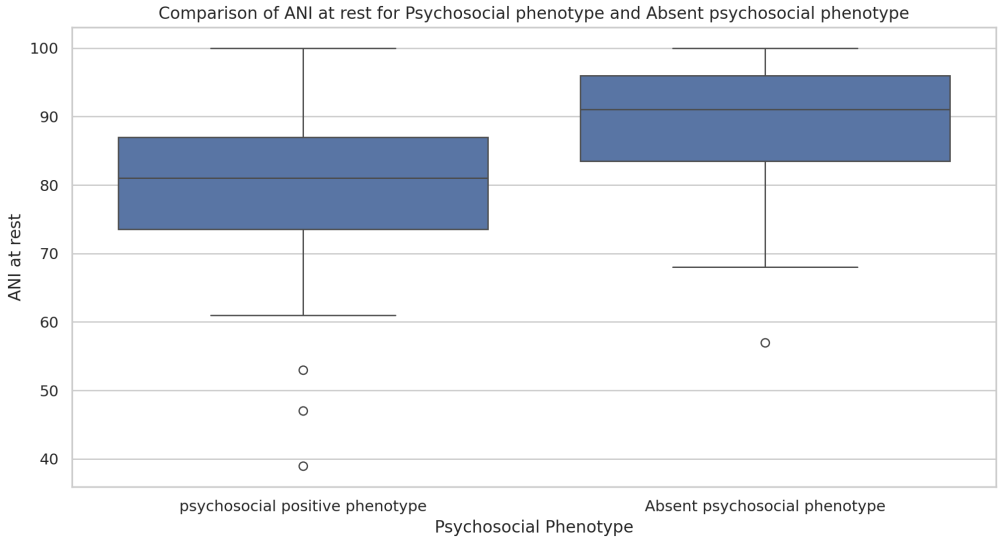

Figure 22 showing box plot of distribution of patients with Psychosocial positive phenotype (patients with active psychosocial component that is collected in initial visit either through questionnaires or patient reported during the initial evaluation) and their ANI at rest and the psychosocial negative phenotype with the ANI at rest .

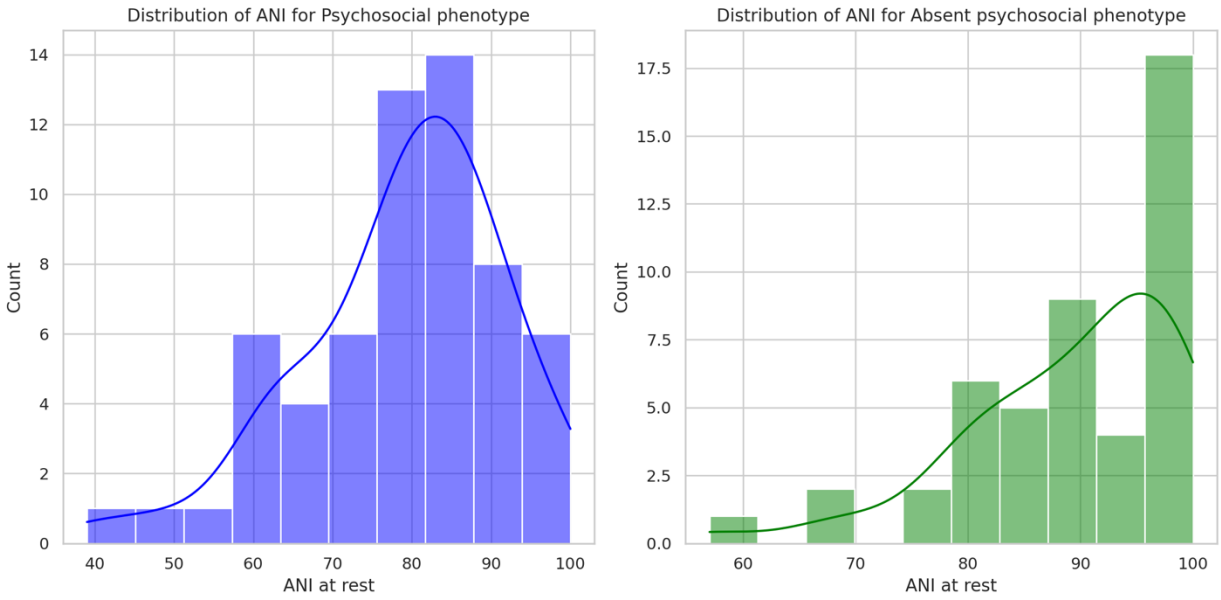

Figure 23 showing on the left side the distribution of ANI at rest in patients with psychosocial phenotype and on the right side the patients of absent psychosocial phenotype.

Analyzing the psychosocial positive phenotype in 2 groups both the low ANI group (<85) and the high ANI group (>86), comprising a total of 54 patients. The correlation between ANI at rest and positive psychosocial scores was found to be 0.394, with a p-value <0.001, indicating a statistically significant moderate positive correlation. (Figure 23)

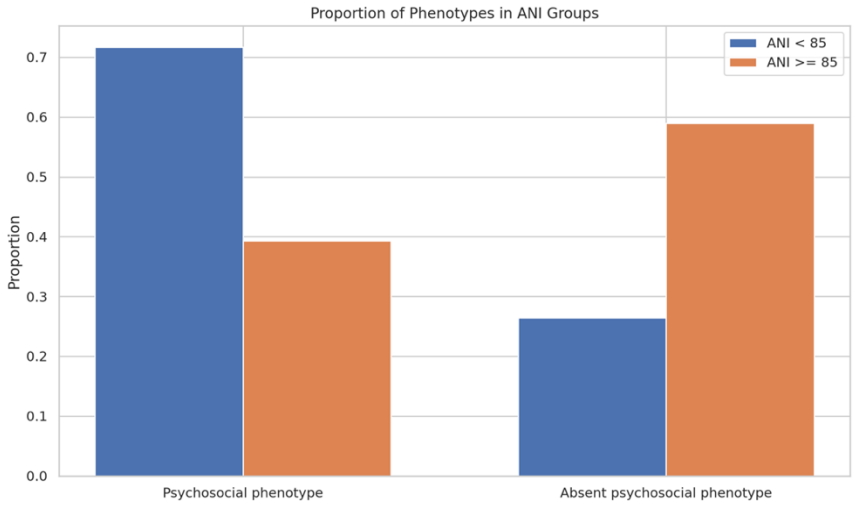

Figure 24, showing the distribution of Patients with positive psychosocial phenotype in both ANI groups (lower than 85 /Higher than 85).

In our further analysis of the psychosocial phenotype, we examined two groups based on ANI scores: the low ANI group (ANI < 85) and the high ANI group (ANI > 86), comprising a total of 54 patients. We found a correlation coefficient of 0.394 between ANI at rest and positive psychosocial scores, with a p-value of less than 0.001. This result indicates a statistically significant moderate positive correlation (see Figure 23).

This finding suggests that for patients with positive psychosocial history the ANI tends to be lower in those patients.

DISCUSSION

We aimed to explore the potential of the Analgesia Nociception Index (ANI) as an objective measure of pain intensity in pediatric patients with chronic pain conditions. We designed the study to address four key research questions regarding the use of ANI in this population.

First, we sought to assess the ANI values in patients with chronic pain conditions. Second, we aimed to examine the relationship between ANI values and self-reported pain intensity, as measured by the Numerical Rating Scale (NRS), in order to determine the correlation between ANI and more subjective measures of pain intensity. Third, we explored the variation of ANI values in response to controlled non-surgical stimuli during Quantitative Sensory Testing (QST) and Conditioned Pain Modulation (CPM) to evaluate ANI's responsiveness to changes in nociceptive input. Lastly, we examined whether psychosocial factors might modulate nociception by comparing ANI values across different psychosocial phenotypes in pediatric patients with chronic pain.

The results of this study offer valuable insights into the potential of the Analgesia Nociception Index (ANI) as an objective measure of pain in pediatric patients with chronic pain conditions. Notably, only half of the subjects had baseline ANI values that differed from the standard value of 85, while the remaining participants exhibited ANI values at rest between 85 and 100. Furthermore, nearly none of the patients demonstrated an ANI value below 50, suggesting possible alterations in nociceptive regulation within this population.

These findings suggest that while ANI may serve as a useful tool in monitoring nociceptive responses and predicting postoperative pain, its limitations must be acknowledged. The variability in ANI's responsiveness and the weak correlation with subjective pain assessments indicate that ANI may not reliably reflect the multifaceted nature of pain perception, particularly in the context of emotional and psychological influences. Therefore, integrating ANI with other assessment methods, such as subjective pain scales and psychosocial evaluations, could enhance our understanding of pain management strategies. Furthermore, investigating ANI in patients facing acute pain superimposed on chronic conditions may be essential for optimizing its clinical application and addressing the complexities of pain in diverse patient populations.

Our study extends the existing literature by focusing specifically on the use of ANI in chronic pain conditions in awake patients with chronic pain conditions, an area that remains less well-explored. While the use of ANI for monitoring acute pain in pediatric populations is well-documented, there is limited research exploring its effectiveness in chronic pain conditions, particularly in children [1,80,81] . Our results suggest that ANI may provide useful insights nociception, rather than into the pain experience given that the weak correlation with self-reported pain intensity in chronic pain cases.

Our findings underscore the necessity of incorporating complementary assessment tools alongside clinical judgment in the management of chronic pain in children. This study adds to the expanding literature on the use of the Analgesia Nociception Index (ANI) as a method for

evaluating pain in pediatric populations. A notable contribution of this research is the indication that ANI values may reflect altered nociceptive regulation in chronic pain patients, highlighting the need for further investigation to establish a specific cutoff that accurately represents this population. This insight has significant implications for the clinical management of pediatric chronic pain, suggesting that ANI can serve as an adjunctive tool to monitor nociceptive responses during treatment.

While the observed weak correlation between ANI and self-reported pain intensity implies that ANI should not fully supplant subjective pain measures, it may be particularly beneficial in circumstances where self-reporting is challenging, such as in non-verbal children or those with cognitive impairments. Moreover, the variability in ANI's responsiveness to controlled stimuli, such as Quantitative Sensory Testing (QST) and Conditioned Pain Modulation (CPM), suggests that ANI can effectively track shifts in nociception under specific conditions, potentially providing real-time feedback to clinicians. This dynamic monitoring capability could enhance the optimization of analgesic treatment, particularly in clinical environments where pain assessment is complex or where there is a need to balance nociceptive input with adequate analgesia, such as in postoperative care.

The observed variation in the Analgesia Nociception Index (ANI) across different psychosocial phenotypes indicates that factors such as anxiety and depression may influence nociceptive processing in patients with chronic pain. This understanding could facilitate a more

personalized approach to pain management by integrating both physiological and psychosocial considerations into treatment plans.

When examining ANI values in patients at rest, particularly those within the 50–70 range, the clinical utility appears to be limited. Notably, the only patients in this study with ANI values below 50 were those experiencing acute conditions superimposed on their chronic pain, which contributed to heightened pain intensity.

Additionally, ANI demonstrated sensitivity to nociceptive changes during controlled non-surgical stimuli, such as cold, heat, and pressure. This responsiveness suggests that ANI may play a role in identifying fluctuations in the nociceptive system among individuals with acute injuries or new inflammatory processes that enhance nociceptive pathways and pain perception. Furthermore, ANI could be utilized to monitor therapeutic changes, offering valuable feedback during follow-up for patients experiencing acute exacerbations of chronic pain.

Further research is warranted, particularly in clinical environments where various treatments are implemented for hospitalized patients. For instance, ANI may provide insights into the efficacy of regional anesthesia techniques employed by pain specialists to manage severe acute-on-chronic pain effectively.

Limitations

Despite the promising findings, several limitations must be acknowledged. A significant limitation of this study is the absence of a control group, which precludes direct comparisons between chronic pain patients and healthy individuals. Without such a control group, it is challenging to definitively conclude whether the observed ANI values in chronic pain patients are significantly different from those of individuals without chronic pain. Future studies should incorporate healthy controls to facilitate a clearer understanding of how ANI values in chronic pain populations relate to baseline values in healthy individuals.

Additionally, this study did not differentiate among various types of chronic pain conditions, such as primary and secondary pain disorders. The lack of distinction between these categories may have influenced the ANI readings, as different pain aetiologies can result in varying autonomic responses. Future research should aim to differentiate these conditions to ascertain whether ANI values fluctuate across different pain Patho physiologies and to provide more precise pain assessments.

Another limitation is the broad age range of participants, which spanned from 8 to 18 years. While this diverse age group reflects the pediatric chronic pain population, it also introduces variability in terms of developmental stages, which could impact both pain perception and autonomic regulation. Younger children may exhibit different autonomic responses and pain perceptions compared to older adolescents, and these differences could influence ANI values. Employing a more age-matched cohort or conducting subgroup analyses could help elucidate

age-related differences in ANI values, thereby enhancing the accuracy of pain assessments across various developmental stages.

Future Research Directions

Future research should concentrate on several key areas. First, larger-scale studies are necessary to further validate the utility of ANI in pediatric chronic pain populations, particularly those with diverse pain aetiologies. Such studies should employ longitudinal designs to evaluate the stability of ANI as a marker of chronic pain and its responsiveness to various treatment modalities over time. Additionally, future investigations should explore the integration of ANI with other pain assessment tools, both subjective and objective, to enhance the accuracy and reliability of pain measurements in pediatric patients.

Future studies could also examine the use of ANI in conjunction with therapeutic interventions, such as Cognitive Behavioral Therapy (CBT) and other psychological treatments commonly employed in chronic pain management. For instance, assessing changes in ANI following cognitive behavioral therapy, biofeedback, autohypnosis, and relaxation techniques would be valuable, as these interventions aim to modify autonomic nervous system activity and could potentially influence ANI readings by reducing pain perception or improving pain management through relaxation and cognitive strategies.

Moreover, research focused on establishing a new cut-off for ANI that accurately reflects nociceptive processing in pediatric patients with chronic pain—distinct from the surgical cut-off

currently utilized—is warranted. Developing a revised cut-off would enable a more precise representation of nociceptive processing in this population, better aligning ANI with the clinical realities of managing chronic pain in children.

CONCLUSION

This study examined the potential use of the Analgesia Nociception Index (ANI) in pediatric patients with chronic pain conditions. Although ANI provides valuable insights into autonomic nervous system responses associated with nociceptive input in surgical settings, it is crucial to recognize that ANI primarily reflects nociceptive processes rather than encompassing the full complexity of the pain experience in such contexts. The subjective experience of pain is influenced by numerous factors, including emotional, psychological, and social elements, all of which can affect ANI values in awake patients with chronic pain conditions.

The observed weak correlation between ANI and self-reported pain intensity in chronic pain patients suggests that, while ANI may be sensitive to nociceptive processes in surgical settings, this sensitivity does not necessarily extend to the broader pain experience.

Nonetheless, ANI's capability to detect changes in nociceptive input, particularly in response to controlled stimuli, highlights its potential for evaluating acute-on-chronic pain conditions and for tracking the efficacy of analgesic interventions. These attributes position ANI as a promising tool for personalized pain management, especially in pediatric populations where subjective pain reporting can pose challenges.

Future research should prioritize refining ANI's application in chronic pain conditions, particularly by investigating the influence of psychosocial interventions on its readings. Additionally, further exploration into the use of ANI for monitoring treatment efficacy and guiding medication adjustments in both acute and chronic pain settings is warranted.

REFRENCES:

1. *Continuous Analgesia Monitoring System Analgesia Nociception Index ANI Monitor V1 User Manual Software Version 1.1.4.0 Continuous Analgesia Monitoring System*. www.mdoloris.com
2. Goldberg DS, McGee SJ. Pain as a global public health priority. *BMC Public Health*. 2011;11. doi:10.1186/1471-2458-11-770
3. Friedrichsdorf SJ, Giordano J, Desai Dakoji K, Warmuth A, Daughtry C, Schulz CA. children Chronic Pain in Children and Adolescents: Diagnosis and Treatment of Primary Pain Disorders in Head, Abdomen, Muscles and Joints. Published online 2016. doi:10.3390/children3040042
4. Boselli E, Bouvet L, Bégou G, et al. Prediction of immediate postoperative pain using the analgesia/nociception index: A prospective observational study. *Br J Anaesth*. 2014;112(4):715-721. doi:10.1093/bja/aet407
5. Jeanne M, Clément C, De Jonckheere J, Logier R, Tavernier B. Variations of the analgesia nociception index during general anaesthesia for laparoscopic abdominal surgery. *J Clin Monit Comput*. 2012;26(4):289-294. doi:10.1007/S10877-012-9354-0
6. Funcke S, Sauerlaender S, Pinnschmidt HO, et al. Validation of Innovative Techniques for Monitoring Nociception during General AnesthesiaA Clinical Study Using Tetanic and Intracutaneous Electrical Stimulation. *Anesthesiology*. 2017;127(2):272-283. doi:10.1097/ALN.0000000000001670
7. Avez-Couturier J, De Jonckheere J, Jeanne M, Valleé L, Cuisset JM, Logier R. Assessment of Procedural Pain in Children Using Analgesia Nociception Index: A Pilot Study. *Clin J Pain*. 2016;32(12):1100-1104. doi:10.1097/AJP.0000000000000360
8. Julien-Marsollier F, Rachdi K, Caballero MJ, et al. Evaluation of the analgesia nociception index for monitoring intraoperative analgesia in children. *Br J Anaesth*. 2018;121(2):462-468. doi:10.1016/j.bja.2018.03.034
9. Sabourdin N, Arnaout M, Louvet N, Guye ML, Piana F, Constant I. Pain monitoring in anesthetized children: first assessment of skin conductance and analgesia-nociception index at different infusion rates of remifentanil. *Paediatr Anaesth*. 2013;23(2):149-155. doi:10.1111/PAN.12071
10. Weber F, Geerts NJE, Roeleveld HG, Warmenhoven AT, Liebrand CA. The predictive value of the heart rate variability-derived Analgesia Nociception Index in children anaesthetized with sevoflurane: An observational pilot study. *Eur J Pain*. 2018;22(9):1597. doi:10.1002/EJP.1242
11. Parker N, Ledowski T, Tiong WS, Lee C, Wong B, Fiori T. Analgesia nociception index: evaluation as a new parameter for acute postoperative pain. *Br J Anaesth*. 2013;111(4):627-629. doi:10.1093/BJA/AET111
12. Evans S, Seidman LC, Tsao JCI, Lung KC, Zeltzer LK, Naliboff BD. Heart rate variability as a biomarker for autonomic nervous system response differences between children with chronic pain and healthy control children. *J Pain Res*. 2013;6:449-457. doi:10.2147/JPR.S43849

13. Koenig J, Loerbroks A, Jarczok MN, Fischer JE, Thayer JF. Chronic Pain and Heart Rate Variability in a Cross-Sectional Occupational Sample: Evidence for Impaired Vagal Control. *Clin J Pain*. 2016;32(3):218-225. doi:10.1097/AJP.0000000000000242
14. Shupler MS, Kramer JK, Cragg JJ, Jutzeler CR, Whitehurst DGT. Pan-Canadian Estimates of Chronic Pain Prevalence From 2000 to 2014: A Repeated Cross-Sectional Survey Analysis. *Journal of Pain*. 2019;20(5):557-565. doi:10.1016/j.jpain.2018.10.010
15. Walker LS, Greene JW. The functional disability inventory: measuring a neglected dimension of child health status. *J Pediatr Psychol*. 1991;16(1):39-58. doi:10.1093/JPEPSY/16.1.39
16. Ocay DD, Ross BD, Moscaritolo L, et al. The Psychosocial Characteristics and Somatosensory Function of Children and Adolescents Who Meet the Criteria for Chronic Nociplastic Pain. *J Pain Res*. 2023;16:487-500. doi:10.2147/JPR.S397829
17. Heinricher MM, Tavares I, Leith JL, Lumb BM. Descending control of nociception: Specificity, recruitment and plasticity. *Brain Res Rev*. 2009;60(1):214-225. doi:10.1016/J.BRAINRESREV.2008.12.009
18. Meints SM, Edwards RR. Evaluating Psychosocial Contributions to Chronic Pain Outcomes. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;87(Pt B):168. doi:10.1016/J.PNPBP.2018.01.017
19. Staudt MD. The Multidisciplinary Team in Pain Management. *Neurosurg Clin N Am*. 2022;33(3):241-249. doi:10.1016/J.NEC.2022.02.002
20. Scholz J. Mechanisms of chronic pain. *Mol Pain*. 2014;10(Suppl 1):O15. doi:10.1186/1744-8069-10-S1-O15
21. Ohashi Y, Uchida K, Fukushima K, Inoue G, Takaso M. Mechanisms of Peripheral and Central Sensitization in Osteoarthritis Pain. *Cureus*. 2023;15(2). doi:10.7759/CUREUS.35331
22. Meacham K, Shepherd A, Mohapatra DP, Haroutounian S. Neuropathic Pain: Central vs. Peripheral Mechanisms. *Curr Pain Headache Rep*. 2017;21(6). doi:10.1007/s11916-017-0629-5
23. López-Ruiz M, Losilla JM, Monfort J, et al. Central sensitization in knee osteoarthritis and fibromyalgia: Beyond depression and anxiety. *PLoS One*. 2019;14(12). doi:10.1371/JOURNAL.PONE.0225836
24. Price DD, Staud R, Robinson ME, Mauderli AP, Cannon R, Vierck CJ. Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients. *Pain*. 2002;99(1-2):49-59. doi:10.1016/S0304-3959(02)00053-2
25. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. *Pain*. 2011;152(3 Suppl):S2. doi:10.1016/J.PAIN.2010.09.030
26. Bannister K. Descending pain modulation: influence and impact. *Curr Opin Physiol*. 2019;11:62-66. doi:10.1016/J.COPHYS.2019.06.004
27. Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. *Curr Opin Support Palliat Care*. 2014;8(2):143-151. doi:10.1097/SPC.0000000000000055
28. Kwon M, Altin M, Duenas H, Alev L. The Role of Descending Inhibitory Pathways on Chronic Pain Modulation and Clinical Implications. doi:10.1111/papr.12145
29. Mücke M, Cuhls H, Radbruch L, et al. Quantitative sensory testing (QST). English version. *Schmerz*. 2021;35:153-160. doi:10.1007/S00482-015-0093-2

30. Cruz-Almeida Y, Fillingim RB. *PSYCHOLOGY, PSYCHIATRY & BRAIN NEUROSCIENCE SECTION Review Article Can Quantitative Sensory Testing Move Us Closer to Mechanism-Based Pain Management?*
31. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. *Pain*. 2006;123(3):231-243. doi:10.1016/J.PAIN.2006.01.041
32. Normand E, Potvin S, Gaumond I, Cloutier G, Corbin JF, Marchand S. Pain inhibition is deficient in chronic widespread pain but normal in major depressive disorder. *J Clin Psychiatry*. 2011;72(2):219-224. doi:10.4088/JCP.08M04969BLU
33. Potvin S, Marchand S. Pain facilitation and pain inhibition during conditioned pain modulation in fibromyalgia and in healthy controls. *Pain*. 2016;157(8):1704-1710. doi:10.1097/J.PAIN.0000000000000573
34. Cathcart S, Winefield AH, Lushington K, Rolan P. Noxious inhibition of temporal summation is impaired in chronic tension-type headache. *Headache*. 2010;50(3):403-412. doi:10.1111/j.1526-4610.2009.01545.x
35. Mücke M, Cuhls H, Radbruch L, et al. Quantitative sensory testing (QST). English version. *Schmerz*. 2021;35:153-160. doi:10.1007/s00482-015-0093-2
36. Rolke R, Magerl W, Campbell KA, et al. Quantitative sensory testing: A comprehensive protocol for clinical trials. *European Journal of Pain*. 2006;10(1):77. doi:10.1016/J.EJPAIN.2005.02.003
37. Pfau DB, Geber C, Birklein F, Treede RD. Quantitative sensory testing of neuropathic pain patients: Potential mechanistic and therapeutic implications. *Curr Pain Headache Rep*. 2012;16(3):199-206. doi:10.1007/s11916-012-0261-3
38. Blankenburg M, Boekens H, Hechler T, et al. Reference values for quantitative sensory testing in children and adolescents: Developmental and gender differences of somatosensory perception. *Pain*. 2010;149(1):76-88. doi:10.1016/j.pain.2010.01.011
39. Cruz-Almeida Y, Fillingim RB. *PSYCHOLOGY, PSYCHIATRY & BRAIN NEUROSCIENCE SECTION Review Article Can Quantitative Sensory Testing Move Us Closer to Mechanism-Based Pain Management?*
40. van den Bosch GE, van Dijk M, Tibboel D, Valkenburg AJ. Thermal quantitative sensory testing in healthy Dutch children and adolescents standardized test paradigm and Dutch reference values. *BMC Pediatr*. 2017;17(1). doi:10.1186/s12887-017-0827-7
41. Meier PM, Berde CB, DiCanzio J, Zurakowski D, Sethna NF. Quantitative assessment of cutaneous thermal and vibration sensation and thermal pain detection thresholds in healthy children and adolescents. *Muscle Nerve*. 2001;24(10):1339-1345. doi:10.1002/mus.1153
42. Ferland CE, Teles AR, Ingelmo P, Saran N, Marchand S, Ouellet JA. Blood monoamines as potential biomarkers for conditioned pain modulation efficacy: An exploratory study in paediatrics. *Eur J Pain*. 2019;23(2):327-340. doi:10.1002/EJP.1307
43. Kennedy DL, Kemp HI, Ridout D, Yarnitsky D, Rice ASC. Reliability of conditioned pain modulation: a systematic review. *Pain*. 2016;157(11):2410. doi:10.1097/J.PAIN.0000000000000689
44. Danilin LK, Spindler M, Sörös P, Bantel C. Heart rate and heart rate variability in patients with chronic inflammatory joint disease: the role of pain duration and the insular cortex. *BMC Musculoskelet Disord*. 2022;23(1). doi:10.1186/s12891-022-05009-1

45. Abdullayev R, Yildirim E, Celik B, Topcu Sarica L. Analgesia Nociception Index: Heart Rate Variability Analysis of Emotional Status. *Cureus*. Published online April 2, 2019. doi:10.7759/cureus.4365
46. Yetwin A, Marks K, Bell T, Gold J. Heart rate variability biofeedback therapy for children and adolescents with chronic pain. *J Pain*. 2012;13(4):S93. doi:10.1016/j.jpain.2012.01.386
47. Forte G, Troisi G, Pazzaglia M, De Pascalis V, Casagrande M. Heart Rate Variability and Pain: A Systematic Review. *Brain Sci*. 2022;12(2). doi:10.3390/brainsci12020153
48. Yoshida K, Obara S, Inoue S. Analgesia nociception index and high frequency variability index: promising indicators of relative parasympathetic tone. *J Anesth*. 2023;37(1):130-137. doi:10.1007/s00540-022-03126-8
49. Berry ME, Chapple IT, Ginsberg JP, Gleichauf KJ, Meyer JA, Nagpal ML. Non-pharmacological Intervention for Chronic Pain in Veterans: A Pilot Study of Heart Rate Variability Biofeedback. *Glob Adv Health Med*. 2014;3(2):28-33. doi:10.7453/gahmj.2013.075
50. McSaykrs BA. Analysis of Heart Rate Variability. *Ergonomics*. 1973;16(1):17-32. doi:10.1080/00140137308924479
51. Yoshida K, Obara S, Inoue S. Analgesia nociception index and high frequency variability index: promising indicators of relative parasympathetic tone. *J Anesth*. 2023;37(1):130-137. doi:10.1007/s00540-022-03126-8
52. *Continouous Analgesia Monitoring System Analgesia Nociception Index ANI Monitor V1 User Manual Software Version 1.1.4.0*. www.mdoloris.com
53. Abdullayev R, Uludag O, Celik B. REVISTA BRASILEIRA DE ANESTESIOLOGIA Publicação Oficial da Sociedade Brasileira de Anestesiologia Índice de Analgesia/Nocicepção: avaliação da dor aguda pós-operatória PALAVRAS-CHAVE. *Rev Bras Anestesiol*. 2019;69(4):396-402. doi:10.1016/j.bjan.2019.01.003
54. Struys MMRF, Vanpeteghem C, Huiku M, Uutela K, Blyaert NBK, Mortier EP. Changes in a surgical stress index in response to standardized pain stimuli during propofol-remifentanil infusion. *Br J Anaesth*. 2007;99(3):359-367. doi:10.1093/bja/aem173
55. Sabourdin N, Arnaout M, Louvet N, Guye ML, Piana F, Constant I. Pain monitoring in anesthetized children: first assessment of skin conductance and analgesia-nociception index at different infusion rates of remifentanil. *Paediatr Anaesth*. 2013;23(2):149-155. doi:10.1111/PAN.12071
56. Tiryaki Ö, Doğu Ö, Okumuş GY, Tuna AT, Bayar F. Analgesia Nociception Index Monitoring in the Evaluation of Postoperative Pain in Children: A Prospective Observational Pilot Study. *Journal of Perianesthesia Nursing*. 2023;38(2):213-218. doi:10.1016/j.jopan.2022.04.002
57. *33rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society : [Proceedings] : August 30-September 3, 2011, Boston, MA, USA*. IEEE; 2011.
58. Boselli E, Bouvet L, Bégou G, et al. Prediction of immediate postoperative pain using the analgesia/nociception index: a prospective observational study. *Br J Anaesth*. 2014;112(4):715-721. doi:10.1093/BJA/AET407
59. Bansal S, Sriganesh K. The analgesia nociception index: Features and application. In: *Features and Assessments of Pain, Anesthesia, and Analgesia*. Elsevier; 2021:463-473. doi:10.1016/B978-0-12-818988-7.00039-X

60. Choi BM, Shin H, Lee JH, Bang JY, Lee EK, Noh GJ. Performance of the Surgical Pleth Index and Analgesia Nociception Index in Healthy Volunteers and Parturients. *Front Physiol*. 2021;12. doi:10.3389/fphys.2021.554026
61. Le Guen M, Jeanne M, Sievert K, et al. The Analgesia Nociception Index: A pilot study to evaluation of a new pain parameter during labor. *Int J Obstet Anesth*. 2012;21(2):146-151. doi:10.1016/j.ijoa.2012.01.001
62. Lee JH, Choi BM, Jung YR, Lee YH, Bang JY, Noh GJ. Evaluation of Surgical Pleth Index and Analgesia Nociception Index as surrogate pain measures in conscious postoperative patients: an observational study. *J Clin Monit Comput*. 2020;34(5):1087-1093. doi:10.1007/s10877-019-00399-5
63. Baroni DA, Abreu LG, Paiva SM, Costa LR. Comparison between Analgesia Nociception Index (ANI) and self-reported measures for diagnosing pain in conscious individuals: a systematic review and meta-analysis. *Sci Rep*. 2022;12(1). doi:10.1038/s41598-022-06993-z
64. Baroni DA, Abreu LG, Paiva SM, Costa LR. Comparison between Analgesia Nociception Index (ANI) and self-reported measures for diagnosing pain in conscious individuals: a systematic review and meta-analysis. *Sci Rep*. 2022;12(1). doi:10.1038/s41598-022-06993-z
65. Baroni DA, Abreu LG, Paiva SM, Costa LR. Comparison between Analgesia Nociception Index (ANI) and self-reported measures for diagnosing pain in conscious individuals: a systematic review and meta-analysis. *Sci Rep*. 2022;12(1). doi:10.1038/s41598-022-06993-z
66. Jess G, Pogatzki-Zahn EM, Zahn PK, Meyer-Frießem CH. Monitoring heart rate variability to assess experimentally induced pain using the analgesia nociception index. *Eur J Anaesthesiol*. 2016;33(2):118-125. doi:10.1097/EJA.0000000000000304
67. Gall O, Champigneulle B, Schweitzer B, et al. Postoperative pain assessment in children: a pilot study of the usefulness of the analgesia nociception index †. Published online 2015. doi:10.1093/bja/aev361
68. Shahiri TS, Richebé P, Richard-Lalonde M, Gélinas C. Description of the validity of the Analgesia Nociception Index (ANI) and Nociception Level Index (NOL) for nociception assessment in anesthetized patients undergoing surgery: a systematized review. *J Clin Monit Comput*. 2022;36(3):623-635. doi:10.1007/s10877-021-00772-3
69. Chanques G, Tarri T, Ride A, et al. Analgesia nociception index for the assessment of pain in critically ill patients: A diagnostic accuracy study. *Br J Anaesth*. 2017;119(4):812-820. doi:10.1093/bja/aex210
70. Solé E, Galán S, de la Vega R, et al. Psychometric properties of the Functional Disability Inventory for assessing Pain-related disability in children from the community. *Disabil Rehabil*. 2019;41(20):2451-2458. doi:10.1080/09638288.2018.1467969
71. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of DSM-IV anxiety and depression in children: a revised child anxiety and depression scale. *Behaviour research and therapy*. 2000;38(8):835-855. doi:10.1016/S0005-7967(99)00130-8
72. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193-213. doi:10.1016/0165-1781(89)90047-4

73. Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain*. 2005;114(1-2):29-36. doi:10.1016/J.PAIN.2004.12.010
74. Crombez G, Bijttebier P, Eccleston C, et al. The child version of the pain catastrophizing scale (PCS-C): a preliminary validation. *Pain*. 2003;104(3):639-646. doi:10.1016/S0304-3959(03)00121-0
75. Sandkühler J. Models and mechanisms of hyperalgesia and allodynia. *Physiol Rev*. 2009;89(2):707-758. doi:10.1152/PHYSREV.00025.2008
76. Jürgens TP, Sawatzki A, Henrich F, Magerl W, May A. An improved model of heat-induced hyperalgesia - Repetitive phasic heat pain causing primary hyperalgesia to heat and secondary hyperalgesia to pinprick and light touch. *PLoS One*. 2014;9(6). doi:10.1371/journal.pone.0099507
77. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9(2):105-121. doi:10.1016/J.JPAIN.2007.09.005
78. Tousignant-Laflamme Y, Pagé S, Goffaux P, Marchand S. An experimental model to measure excitatory and inhibitory pain mechanisms in humans. *Brain Res*. 2008;1230:73-79. doi:10.1016/J.BRAINRES.2008.06.120
79. Bansal S, Sriganesh K. The analgesia nociception index: Features and application. In: *Features and Assessments of Pain, Anesthesia, and Analgesia*. Elsevier; 2021:463-473. doi:10.1016/B978-0-12-818988-7.00039-X
80. *Continouous Analgesia Monitoring System Analgesia Nociception Index ANI Monitor V1 User Manual Software Version 1.1.4.0*. www.mdoloris.com
81. *Continuous Analgesia Monitoring System Analgesia Nociception Index ANI Monitor V1 User Manual Software Version 1.1.4.0 Continuous Analgesia Monitoring System*. www.mdoloris.com

APPENDIX

1. Research Initial Submission Protocol to Ethics BOARD.

Study title: Validity of the Analgesia Nociception Index in children and adolescents with Chronic Pain

Principal investigator: Sabrina Carrie, Assistant Professor, Department of Anesthesia, Edwards Family Interdisciplinary Centre for Complex Pain, McGill University Health Center, Montreal Children's Hospital. Tel: (514) 412-4448

Co-investigator(s):

Pablo Angelo, Professor of Anesthesia, McGill University, Director of the Edwards Family Interdisciplinary Centre for Complex Pain, Department of Anesthesia, Montreal Children's Hospital, McGill University Health Center

Courtenay Wood, MDCM student at McGill University

Nada Mohamed, MD, Research Coordinator, Edwards Family Interdisciplinary Centre for Complex Pain

Marie-Linda Baghdadi**,** Clinical Research and Education Coordinator**,** Edwards Family Interdisciplinary Centre for Complex Pain

Jonathan Hudon, MD, Pain Specialist, Family physician, Edwards Family Interdisciplinary Centre for Complex Pain

Don Daniel Ocay PhD Candidate at McGill University

Chronic Pain Fellows of the Edwards Family Interdisciplinary Centre for Complex Pain

Lorenzo Moscaritolo, MD

Justine Turmel-Roy, MD

Hanadi Almashooq, MD

Background and study rationale

Pediatric chronic pain is estimated to affect 20-35% of children and adolescents around the world and can have a negative impact on function and overall well-being of these individuals [1]. It is important to treat chronic pain effectively, as failing to do so can increase the risk of further pain and the development of psychiatric disorders [1].

The Analgesia Nociception Index (ANI) is a non-invasive tool that uses heart-rate variability (HRV) to assess parasympathetic tone. It has been used as a bedside tool as surrogate for nociception. More specifically, it has been used to evaluate the individual's response to nociceptive stimulation; ANI has also been used to evaluate the response to treatment that are used to prevent or control nociceptive stimulation in patients under general anesthesia. The ANI score ranges from 0-100 with a high score indicating high HRV and high parasympathetic control, which are indicators of low nociception. A low score in contrast

indicates low HRV and low parasympathetic control, which are indicators of high nociception. One benefit of ANI is that it has a higher sensitivity to nociception than other measurements, such as heart rate and blood pressure [2, 3]. ANI has been tested in the pediatric population for its utility during surgery; ANI decreases significantly with nociceptive stimuli [4, 5, 6] and increases after opioid administration [7]. In adults, a negative correlation has been found post-operatively [8, 9, 10, 11] between ANI and the Numerical Rating Scale (NRS). There is also some evidence that post-operatively, ANI corresponds to objective tools to quantify pain behavior such as the Face, Legs, Activity, Cry, Consolability (FLACC) score in children [12].

Currently, there is a gap in the literature regarding the validity of ANI as a nociceptive assessment tool in the pediatric population affected with chronic pain conditions. This population is of particular interest because patients with chronic pain have a lower resting HRV and a blunted HRV response to nociceptive stimuli compared to patients without chronic pain [13, 14, 15]. An objective measure of parasympathetic tone (and restoration thereof) using ANI may be able to serve as a yardstick for treatment effectiveness in this population.

ANI serves as an objective measure of nociception and it is a very fast, easy-to-use device during clinical evaluations and follow-ups during the everyday clinical practice. Moreover, ANI may allow clinician to evaluate patients unable to verbally report their pain and where other pain measurement tools (such as FLACC, Visual Analog scale or Numeric Ranging Scale) may not be sensitive enough to detect pain. We're interested in answering the following questions:

- Do ANI values correlate with the pain intensity of children and adolescents with chronic pain conditions?
- Do ANI values correlate with the values of standard questionnaires validated to measure the psychosocial impact of chronic pain conditions in children and adolescents?
- Do ANI values correlate with the nociceptive profile of children with chronic pain conditions measured with Quantitative Sensory Testing (QST)/ Conditioned Pain Modulation (CPM)?
- Can we use ANI to detect changes associated with the treatment of children and adolescents with chronic pain conditions when measured with pain intensity and with the Patient Global Impression of Change scale (PGIC)?

Objectives AND hypotheses

To investigate the correlation between ANI and NRS scores in children and adolescents with chronic pain

To evaluate the correlation between ANI and the Quantitative Sensory Testing (QST) and Conditioned Pain Modulation (CPM) in children and adolescents with chronic pain conditions

To evaluate the correlation of ANI and the impact of chronic pain conditions measured with validated questionnaires evaluating physical function, psychological function and social function

To evaluate the correlation between ANI variation and efficacy of treatment measured with the change in NRS scores, and the changes the PGIC.

We hypothesize that pain management in a multidisciplinary setting in children and adolescents with chronic pain conditions will result in a restoration of HRV and therefore increased ANI scores. We expect to find:

1) A negative correlation between the ANI and NRS scores at the various time points of the study (initial, follow-ups, discharge)

2) Patients with lower ANI will have a higher likelihood of abnormal QST/CPM results measured by presence of peripheral sensitization, central sensitization and/or inefficient CPM. Patients with lower ANI will also have a higher likelihood of a positive DN4.

3) A negative correlation between ANI and score on the measures of chronic pain impact (PSQI, FDI, and RCADS)

4) Baseline ANI scores will increase and HRV will be restored in conjunction with effective pain management (as indicated by decreased NRS scores and increase in the score of global impression of change scale (PGIC).

Study Methods

Study design

This will be a prospective observational study. All patients enrolled in the study will receive standard of care in the interdisciplinary outpatient program of the Edwards Family Interdisciplinary Center for Complex Pain. This includes an interdisciplinary evaluation, a set of questionnaires, and quantitative sensory testing/conditioned pain modulation (QST/CPM) evaluation protocols. (see below). In addition to the standard of care, we will add ANI as part of the study to assess if ANI values correlate with the other measures used in the interdisciplinary program as well as with efficacy of treatment.

Interdisciplinary evaluation

All Patients enrolled in the study will have received standard of care including interdisciplinary evaluation. The interdisciplinary outpatient program of the Edwards Family Interdisciplinary Center for Complex Pain focuses on optimizing physical and psychological function, normalizing

sleep and social function, and increasing levels of activity, while assisting with the management of the pain. The core team at each evaluation includes a nurse, psychologist, social worker, physiotherapist, a clinical fellow and a pain physician.
During an interdisciplinary face-to-face interview, we evaluate the intensity, duration and frequency of the pain over the previous month using the numerical rating scale (NRS) ranging from 0 (no pain at all) to 10 (worst pain imaginable).
After the interdisciplinary interview which includes pain assessment, the patient undergoes a physical examination (clinical fellow, physician and physiotherapist) that includes a detailed neurological exam with particular attention to changes in sensations. The clinicians report the presence and distribution of hyperalgesia, allodynia, dysesthesia, loss of sensation, and any other specific finding relevant changes on the standard neurological exam.

Patient reported psychosocial outcome measures

As part of the standard of care in the Edwards Family Interdisciplinary Center for Complex Pain, all patient referred undergo a baseline evaluation that includes of sleep quality, physical function, and psychological function using the Pittsburgh Sleep Quality Index (PSQI), the Functional Disability Inventory (FDI), and the Revised Child Anxiety and Depression Scale (RCADS), respectively. The Pittsburgh Sleep Quality Index (PSQI) questionnaire is completed by patients to assess sleep quality. [16] The Functional Disability Inventory (FDI) questionnaire is completed by patients, in which the total score is summed to detect different levels of disability. [17] The Revised Child Anxiety and Depression Scale (RCADS) questionnaire is completed by patients to assess children's self-report of depression and anxiety.[18] 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). To identify if their pain had a neuropathic component, the Douleur Neuropathique 4 (DN4) questionnaire is completed by patients and the physicians. [19] The Pain Catastrophizing Scale for Children (PCS-C) is completed by patients to assess the degree to which they experienced negative thoughts or feelings while experiencing pain. [20]

QST/CPM evaluation protocol
Since 2016, as part of the standard evaluation in the Edwards Family Interdisciplinary Center for Complex Pain, a comprehensive QST protocol is used to assess mechanisms of pain as well; a CPM protocol is also used to evaluate the endogenous descending pain inhibitory control of patients before the initiation of a treatment. The evaluation take place before the initial evaluation at the Center for complex Pain and is used to personalize the pharmacological treatment.
The full evaluation is termed QST/CPM evaluation but may be abbreviated to "QST" only for short in the tables/figures. The QST protocol was based on previous comprehensive studies [21] and includes assessments of mechanical detection threshold, vibration detection threshold, dynamic mechanical allodynia, pain pressure threshold, heat pain threshold, and mechanical pain summation. Results were evaluated and compared to reference values from the literature

when available, with respect to protocol and test sites [22]. The endogenous descending pain inhibitory pathway is evaluated using a CPM paradigm of tonic thermal stimulations [23].
The pain pressure threshold (PPT) is measured using a pressure algometer (Jtech). If the PPT is significantly below the lower bound of the 95% CI of the reference values at a control site [22] or significantly lower (difference of at least 30%) compared to a same-subject's contralateral site in the instance of unilateral pain, deep-tissue pressure pain sensitivity is reported. A high pain sensitivity indicates enhanced mechanical sensitivity.[22]
The presence of dynamic mechanical allodynia is reported using a standardized brush (Somedic SENSELab – Brush-05). Allodynia is defined by the IASP as "pain due to a stimulus that does not normally provoke pain" [24]. On a mechanistic level, allodynia is proposed as a lack of inhibition of excitatory crosstalk between sensory modalities (touch and pain) by interneurons in the spinal dorsal horn [25]. In other words, there is a failure to separate the input from Aβ-fibers (touch) and nociceptive-specific neurons [25, 26].
The presence of temporal summation is evaluated both mechanically and thermally. Mechanical temporal summation is evaluated using the difference in the self-reported pain between one and ten stimulations with a Neuropen (Owen Mumford) with a 40g Neurotip at a rate of 1 per second. Thermal temporal summation is measured during a constant heat stimulus over a period of 2 minutes at a pre-determined temperature self-reported to cause ≥5/10 pain and interpreted as the difference in pain intensity between the numerical rating score at 60s and at 120s of the test. For both temporal summation tests, a significant increase of >2/10 in pain rating is considered a positive result based on IMMPACT recommendations for clinically important differences in pain intensity [27]. All thermal testing is performed using the Medoc Qsense apparatus and a computerized visual analogue scale (CoVAS). Mechanistically, temporal summation, also called wind-up, may reflect an increase in the excitatory postsynaptic potentials in response to repeated C-fiber stimulation [25, 26]. Studies suggest that temporal summation is stronger in individuals with primary chronic pain (including chronic widespread pain) compared to normal controls [28, 29].
Mechanical detection threshold and vibration detection thresholds is investigated using Von Frey Filaments and a 64Hz tuning fork (Rydel-Seiffer) respectively and compared to reference values [22]. These measures are used as additional information regarding the integrity of the Aβ-fibers as complimentary information to suggest the possibility of deafferentation pain.
The endogenous descending pain inhibitory pathway control is quantitatively evaluated using the conditioned pain modulation (CPM) paradigm developed by Marchand and colleagues [30] and simplified to be used in younger patients [31]. The paradigm consists in the difference in continuous pain rating during two tonic thermal heat pain stimulations on the right forearm separated by a cold-water conditioning stimulus consisting of a left forearm immersion of 2 minutes at 12°C. The thermal heat component is performed using the Medoc Qsense and a computerized visual analogue scale (CoVAS). The two-minute painful thermal stimulation temperature is predetermined as the temperature at which the patient experienced a self-reported pain of ≥5/10. The efficacy of the CPM test is categorized as efficient, suboptimal or inefficient. An efficient CPM score corresponded to a pain reduction of 30% or more, whereas an inefficient CPM score corresponded to a pain reduction of less than 10%. [23, 32]. The

numerical value is also reported. The suboptimal CPM category is included as a conservative buffer to allow for a margin of error of 20% [23, 34], An inefficient CPM result is suggested to reflect an incapacity to trigger a proper endogenous pain inhibition [35, 36].

Meaningful clinical outcome and end of treatment

In the interdisciplinary outpatient program of the Edwards Family Interdisciplinary Center for Complex Pain We use the patients' global impression of change scale (PGIC) as primary clinical outcome measure. [37, 38] The PGIC is a 7-point scale and reflects a patient's belief about treatment efficacy and overall improvement in their health condition: 1. No change (or condition has got worse), 2. Almost the same, hardly any change at all, 3. A little better, but not noticeable change at all, 4. Somewhat better, but the change has not made any real difference, 5. Moderately better, and a slight but noticeable change, 6. Better, and a definite improvement that has made a real and worthwhile difference, and 7. A great deal better, and a considerable improvement that has made all the difference. The treatment provided by the Center for Complex Pain ends when the patient achieved a meaningful improvement defined as the patient having normal school attendance, normal physical function, no pain, not using pain medication and reporting a PGIC score of 6 or 7. [39]

ANI

The ANI device and the pads required to obtain ANI values for this study has been made available to the department of anesthesia and the Edwards Family Interdisciplinary Centre for Complex Pain for the purpose of clinical research. As part of the study, ANI values will be recorded at different time points. ANI values will be collected at the appointment for the QST/CPM protocol. These ANI values will the pre-treatment ANI values and this will be correlated with the NRS scores at the initial evaluation. The pre-treatment ANI values will also be correlated with the impact of chronic pain conditions on physical function, psychological function and social function (PSQI, FDI, and RCADS).

ANI values will be recorded at discharge and correlated with the NRS, PSQI, FDI, and RCADS, and the PGIC at discharge. In addition, patients who will be undergoing an interventional procedure as part of their treatment plan will have their ANI and NRS scores recorded pre-intervention, and post-intervention in the Post anesthesia care unit (PACU).

Below are images of the ANI sensors and the ANI monitor

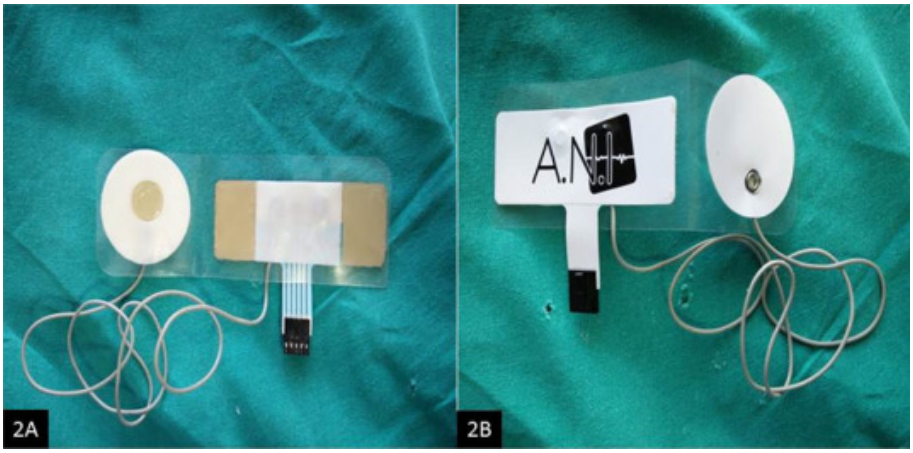

Figure 4: ANI sensor. 2A shows the patient side and 2B shows the free surface. [40]

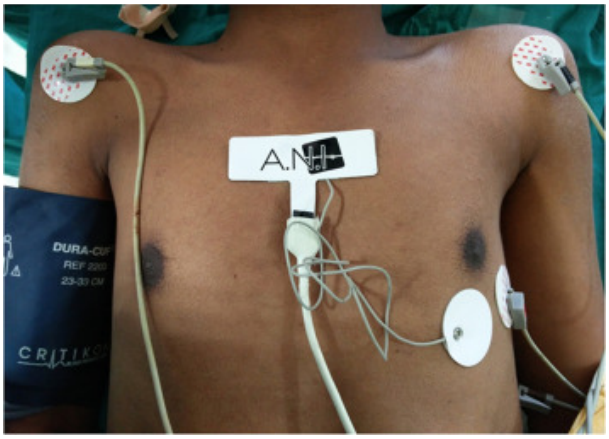
Figure 5: The ANI sensor attached to the patient [40]

Figure 6: the display screen of the ANI monitor [40]
A video that explains how the ANI sensors are attached and how to interpret the monitor is also described in the following link: https://www.youtube.com/watch?v=OdbbO0b3Gi8

Study population

All patients referred to the Edwards Family Interdisciplinary Center for Complex Pain of the Montreal Children's Hospital Potential patients will be invited to participate. At the appointment for the QST, patients will be approached by a research assistant to participate in the study and to confirm eligibility criteria prior to receiving signed consent.

Inclusion criteria

Patients must fulfill the following criteria:

Be between 9-17 years old
Experiencing chronic pain defined by: persistent or recurrent pain at least once a week for at least three months in their electronic medical charts or by reference of the patient's physician. Patients will be divided according to the ICD-11 classification of Chronic pain [41] into either chronic primary or chronic secondary pain conditions. Primary pain conditions are those without a known underlying etiology and generally considered a disease in its own right; these include conditions such as primary headaches, chronic amplified musculoskeletal pain of unknown etiology (chronic widespread pain and complex regional syndrome type I), functional abdominal pain syndrome. Secondary pain conditions are those with an identifiable cause such as post-surgical or post-traumatic pain, cancer related pain, neuropathic pain secondary to a known nerve injury, visceral pain such as inflammatory bowel disease, sickle cell disease, and inflammatory musculoskeletal pain such as juvenile arthritis.

Exclusion criteria
taking medications known to affect the sympathetic or parasympathetic nervous systems such as cholinomimetics (e.g., pilocarpine), anticholinergics (e.g., ipratropium), sympathomimetics (e.g, salbutamol), and adrenergic antagonists (e.g., propranolol).
cardiac or neurological conditions will also be excluded, including patients with arrhythmias, heart block, postural orthostatic tachycardia syndrome, Guillain-Barre syndrome, or spinal cord injury
cancer diagnosis

conditions that may interfere with the ability to understand instructions or complete measures including: cognitive, or developmental delay, as well as patients who do not speak English or French
not candidate for QST/CPM testing

Sample size

A sample of 120 participants will be recruited from the Montreal Children's Hospital. Recruited patients will be clustered in five categories: 60 patients with primary pain, 60 patients will secondary pain; 20 patients between 9-12 years, 30 patients between 13-15 years old and 70 patients between 16-17 years old.

Evaluations
This study includes 2 evaluations: one initial evaluation (baseline) and one evaluation during the discharge visit. The evaluations include the following:

Questionnaires: 45 minutes, through the Atlas Platform or using a PDF format. This will be done by patients at home as part of the usual center protocol
QST/CPM evaluation: 40 minutes at the Center for Innovative Medicine (CIM)
ANI: 20 minutes: At the CIM on the same day of the QST/CPM and at discharge.
If a discharge visit is not planned at the CIM, the patient will still be asked to come in to the CIM to undergo the evaluations necessary for the study (ANI).

Description of data being retrieved

The current pain intensity and average, worst and best pain intensity over the last month is reported using the numerical rating scale (NRS) ranging from 0 (no pain at all) to 10 (worst pain imaginable). This will be recorder at the initial evaluation, as well as the follow-ups and discharge.
Pittsburgh Sleep Quality Index [16] (PSQI) consists of 19 self-rated items under 7 different components. Each question is rated from "very good" which is a score of 0 to "very bad" which is a score of 3. A score of 0 indicates no difficulty and 21 indicates severe difficulty in all areas.
Functional Disability Inventory [17] (FDI) is a series of 15 questions that the patient self-rates. The score for each question ranges from 0 (no trouble with the activity) to 4 (impossible to do the activity).
Revised Child Anxiety and Depression Scale [18] (RCADS) is a 47 item self-report questionnaire with subscales for separation anxiety disorder, social phobia, generalized anxiety disorder, panic disorder, obsessive compulsive disorder and major depressive disorder. Items are on a scale from 0 ("never") to 4 ("always").

Douleur Neuropathique 4 (DN4) questionnaire to assess for the presence of neuropathic pain with a series of ten questions. Scores of equal to or greater than 4 indicate that the pain experienced by the patient is likely neuropathic [19].
physical examination (clinical fellow, physician and physiotherapist) that includes a detailed neurological exam with particular attention to changes in sensations. The clinicians report the presence and distribution of hyperalgesia, allodynia, dysesthesia, loss of sensation, and any other specific finding relevant changes on the standard neurological exam.
ANI scores range from 0-100. This score indicates heart-rate variability and provides an assessment of parasympathetic tone and nociception. A high score indicates low nociception and a low score indicates high nociception.
QST/CPM as described above will measure the mechanical detection threshold, vibration detection threshold, dynamic mechanical allodynia, pain pressure threshold, heat pain threshold, and mechanical pain summation. Depending on the results, patients will be categorized as having or not the presence of peripheral sensitization or central sensitization. The efficacy of the CPM test is categorized as efficient, suboptimal or inefficient.

Data for QST/CPM as well as ANI values will be collected in redcap. The data of the questionnaires will be retrieved from the Atlas/telehealth platform or from the patient chart (OACIS)

Duration of the study

Participant recruitment will occur between April 2022 and March 2024; therefore study duration will be 2 years.

Data analysis

Descriptive statistics

Data of patients including age, gender, type of pain condition and parameters recorded at physical examination (weight, height, and vital parameters) will be presented as recorded on the patient chart. Categorical variables will be presented as a frequency distribution.

Data comparing baseline, follow ups and end of treatment will be analyzed as follows:
Global impression of change: Chi-Square or Fisher Exact test
Numerical rating scale (NRS): t-test or Mann-Whitney/Wilcoxon test
Reduction in pain intensity: Chi-Square or Fisher exact test
Functional Disability Inventory: Chi-Square or Fisher exact test
Revised Child Anxiety and Depression Scale: t-test or Mann-Whitney/Wilcoxon test
Pittsburgh Sleep Quality Index (PSQI): t-test or Mann-Whitney/Wilcoxon test

Role functioning (number of missing school days): t-test or Mann-Whitney/Wilcoxon test
Douleur Neuropathique 4 (DN4): t-test or Mann-Whitney/Wilcoxon test
ANI scores range from 0-100: t-test or Mann-Whitney/Wilcoxon test.
QST/CPM: Chi-Square or Fisher exact test

Ethical considerations

Oversight

This study will be conducted in accord with the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (2014), as well as in respect of the requirements set out in the applicable standard operation procedures of the Research Institute of the McGill University Health Centre Research Institute and of the McGill University Health Centre Research Ethics Board. The McGill University Health Centre Research Ethics Board will review this study and will be responsible for monitoring it at all participating institutions in the health and social services network in Québec.

Confidentiality

Only data relevant to this study as outlined in this protocol will be collected by the research team. All the information collected during the research project will remain confidential to the extent required and provided by law.

Patient data will be deidentified and coded. The code will be kept by the principal investigator in a password protected digital file behind the MUHC firewall.

Informed consent

Written and informed consent will be obtained using a modified McGill University Health Centre pediatric research information and consent form template.

Dissemination plan

Research findings will be shared in publications and conferences, if applicable.

Whenever the study results are published or shared during scientific meetings or otherwise, it will not be possible to identify the participants.

References

[1] Friedrichsdorf SJ, Giordano J, Desai Dakoji K, Warmuth A, Daughtry C, Schulz CA. Chronic pain in children and adolescents: diagnosis and treatment of primary pain disorders in head, abdomen, muscles and joints. Children. 2016 Dec;3(4):42.

[2] Jeanne M, Clément C, De Jonckheere J, Logier R, Tavernier B. Variations of the analgesia nociception index during general anaesthesia for laparoscopic abdominal surgery. Journal of clinical monitoring and computing. 2012 Aug;26(4):289-94.

[3] Funcke S, Sauerlaender S, Pinnschmidt HO, Saugel B, Bremer K, Reuter DA, Nitzschke R. Validation of innovative techniques for monitoring nociception during general anesthesia: a clinical study using tetanic and intracutaneous electrical stimulation. Anesthesiology. 2017 Aug;127(2):272-83.

[4] Avez-Couturier J, De Jonckheere J, Jeanne M, Vallée L, Cuisset JM, Logier R. Assessment of procedural pain in children using Analgesia Nociception Index. The Clinical journal of pain. 2016 Dec 1;32(12):1100-4.

[5] Sabourdin N, Arnaout M, Louvet N, Guye ML, Piana F, Constant I. Pain monitoring in anesthetized children: first assessment of skin conductance and analgesia-nociception index at different infusion rates of remifentanil. Pediatric Anesthesia. 2013 Feb;23(2):149-55.

[6] Julien-Marsollier F, Rachdi K, Caballero MJ, Ayanmanesh F, Vacher T, Horlin AL, Skhiri A, Brasher C, Michelet D, Dahmani S. Evaluation of the analgesia nociception index for monitoring intraoperative analgesia in children. British journal of anaesthesia. 2018 Aug 1;121(2):462-8.

[7] Weber F, Geerts NJ, Roeleveld HG, Warmenhoven AT, Liebrand CA. The predictive value of the heart rate variability-derived Analgesia Nociception Index in children anaesthetized with sevoflurane: An observational pilot study. European Journal of Pain. 2018 oct;22(9):1597-605.

[8] Abdullayev R, Uludag O, Celik B. Índice de Analgesia/Nocicepção: avaliação da dor aguda pós-operatória. Revista Brasileira de Anestesiologia. 2019 Oct 10; 69:396-402.

[9] Boselli E, Bouvet L, Bégou G, Dabouz R, Davidson J, Deloste JY, Rahali N, Zadam A, Allaouchiche B. Prediction of immediate postoperative pain using the analgesia/nociception index: a prospective observational study. British journal of anaesthesia. 2014 Apr 1;112(4):715-21.

[10] Köprülü AŞ, Haspolat A, Gül YG, Tanrikulu N. Can postoperative pain be predicted? New parameter: analgesia nociception index. Turkish journal of medical sciences. 2020 Feb 13;50(1):49-58.

[11] Ledowski T, Tiong WS, Lee C, Wong B, Fiori T, Parker N. Analgesia nociception index: evaluation as a new parameter for acute postoperative pain. British journal of anaesthesia. 2013 Oct 1;111(4):627-9.

[12] Gall O, Champigneulle B, Schweitzer B, Deram T, Maupain O, Montmayeur Verchere J, Orliaguet G. Postoperative pain assessment in children: a pilot study of the usefulness of the analgesia nociception index. BJA: British Journal of Anaesthesia. 2015 Dec 1;115(6):890-5.

[13] Evans S, Seidman LC, Tsao JC, Lung KC, Zeltzer LK, Naliboff BD. Heart rate variability as a biomarker for autonomic nervous system response differences between children with chronic pain and healthy control children. Journal of pain research. 2013; 6:449.

[14] Koenig J, Loerbroks A, Jarczok MN, Fischer JE, Thayer JF. Chronic pain and heart rate variability in a cross-sectional occupational sample. The Clinical journal of pain. 2016 Mar 1;32(3):218-25.

[15] Tracy LM, Ioannou L, Baker KS, Gibson SJ, Georgiou-Karistianis N, Giummarra MJ. Meta-analytic evidence for decreased heart rate variability in chronic pain implicating parasympathetic nervous system dysregulation. Pain. 2016 Jan 1;157(1):7-29.

[16] Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry research. 1989;28(2):193-213.

[17] Walker LS, Greene JW. The functional disability inventory: measuring a neglected dimension of child health status. J Pediatr Psychol. 1991;16(1):39-58.

[18] (formerly 14)] Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of DSM-IV anxiety and depression in children: a revised child anxiety and depression scale. Behav Res Ther. 2000 ;38(8):835-55.

[19] Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005;114(1-2):29-36.

[20] Crombez G, Bijttebier P, Eccleston C, Mascagni T, Mertens G, Goubert L, et al. The child version of the pain catastrophizing scale (PCS-C): a preliminary validation. Pain. 2003;104(3):639-46.

[21] Ferland CE, Villemure C, Michon P-E, Gandhi W, Ma M-L, Chouchou F, Parent AJ, Bushnell MC, Lavigne G, Rainville P, Ware MA, Jackson PL, Schweinhardt P and Marchand S. Multicenter

assessment of quantitative sensory testing (QST) for the detection of neuropathic-like pain responses using the topical capsaicin model. *Canadian Journal of Pain* 2018;2:266-279.

[22] Blankenburg M, Boekens H, Hechler T, Maier C, Krumova E, Scherens A, Magerl W, Aksu F and Zernikow B. Reference values for quantitative sensory testing in children and adolescents: Developmental and gender differences of somatosensory perception. *PAIN* 2010;149:76-88.

[23] Teles AR, Ocay DD, Bin Shebreen A, Tice A, Saran N, Ouellet JA and Ferland CE. Evidence of impaired pain modulation in adolescents with idiopathic scoliosis and chronic back pain. *Spine J* 2018.

[24] IASP. Terminology - Allodynia [Web Page]. Available at https://www.iasp-pain.org/resources/terminology/. 2021.

[25] Sandkühler J. Models and mechanisms of hyperalgesia and allodynia. *Physiol Rev* 2009;89:707-58.

[26] Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011;152:S2-s15.

[27] Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, Haythornthwaite JA, Jensen MP, Kerns RD, Ader DN, Brandenburg N, Burke LB, Cella D, Chandler J, Cowan P, Dimitrova R, Dionne R, Hertz S, Jadad AR, Katz NP, Kehlet H, Kramer LD, Manning DC, McCormick C, McDermott MP, McQuay HJ, Patel S, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Revicki DA, Rothman M, Schmader KE, Stacey BR, Stauffer JW, von Stein T, White RE, Witter J and Zavisic S. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. *The Journal of Pain* 2008;9:105-121.

[28] Price DD, Staud R, Robinson ME, Mauderli AP, Cannon R and Vierck CJ. Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients. *Pain* 2002;99:49-59.

[29] Staud R, Vierck CJ, Robinson ME and Price DD. Effects of the N-methyl-D-aspartate receptor antagonist dextromethorphan on temporal summation of pain are similar in fibromyalgia patients and normal control subjects. *The journal of pain : official journal of the American Pain Society* 2005;6:323-32.

[30] Tousignant-Laflamme Y, Pagé S, Goffaux P and Marchand S. An experimental model to measure excitatory and inhibitory pain mechanisms in humans. *Brain Research* 2008;1230:73-79.

[31] Goffaux P, Lafrenaye S, Morin M, Patural H, Demers G and Marchand S. Preterm births: can neonatal pain alter the development of endogenous gating systems? *Eur J Pain* 2008;12:945-51.

[32] Potvin S and Marchand S. Pain facilitation and pain inhibition during conditioned pain modulation in fibromyalgia and in healthy controls. *Pain* 2016;157:1704-10.

[33] Normand E, Potvin S, Gaumond I, Cloutier G, Corbin JF and Marchand S. Pain inhibition is deficient in chronic widespread pain but normal in major depressive disorder. *J Clin Psychiatry* 2011;72:219-24.

[34] Ferland CE, Teles AR, Ingelmo P, Saran N, Marchand S and Ouellet JA. Blood monoamines as potential biomarkers for conditioned pain modulation efficacy: An exploratory study in paediatrics. *Eur J Pain* 2019;23:327-340.

[35] Schweinhardt P and Bushnell MC. Pain imaging in health and disease--how far have we come? *J Clin Invest* 2010;120:3788-97.

[36] Nir RR and Yarnitsky D. Conditioned pain modulation. *Curr Opin Support Palliat Care* 2015;9:131-7.

[37] Farrar JT, Young JP, Jr., LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001;94(2):149-58.

[38] Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. The Journal of Pain. 2008;9(2):105-21.

[39] Vega E, Beaulieu Y, Gauvin R, Ferland C, Stabile S, Pitt R, et al. Chronic non-cancer pain in children: we have a problem, but also solutions. Minerva Anestesiol. 2018;84(9):1081-92

[40] Bansal S, Sriganesh K. Features and Assessments of Pain, Anaesthesia, and Analgesia [Internet]. In: Rajendram R, Patel VB, Preedy VR, Martin CR, editors. The analgesia nociception index: Features and application. London: Academic Press; 2021. Chapter 42, pp 463-473. Available from https://doi.org/10.1016/B978-0-12-818988-7.00039-X

[41] World Health Organization. ICD-11 for Mortality and Morbidity Statistics [internet]. Geneva: World Health Organization; 2021 Jan 1. Chronic Pain; [cited 2021 Dec 4] Available from: https://icd.who.int/browse11/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f1581976053

2.QUESTIONNAIRES USED IN THE STUDY:

Chronic Pain Clinic
Department of Anesthesia
514-412-4448

Hôpital de Montréal pour enfants
Centre universitaire de santé McGill

Montreal Children's Hospital
McGill University Health Centre

Evaluation tool: Functional Disability Inventory (FDI)*

NAME _____

DATE _____

TO BE FILLED BY PATIENT ONLY					
When people are sick or not feeling well, it is sometimes difficult for them to do their regular activities. In the last few days, would you have had any physical trouble or difficulty doing these activities? Please put an "X" in the square that shows how often each of these things happen to you. There is no right or wrong answer.	No trouble	A little trouble	Some trouble	A lot of trouble	Impossible
1 Walking to the bathroom					
2 Walking up stairs					
3 Doing something with a friend (for example playing a game)					
4 Doing chores at home					
5 Eating regular meals					
6 Being up all day without a nap or rest					
7 Riding the school bus or traveling in the car					
Remember, you are being asked about difficulty due to physical health					
8 Being at school all day					
9 Doing the activities in gym class (or playing sports)					
10 Reading or doing homework					
11 Watching TV					
12 Walking the length of a football field					
13 Running the length of a football field					
14 Going shopping					
15 Getting to sleep at night and staying asleep					

* Walker L and Greene JW. Journal of Pediatric Psychology, Vol. 16, No 1, 1991, pp 39-58

Chronic Pain Clinic
Department of Anesthesia
514-412-4448

Hôpital de Montréal pour enfants
Centre universitaire de santé McGill

Montreal Children's Hospital
McGill University Health Centre

IOFS*

NAME _____

FILLED OUT BY: ☐ Mother ☐ Father

DATE _____

TO BE FILLED BY PARENTS ONLY					
The following is a list of statements which describe how some parents of children with a disability feel that the disability has affected their family. Please rate, by putting an "X" in the square, whether you agree with each statement. There are no right or wrong answers.		**Strongly agree**	**Agree**	**Disagree**	**Strongly disagree**
1	Fatigue is a problem for me because of my child's diagnosis				
2	We see family and friends less because of the diagnosis				
3	Sometimes we have to change plans about going out at the last minute because of my child's state				
4	We have a little desire to go out because of my child's diagnosis				
5	I don't have much time left over for other family members after caring for my child				
6	I live from day to day and don't plan for the future				
7	It is hard to find a reliable person to take care of my child				
8	My family gives up things because of my child's diagnosis				
9	Nobody understands the burden I carry				
10	Because of my child's diagnosis, we are not able to travel out of the city				
11	Sometimes I feel like we live on a roller coaster : in crisis when my child is acting out, OK when things are stable				
12	People in the neighborhood treat us specially because of my child's diagnosis				
13	Traveling to appointments with therapists and specialists is a strain on me				
14	I think about not having more children because of the diagnosis				
15	Sometimes I wonder whether my child should be treated "special" or the same as a normal child				

Chronic Pain Clinic
Department of Anesthesia

Hôpital de Montréal pour enfants
Centre universitaire de santé McGill

Montreal Children's Hospital
McGill University Health Centre

PCS-C Thoughts and feelings during pain

NAME _____

DATE _____

TO BE FILLED BY PATIENT ONLY						
We are interested in the thoughts and feelings you have when you are in pain. Below are 13 sentences of different thoughts and feelings you can have when you are in pain. Try to show us as clearly as possible what you think and feel by putting an "X" in the square that corresponds to your answer that best reflects how strongly you have each thought. Please answer all questions. There is no right or wrong answers.	Not at all	To a slight degree	To a moderate degree	To a great degree	All the time
1 When I am in pain, I worry all the time about whether the pain will end.					
2 When I am in pain, I feel I can't go on like this much longer.					
3 When I am in pain, it's terrible and I think it's never going to get better.					
4 When I am in pain, it's awful and I feel that it takes over me.					
5 When I am in pain, I can't stand it anymore.					
6 When I am in pain, I become afraid that the pain will get worse.					
7 When I am in pain, I keep thinking of other painful events.					
8 When I am in pain, I want the pain to go away.					
9 When I am in pain, I can't keep it out of my mind.					
10 When I am in pain, I keep thinking about how much it hurts.					
11 When I am in pain, I keep thinking about how much I want the pain to stop.					
12 When I am in pain, there is nothing I can do to stop the pain.					
13 When I am in pain, I wonder whether something serious may happen.					

Chronic Pain Clinic
Department of Anesthesia

Hôpital de Montréal pour enfants
Centre universitaire de santé McGill

Montreal Children's Hospital
McGill University Health Centre

PCS-P Thoughts and feelings when your child is in pain

NAME _____

DATE _____

TO BE FILLED BY PARENTS ONLY

We are interested in the thoughts and feelings you have when you are in pain. Below are 13 sentences of different thoughts and feelings you can have when you are in pain. Try to show us as clearly as possible what you think and feel by putting an "X" in the square that corresponds to your answer that best reflects how strongly you have each thought. Please answer all questions. There is no right or wrong answers.

		Not at all	To a slight degree	To a moderate degree	To a great degree	All the time
1	When my child is in pain, I worry all the time about whether the pain will end.	☐	☐	☐	☐	☐
2	When my child is in pain, I feel I can't go on like this much longer.	☐	☐	☐	☐	☐
3	When my child is in pain, it's terrible and I think it's never going to get better.	☐	☐	☐	☐	☐
4	When my child is in pain, it's awful and I feel that it takes over me.	☐	☐	☐	☐	☐
5	When my child is in pain, I can't stand it anymore.	☐	☐	☐	☐	☐
6	When my child is in pain, I become afraid that the pain will get worse.	☐	☐	☐	☐	☐
7	When my child is in pain, I keep thinking of other painful events.	☐	☐	☐	☐	☐
8	When my child is in pain, I want the pain to go away.	☐	☐	☐	☐	☐
9	When my child is in pain, I can't keep it out of my mind.	☐	☐	☐	☐	☐
10	When my child is in pain, I keep thinking about how much he/she is suffering.	☐	☐	☐	☐	☐
11	When my child is in pain, I keep thinking about how much I want the pain to stop.	☐	☐	☐	☐	☐
12	When my child is in pain, there is nothing I can do to stop the pain.	☐	☐	☐	☐	☐
13	When my child is in pain, I wonder whether something serious may happen.	☐	☐	☐	☐	☐

*Crombez,Bijttebier, Eccleston, Mascagni, Martens, Goubert and Verstraeten. (2012). Pain

Chronic Pain Clinic
Department of Anesthesia
514-412-4448

Hôpital de Montréal pour enfants
Centre universitaire de santé McGill

Montreal Children's Hospital
McGill University Health Centre

Pittsburgh Sleep Quality Index*
page 1 of 2

NAME _____

DATE _____

TO BE FILLED BY PATIENT ONLY		
Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.		
1	During the past month, what time have you usually gone to bed at night?	Bed time _____
2	During the past month, how long (in minutes) has it usually taken you to fall asleep each night?	Number of minutes _____
3	During the past month, what time have you usually gotten up in the morning?	Getting up time _____
4	During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)	Hours of sleep per night _____

For each remaining question, please put an "X" in the square to the best response. Please answer all questions.		Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
5	During the past month, how often have you had trouble sleeping because you:				
a	Cannot get to sleep within 30 minutes				
b	Wake up in the middle of the night or early morning				
c	Have to get up to use the bathroom				
d	Cannot breathe comfortably				
e	Cough or snore loudly				
f	Feel too cold				
g	Feel too hot				
h	Have bad dreams				
I	Have pain				
j	Other reason(s), please describe: _____				
k	How often during the past month have you had trouble sleeping because of this?				

Pittsburg Sleep Quality Index* **NAME** _____

page 2 of 2

DATE _____

TO BE FILLED BY PATIENT ONLY				
Please put an "X" in the square that corresponds to your answer. Please answer all questions.	**Very good**	**Farily good**	**Fairly bad**	**Very bad**
6 During the past month, how would you rate your sleep quality overall?				
Please put an "X" in the square that corresponds to your answer. Please answer all questions.	**Not during the past month**	**Less than once a week**	**Once or twice a week**	**Three or more times a week**
7 During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?				
8 During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
Please put an "X" in the square that corresponds to your answer.	**No problem at all**	**Only a very slight problem**	**Somewhat of a problem**	**A very big problem**
9 During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?				

*Buysse, D.J., Reynolds III, C.F., Monk, T.H., Berman, S.R., & Kupfer, D.J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. Journal of Psychiatric Research, 28(2), 193-213.

Chronic Pain Clinic
Department of Anesthesia
514-412-4448

Hôpital de Montréal pour enfants
Centre universitaire de santé McGill

Montreal Children's Hospital
McGill University Health Centre

RCADS*
page 1 of 2

NAME _____

DATE _____

TO BE FILLED BY PATIENT ONLY					
Please put an "X" in the square that shows how often each of these things happen to you. There is no right or wrong answers.		**Never**	**Sometimes**	**Often**	**Always**
1	I worry about things				
2	I feel sad or empty				
3	When I have a problem, I get a funny feeling in my stomach				
4	I worry when I think I have done poorly at something				
5	I would feel afraid of being on my own at home				
6	Nothing is much fun anymore				
7	I feel scared when I have to take a test				
8	I feel worried when I think something is angry with me				
9	I worry about being away from my parents				
10	I get bothered by bad or silly thoughts or pictures in my mind				
11	I have trouble sleeping				
12	I worry that I will do badly at my school work				
13	I worry that something awful will happen to someone in my family				
14	I suddenly feel as if I can't breathe when there is no reason for this				
15	I have problems with my appetite				
16	I have to keep checking that I have done things right (like the switch is off, or the door is locked)				
17	I feel scared if I have to sleep on my own				
18	I have trouble going to school in the mornings because I feel nervous or afraid				
19	I have no energy for things				
20	I worry I might look foolish				
21	I am tired a lot				
22	I worry that bad things will happen to me				
23	I can't seem to get bad or silly thoughts out of my head				
24	When I have a problem, my heart beats really fast				
25	I cannot think clearly				
26	I suddenly start to tremble or shake when there is no reason for this				
27	I worry that something bad will happen to me				
28	When I have a problem, I feel shaky				
29	I feel worthless				
30	I worry about making mistakes				

RCADS*
page 2 of 2

NAME _____

DATE _____

TO BE FILLED BY PATIENT ONLY					
Please put an "X" in the square that shows how often each of these things happen to you. There is no right or wrong answers.		**Never**	**Sometimes**	**Often**	**Always**
31	I have to think of special thoughts (like numbers or words) to stop bad things from happening				
32	I worry what other people think on me				
33	I am afraid of being in crowded places I (like shopping centers, the movies, buses, busy playgrounds)				
34	All of a sudden I feel really scared for no reason at all				
35	I worry about what is going to happen				
36	I suddenly become dizzy or faint when there is no reason for this				
37	I think about death				
38	I feel afraid if I have to talk in front of my class				
39	My heart suddenly starts to beat too quickly for no reason				
40	I feel like I don't want to move				
41	I worry that I will suddenly get a scared feeling when there is no reason to be afraid of				
42	I have to do some things over and over again (like washing my hands, cleaning or putting things in a certain order)				
43	I feel afraid that I will make a fool of myself in front of people				
44	I have to do some things in just the right way to stop bad things from happening				
45	I worry when I go to bed at night				
46	I would feel scared if I had to stay away from home overnight				
47	I feel restless				

*Chorpita BF, et al. Behaviour Research and Therapy , 2000. 27, 835-855.

3. CONSENT FORMS ENGLISH AND FRENCH VERSIONS

Centre universitaire de santé McGill
McGill University Health Centre

X HME MCH X HGM MGH X HRV RVH
X HNM MNH X ITM MCI X CL LC

FMU-9997

L'Hôpital de Montréal pour enfants
The Montreal Children's Hospital
Centre universitaire de santé McGill
McGill University Health Centre

PEDIATRIC RESEARCH INFORMATION AND CONSENT FORM

Title: Validity of the Analgesia Nociception Index in Children and Adolescents with Chronic Pain

Persons responsible:

- Research Institute, McGill University Health Centre: Dr. Sabrina Carrié MD, Complex Pain Center (CPC), Department of Anesthesia at the Montreal Children's Hospital
- Ingelmo, Pablo Mauricio
- Hudon, Jonathan
- Nada Mohamed MSc student, McGill University, Experimental Medicine

Funding Source: No funding.

WHY ARE YOU BEING INVITED TO TAKE PART IN THIS STUDY?

The Edwards Family Interdisciplinary Center for Complex Pain (CCP) participates in research studies to try to improve treatments for children living with chronic pain. Today, we are inviting you to take part in a research study. Please read this information to help you decide if you want to participate in this research project. It is important that you understand this information. We encourage you to ask questions. Please take all the time you need to make your decision.

We encourage parents to include their child in the discussion and decision making to the extent that the child is able to understand.

In this research information and consent form, "you" means you or your child.

WHY IS THIS STUDY BEING DONE?

Chronic pain is a condition that affects many children and adolescents. Although treatments exist for chronic pain, we don't have many ways to measure how well these treatments are working. The Analgesia Nociception Index is a good tool to measure pain levels in people under anesthesia. We would like to find out if the Analgesia Nociception Index could be a good tool to measure pain in adolescents with chronic pain as well.

You are being invited to participate in a research study that aims to compare Analgesia Nociception Scores before and after pain treatment.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 120 patients will take part in this study from the Montreal Children's Hospital.

WHAT WILL HAPPEN ON THIS RESEARCH STUDY?

Your participation will include an initial evaluation and an evaluation at discharge as per the complex Pain Center usual protocol. There will be no extra tasks required on your part. We are asking you to grant approval to the Complex Pain Center to collect additional data (Analgesia Nociception Index) during these appointments for research purposes. This data will be collected using a device that records your heart rate. We will place one electrode sticker on your right collarbone and a second electrode sticker under your left armpit. The electrode stickers will remain in place while we complete the rest of our evaluation as per our usual protocol. The

electrode stickers will then be removed once the evaluation is complete. These electrode stickers do not cause any discomfort but may take a few minutes to put them on and take them off. The evaluation is done during the same appointment as the Quantitative Sensory Testing (QST) and the entire session should take about 60 minutes. If during the course of your pain treatment, an interventional block is offered to you, we will also collect additional data with the Analgesia Nociception Index. This should not add any time to your visit as you will be monitored during and after the intervention as per usual protocol.

In addition to collecting information about your heart rate, we would also like to use the information in the questionnaires we use in our regular evaluations. These questionnaires include: Pittsburgh Sleep Quality Index, Functional Disability Inventory, Revised Child Anxiety and Depression Scale, Numerical Rating Scale for pain, Adolescent Pediatric Pain Tool, and the DN4 for Neuropathic Pain. We will also review your medical chart to collect demographic information such as gender, age as well as information pertaining to your pain diagnosis.

FOR HOW LONG WILL YOU PARTICIPATE IN THIS STUDY?

Participants in this study will be assessed at two time periods:

1) At the initial evaluation at the complex pain center

2) An evaluation at discharge from the complex pain center

The duration of each evaluation will last about 60 minutes

WHAT ARE THE RISKS?

Additional time to place the electrode stickers may inconvenience you.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There is no direct benefit to you for participating in this research. We hope that what we learn from doing this study will help us find better ways to assess the effectiveness of treatment for patients with chronic pain in the future.

WHAT OTHER OPTIONS ARE THERE?

Instead of participating in this research project, you could choose the standard treatment, which also includes questionnaires including the Pittsburgh Sleep Quality Index, the Functional Disability Inventory, the Revised Child Anxiety and Depression Scale, the Numerical Rating Scale, the Adolescent Pediatric Pain Tool, and the DN4 for Neuropathic Pain., and the physical examination including a detailed neurological exam.

Please discuss the different options you have with your doctor.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

There are no financial costs to participants.

ARE THERE OTHER FINANCIAL ASPECTS?

You will not receive financial compensation for participating in this research study.

SHOULD YOU SUFFER ANY HARM

Should you suffer harm of any kind following any procedure related to this research study, you will receive all the care and services required by your state of health.

By agreeing to participate in this research study, you are not waiving any of your rights nor discharging the doctor in charge of the study, the sponsor, or the institution of their civil and professional responsibilities.

HOW IS PRIVACY ENSURED?

During your participation in this study, the doctor in charge of the study and the research team will collect in a study file the information about you needed to meet the scientific objectives of the study.

The study file may include information from your medical charts including your: identity, such as your name, gender, date of birth, ethnicity , past and present health status, lifestyle, and the results of all tests, exams, and procedures that will be performed.

All study data collected during this research study will remain confidential to the extent provided by law. You will be identified by a code number only. The key to the code linking your name to your study file will be kept by the doctor in charge of this research study.

To ensure your safety, a document indicating your participation in this study e.g., a copy of the Informed Consent Form OR a data information sheet is included in your medical chart. The results of certain tests conducted as part of the research may be included as well, depending on the situation. As a result, any person or company to whom you give access to your medical chart will have access to this information.

Study data will be stored for at least 15 years following the end of the study by the doctor in charge of this research study. The questionnaires, and Analgesia Nociception Index recordings will be destroyed 25 years after the completion of the research project.

In order to ensure your protection and quality control of the research project, the following organizations could consult your research and medical records:

The sponsor(s) of this project (The research Institute at the Montreal Children's Hospital);

The McGill University Health Center Research Ethics Board

All these individuals and organizations will have access to your personal data, but they adhere to a confidentiality policy.

The study data may be published or shared at scientific meetings; however, it will not be possible to identify you. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

You have the right to consult your study file in order to verify the information gathered, and to have it corrected if necessary.

IS YOUR PARTICIPATION VOLUNTARY?

Your participation in this research study is voluntary. Therefore, you may refuse to participate. You may also withdraw at any time, without giving any reasons, by informing the doctor in charge of this research study or a member of the research team.

Your decision not to participate in the study, or to withdraw from it, will have no impact on the quality of care and services to which you are otherwise entitled, or on your relationship with the teams providing them.

The doctor in charge of this research study, the Research Ethics Board, or the sponsor may put an end to your participation without your consent. This may happen if new findings or information indicate that participation in this research study is no longer in your best interests, if you do not follow study instructions, or if there are administrative reasons to terminate the study.

If you withdraw or are withdrawn from the study, no further data will be collected. However, the information already collected for the study will be stored, analyzed and used to ensure the integrity of the study, as described in this document.

Any new findings acquire during the course of the study that could influence your decision to continue your participation will be shared with you quickly.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have any questions about this research project or if you suffer any problems, you believe are related to your participation in this research, you can call the researcher responsible for the project in your hospital:

Montreal Children's Hospital: Dr. Sabrina Carrié at (514) 412-4448

In case of emergency, please go directly to the closest emergency room.

If you would like information about your rights related to your participation in the research, or if you wish to file a complaint, you may contact the hospital Ombudsman (Patient Representative):

- Montreal Children's Hospital: 514-412-4400, extension 22223

WHERE CAN I GET MORE INFORMATION?

You may ask to receive a copy of the results of this research project; these will only be available after the entire project has been completed.

You will receive a signed copy of this form. You may ask the research team questions at any time.

RESEARCH ETHICS COMMITTEE

The research ethics committee of McGill University Health Centre approved this project and will monitor the project.

CONSENT AND ASSENT FORM

Title of this research project: Validity of the Analgesia Nociception Index in Children and Adolescents with Chronic Pain

I have reviewed the Informed Consent Form. Both the research study and the Informed Consent Form were explained to me. My questions were answered, and I was given sufficient time to decide. After reflection, I consent to participate, or that my child will participate in this research study in accordance with the conditions stated above, including the use of all personal data and samples collected.

I authorize the study team to access my medical chart or the medical chart of my child.

In addition, I authorize the researcher or research team to inform the family doctor or treating physician, in writing, that I am/my child is taking part in this research study, and to send them all relevant information.

Name of participant Assent of minor, capable of understanding

Date

(Print) the nature of the research (signature) or

Verbal assent of minor obtained by:

_____

Name of parent(s) or legal guardian Signature Date

(Print)

Name of participant (18 years +) Signature

Date

(Print)

I have explained to the participant and/or his parent/legal guardian all the relevant aspects of this study. I answered any questions they asked. I explained that participation in a research project is free and voluntary and that they are free to stop participating at any time they choose.

Name of Person obtaining consent (signature)

Date

(Print)

Addendum to consent form

Participant who has now become an adult (18)

Title of research project: Validity of the Analgesia Nociception Index in Pediatric Adolescents with Chronic Pain

Today, I reviewed the information and consent form that my parents signed on my behalf when I enrolled in this research project and a copy of that signed consent was given to me.

I agree to continue my participation in this research project.

I understand that my participation is free and voluntary and that I can stop participating in this research project at any time I choose.

I authorize the research team to consult my medical records to collect the information relevant to this project.

If I withdraw, any remaining data that has not already been analyzed will be destroyed.

_____

Name of participant Signature Date

Name of person Signature Date

obtaining consent

French consent form

Ethics approval letter from Nagano