Distribution agreement

In presenting this thesis as a partial fulfillment of the requirements for a degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis in whole or in part in all forms of media, now or hereafter now, including display on the World Wide Web. I understand that I may select some access restrictions as part of the online submission of this thesis. I retain all ownership rights to the copyright of the thesis. I also retain the right to use in future works (such as articles or books) all or part of this thesis.

Mayuri Charan Date: 03/31/2025

Correlation of Warmth Detection with Sensitivity of Modalities such as Temperature Thresholds and Pain Thresholds

By

Mayuri Charan

Dr. Daniel Harper, PhD.

Adviser

Neuroscience and Behavioral Biology

Dr. Daniel Harper, PhD.
Adviser

Dr. Leah Roesch, PhD
Committee Member

Dr. Rick Thompson, PhD
Committee Member

2025

Correlation of Warmth Detection with Sensitivity of Modalities such as Temperature Thresholds and Pain Thresholds

By

Mayuri Charan

Dr. Daniel Harper, PhD.

Advisor

An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
of the requirements of the degree of
Bachelor of Sciences with Honors

Neuroscience & Behavioral Biology

2025

Abstract

Correlation of Warmth Detection with Sensitivity of Modalities such as Temperature Thresholds and Pain Thresholds
By Mayuri Charan

Introduction and Background:

The ability to perceive temperature is crucial for human interaction with the environment. The mechanisms behind thermal detection and pain processing involve specialized receptors, sensory fibers, and pathways. This study aims to understand how warmth detection influences sensitivity to temperature and pain, particularly concerning warmth-insensitive fields (WIFs), areas with impaired warmth detection. Understanding the relationship between warmth detection and thermal modalities such as heat pain, cool detection and cold pain could provide insights into sensory processing and chronic pain mechanisms. It allows us to understand the physiology, integration and processing of both innocuous and noxious thermal stimuli.

Materials and Methods:

The study included 44 sites (22 WIFs and 22 non WIFs) from 22 pain-free participants. Warmth-insensitive fields (WIFs) were identified using thermal stimulation. Sensitivity to thermal stimuli, including warmth, cool, heat pain, and cold pain thresholds, were measured in WIFs and normally sensitive regions using quantitative sensory testing. Data analysis involved correlation tests to examine relationships between thermal thresholds.

Results:

The study revealed correlations between warmth detection thresholds and nociceptive sensitivity. Higher warmth detection thresholds were associated with higher heat pain thresholds in WIFs and normally sensitive regions. Warmth detection thresholds were inversely correlated with cold-related measures, indicating that reduced warmth sensitivity was associated with reduced cold sensitivity.

Conclusion:

This study demonstrates a relationship between warmth detection, cold sensitivity, and pain thresholds. Further, it also opens avenues of research into the integrated processing of cold and warm stimuli which has traditionally been thought to have distinct processing. The findings suggest that thermal and nociceptive processing are interconnected, which may have implications for understanding and managing chronic pain conditions such as Fibromyalgia where hypersensitivity is a symptom and other conditions characterized by altered thermal perception.

Correlation of Warmth Detection with Sensitivity of Modalities such as Temperature Thresholds and Pain Thresholds

By

Mayuri Charan

Dr. Daniel Harper, PhD.

Advisor

A thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
of the requirements of the degree of Bachelor of Sciences with Honors

Neuroscience & Behavioral Biology

2025

Acknowledgements

I would like to start by thanking Dr. Harper for his support and guidance throughout this project and his continued mentorship during my time at the Harper PaIN Lab. His constant encouragement and passion for science helped me gain skills both in research and in critical thinking and problem solving. I want to thank him for his time and support in this project and for his invaluable mentorship. I am incredibly thankful to my fellow lab members for their help, support, and willingness to collaborate. Their enthusiasm and dedication to research have made this experience even more enriching. I would also like to express my gratitude to Dr. Leah Roesch and Dr. Rick Thompson for their insightful feedback and valuable suggestions throughout this process. Their expertise and perspectives have greatly contributed to the development of this project. Thank you all for your time and support.

Table of Contents

Introduction and Background

The ability to perceive temperature is a fundamental aspect of human survival, playing a crucial role in how we interact with our environment. From the moment we react to the searing heat of a hot stove or the chilling touch of cold tile, our sensory systems are at work, allowing us to navigate life with awareness and caution. The mechanisms underlying thermal detection and pain processing are remarkably intricate, involving specialized receptors, distinct sensory fibers, and dedicated pathways that relay information from the skin to the brain (Proksch et al., 2008)

Understanding how the ability to detect warmth influences sensitivity to other temperatures and pain sensations is central to this study. The discovery of warmth-insensitive fields (WIFs) which are areas of skin where warmth detection is selectively impaired—by Green & Cruz (1998) marked an important milestone in the understanding of thermal perception (Green and Cruz,1998). These fields, found in approximately 65% of tested participants, raise the intriguing possibility that warmth perception is inherently linked to broader sensory and nociceptive processes (Green and Cruz,1998.

WIFs are particularly significant in research as they challenge traditional models of thermal sensation and provide a unique opportunity to investigate the organization of peripheral sensory pathways. Their existence suggests that warmth detection is not uniformly distributed across the skin but instead exhibits regional variability, which may be tied to distinct neural mechanisms. Studying WIFs could help refine our understanding of how different classes of thermoreceptors interact, particularly in relation to C-fiber-mediated warmth perception and A-delta fiber-mediated cold and pain detection. A key advantage of studying WIFs is that, in these regions, it is possible to selectively activate C-nociceptors responsible for thermal pain without simultaneously stimulating innocuous warmth fibers. This allows for a more precise investigation

of pain mechanisms, as it isolates the activity of nociceptive pathways from non-painful thermal perception. Such selective activation can provide crucial insights into how nociceptive C-fibers contribute to pain processing, both in healthy individuals and in those with chronic pain conditions. In the context of chronic pain, WIFs are especially relevant because altered thermal perception is a common feature of conditions such as fibromyalgia, neuropathy, and complex regional pain syndrome.

If warmth insensitivity correlates with heightened sensitivity to noxious stimuli, it could indicate changes in peripheral or central pain processing. Investigating WIFs may provide insight into why some individuals experience exaggerated pain responses while others exhibit sensory deficits, potentially helping identify new approaches to diagnosing and treating chronic pain conditions. By understanding the mechanisms underlying warmth detection and its interaction with pain sensitivity, researchers may uncover novel biomarkers or therapeutic targets for pain management.

Processing Thermal and Painful Stimuli: Separate but Overlapping Pathways

The processing of thermal and pain stimuli involves a complex, intricate system that separates innocuous thermal signals (warm and cool) from noxious thermal signals (heat pain and cold pain) at the peripheral, spinal, and central levels. While these modalities are initially detected by distinct receptors and fibers, they gradually converge within the central nervous system, which is supported by prior research (Craig, 2002; Craig et al., 1994). Understanding this balance between segregation and convergence is critical to explaining how impairments in one thermal modality (like warmth detection) might influence pain perception or the detection of other thermal modalities—the core focus of this thesis.

Historical Context of Thermal Perception

The scientific understanding of thermal perception has evolved significantly over the last century. Early research by Von Frey proposed that the skin contains distinct receptors responsible for touch, warmth, cold, and pain. His work laid the groundwork for the separate receptor theory, which proposed specialized end-organs for each modality (Rey, 1995). As technology advanced, the development of microneurography in the mid-20th century enabled researchers to directly record from single nerve fibers, providing direct evidence of low-threshold warmth-sensitive C fibers (Hensel & Iggo, 1971). These studies were grounded on the labeled line theory that proposed that specific sensory fibers were dedicated to each modality- one for warmth, one for cold, and separate pathways for heat pain and cold pain (Rey, 1995; Iggo, 1976).

In the late 20th century, the rise in neurophysiological studies, revealed a more complex network where there are separate sensory modalities partially converged in the spinal cord and brain (Craig, 2002; Craig et al., 1994). This work revolutionized the field by identifying that while separate afferent fibers carry warm, cool, and pain signals to the spinal dorsal horn, these signals begin to converge in the spinothalamic tract and higher-order brain regions like the thalamus and insular cortex.

In the 1990s, the discovery of transient receptor potential (TRP) channels revolutionized the field, demonstrating that thermal sensation relies heavily on these molecular sensors (Caterina et al., 1997). This historical progression underscores how evolving methodologies—ranging from behavioral testing to molecular biology—have continuously refined our understanding of how the skin senses thermal stimuli and how these signals are integrated with pain perception.

The skin as a sensory interface

Covering the entirety of the human body, the skin serves not only as a protective barrier but also as a highly complex sensory interface between the internal physiological environment and the external world (Proksch et al., 2008). This organ contains a dense network of specialized receptors and afferent fibers that detect mechanical, thermal, and nociceptive stimuli (Purves et al., 2001). Sensory information gathered at the periphery is transmitted to the spinal cord and eventually to higher brain centers for processing and interpretation, enabling adaptive behavioral responses (Craig, 2003).

The skin's role extends far beyond a passive barrier; it actively contributes to thermoregulation and pain processing through its densely packed sensory fibers, which constantly monitor environmental conditions. The ability to detect subtle temperature changes allows the body to adjust internal responses, such as shivering, vasoconstriction, and sweating, to maintain homeostasis. In this way, thermal perception is tightly coupled to survival mechanisms, highlighting its evolutionary importance (Green, 2009).

Peripheral Detection and Separation

Thermal perception involves a diverse population of sensory neurons and receptors embedded in the skin, each tuned to detect specific forms of stimulation. These fibers are traditionally classified into Aβ- fibers, Aδ- fibers, and C-fibers (Lumpkin & Caterina, 2007). Each of these different types of fibers contributes to the sensory experience of touch and pain differently, proving the complexity of the sensory system.

Aβ fibers are large-diameter, myelinated fibers that have rapid conduction velocities. They are primarily responsible for perceiving touch, pressure, and vibration. Their role in the sensory system extends beyond touch detection; research has shown that they are also significant in the

central sensitization of pain (Abraira & Ginty, 2013). Central sensitization describes the heightened reactivity of nociceptive neurons in the central nervous system to their usual stimuli. This process can increase heightened pain sensations, even without a specific injury (Latremoliere & Woolf, 2009). The modulation of Aβ fiber activity is crucial, as it may influence conditions such as neuropathic pain and chronic pain syndromes, where the sensory processing system is hypersensitive.

Conversely, Aδ fibers are small-diameter, fast conduction velocity, thinly myelinated nerve fibers responsible for quickly transmitting pain signals that are sharp, localized, and rapid. These fibers are activated by abrupt changes in temperature, such as sudden skin cooling or exposure to harmful heat that exceeds a certain threshold (Darian-Smith & Johnson, 1977)).

In contrast, C fibers are small-diameter unmyelinated, low-velocity and convey slower, dull, and prolonged sensations of warmth and pain. C fibers are polymodal, meaning they can respond to a variety of stimuli, including mechanical, thermal, and chemical triggers, thus contributing to diverse pain pathways. The cell bodies of the C-fibers are located in the dorsal root ganglia, they innervate both the skin and internal organs, forming a complex network essential for protective responses to harmful stimuli (Lumpkin & Caterina, 2007). Furthermore, these fibers can become sensitized by inflammatory mediators, heightening their responsiveness during tissue injury and leading to conditions like hyperalgesia and allodynia. Hyperalgesia refers to the condition in which there is an enhanced response from the nociceptive system to a stimulus usually occurring after tissue injury. Allodynia refers to drastic reduction in pain thresholds (Treede et al., 1992). Therefore, understanding the role of C fibers is crucial in pain management strategies, particularly for addressing chronic pain syndromes. These fibers terminate in different

layers of the epidermis and can be categorized into two types: peptidergic and nonpeptidergic C fibers (Arcilla & Tadi, 2025).

To summarize, C fibers are primarily involved in warmth detection with low conduction velocities and Aδ fibers are responsible for cool detection with a faster conduction velocity. Heat pain is detected by both Aδ fibers (sharp pain) and C nociceptors (burning pain both cold and heat), while cold pain is primarily detected by Aδ fibers. This follows the labeled lines theory that Von Frey proposed early on, ensuring that innocuous thermal stimuli (warm and cool) are processed differently than noxious thermal stimuli (heat and cold pain) (Rey, 1995; Darian-Smith & Johnson, 1977)

Molecular Thermometers: TRP Channels

Thermal perception at the molecular level relies heavily on Transient Receptor Potential (TRP) channels, a family of cation channels controlled by calcium levels that detect specific temperature ranges and convert them into neural signals (Samanta et al., 2018). There are two subfamilies essential to explore in this context- TRPV and TRPM families. TRPV channels (vanilloid subfamily) are critical for detecting warmth and noxious heat. TRPV1, in particular, responds to heat above 43°C, as well as capsaicin, and plays a role in heat pain perception (Rosenbaum & Simon, 2007). TRPM channels (melastatin subfamily) mediate cool and cold pain detection. TRPM8 is the primary cold sensor, activated by temperatures below 28°C and substances like menthol (Samanta et al., 2018).

This temperature-tuned molecular tool underlies our ability to detect temperature changes and calibrate pain perception. Dysfunction or selective loss of these channels, such as in warmth-insensitive fields (WIFs), could disrupt the entire sensory network.

Thermal TRP Channels: TRPV1, TRPV2, TRPV3, and TRPV4

Thermal perception relies heavily on a specialized group of ion channels known as Transient Receptor Potential Vanilloid (TRPV) channels, which are embedded in sensory nerve endings within the skin (Samanta et al., 2018). These cation channels detect heat and warmth stimuli, translating physical temperature changes into electrical signals that travel to the brain. Each member of the TRPV family is tuned to a specific temperature range, contributing to the detection of either innocuous warmth or noxious heat (Samanta et al., 2018).

TRPV1: The Heat Pain Sensor

TRPV1 is one of the most well-characterized thermal sensors. It responds to noxious heat—temperatures above approximately 43°C and is also activated by capsaicin, the compound responsible for the burning sensation from chili peppers (Caterina et al., 1997). This receptor is heavily involved in heat pain perception and serves as a critical player in nociceptive signaling, alerting the body to potentially tissue-damaging heat. Beyond its thermal role, TRPV1 can also be sensitized by inflammatory mediators, meaning it plays a role in thermal hyperalgesia during injury or inflammation (Dhaka et al., 2006; Rosenbaum & Simon, 2007).

TRPV2: The Extreme Heat Detector

TRPV2 detects even higher temperatures than TRPV1, typically responding to temperatures above 52°C (Dhaka et al., 2006). While its role in day-to-day sensory perception is less prominent, TRPV2 becomes particularly important in extreme environmental conditions or during exposure to severe burns. Unlike TRPV1, TRPV2 does not respond to capsaicin, highlighting functional specialization within the TRPV family.

TRPV3: The Warmth Detector

TRPV3 is activated by moderate warmth, within the range of 33°C to 39°C—well below the noxious threshold (Peier et al., 2002). This channel is critical for the perception of comfortable

warmth. TRPV3 is predominantly expressed in keratinocytes (skin cells) rather than in nerve fibers themselves, suggesting that these skin cells play an active role in sensing warmth and communicating with nearby sensory neurons (Dhaka et al., 2006).

TRPV4: Overlapping Warmth Sensation

TRPV4 also contributes to warmth detection, overlapping with TRPV3 in terms of its activation range (approximately 27°C to 34°C), but with slightly lower thresholds (Dhaka et al., 2006; Lumpkin & Caterina, 2007). TRPV4 is expressed in both cutaneous sensory neurons and keratinocytes, where it helps detect subtle increases in skin temperature that are not yet painful. Its dual expression in neurons and skin cells suggests that TRPV4 helps fine-tune warmth perception, providing redundancy and robustness to this sensory system (Dhaka et al., 2006).

TRPM8 cold-detecting receptors

These receptors are responsible for cold detection but are also involved in pain sensation, cancer, and bladder control (Liu et al., 2016). It is activated by cooling agents such as eucalyptus and icilin (Liu et al., 2016).

Pathways of perception

Thermal perception and other sensory experiences are processed through the somatosensory system, a vital nervous system component that integrates signals from both the central and peripheral nervous systems. This system comprises peripheral afferent nerve fibers, specialized receptors, and cutaneous sensitivity, contributing to our daily sensory experiences (McGlone & Reilly, 2010). It detects and interprets various sensations such as touch, temperature, pain, and body position, and consists of three major receptor types: mechanoreceptors, which sense mechanical pressure or distortion; thermoreceptors, which respond to temperature changes; and nociceptors, which detect pain (Arezzo et al., 1982).

Thermal and pain signals converge for the first time in the spinal cord, specifically in the Lamina I of the dorsal horn. A landmark study in primates and cats mapped the thermosensory-specific neurons in the lamina I, showing that some neurons responded exclusively to innocuous warmth, some to cool, and others to noxious heat or cold pain. However, there were also multimodal neurons that could integrate the input from different modalities, particularly between noxious cold and conscious heat. This suggests that while thermal and pain signals are partially segregated they are also capable of interacting in the early spinal pathway creating the possibility of cross-modal sensory interactions (Craig, 2003).

More recently, modern research has refined and expanded this understanding by exploring the role of Lamina I neurons in states of injury or damage. Studies have shown that neurons can become hyperresponsive not only to their usual thermal or noxious inputs but also to normally innocuous mechanical stimuli after injury to the nerve (Peirs & Seal, 2016; Todd, 2010). This phenomenon, known as tactile allodynia, underscores the plasticity of spinal thermal and pain circuits, demonstrating that these neurons can shift their tuning depending on the broader sensory context (Peirs & Seal, 2016; Todd, 2010). This supports the hypothesis that loss of warmth detection, for example, could trigger compensatory sensitization in nociceptive pathways, lowering pain thresholds in nearby skin regions.

Ascending Pathways: Spinothalamic tract

Ascending from the spinal cord, thermal and pain signals travel through the spinothalamic tract (STT), maintaining partial modality segregation at the thalamic level. It was identified that innocuous warmth and cool signals target the ventromedial posterior nucleus (VMpo), while noxious heat and cold pain signals project to the ventral posterior inferior (VPI) and the medial dorsal nucleus (MDvc)(Craig, 2003). This separation allows for sensory discrimination—

distinguishing warm from hot, for example—while keeping the nociceptive and non-nociceptive channels anatomically close enough to influence one another, particularly in situations of sensory ambiguity or central sensitization (Craig, 2003).

Newer research continues to underscore the importance of these ascending pathways, particularly highlighting their plasticity following chronic injury. Peirs et al demonstrated that Lamina I neurons projecting to the parabrachial nucleus undergo structural and functional reorganization after nerve injury, amplifying nociceptive transmission and contributing to central sensitization (Peirs & Seal, 2016). This plasticity alters how thermal and pain signals are prioritized, increasing the likelihood that innocuous stimuli, such as warmth or gentle touch, could be misinterpreted as painful in chronic pain states (Peirs & Seal, 2016). This aligns with clinical findings in chronic pain patients, where altered warmth and cool detection thresholds often correlate with increased sensitivity to pain (Finnerup et al., 2016).

At the cortical level, the insula has been identified as the primary "thermal cortex," where thermal signals from the thalamus are discriminated (posterior insula) and assigned affective value (anterior insula) (Craig et al., 2000). This posterior-to-anterior gradient has been confirmed by functional imaging studies, which consistently show that non-painful warmth and cool activate the posterior insula, while heat and cold pain recruit the anterior insula and anterior cingulate cortex (ACC) (Craig, 2003). More recent neuroimaging work has refined this picture, demonstrating that insula subregions show highly specific connectivity patterns, with the posterior insula linking to sensory-discriminative networks and the anterior insula linking to limbic and affective networks (Geuter et al., 2017). This reinforces the dual-processing model of thermal perception, where sensory and affective processing run in parallel but continuously interact to generate a unified thermal experience.

These findings have important implications for understanding sensory dysfunction. Disruption of warmth detection, such as in warmth-insensitive fields (WIFs), could distort both thermal discrimination and the affective evaluation of temperature and pain, potentially contributing to the development of thermal hyperalgesia. This creates the rationale for examining how reduced warmth detection correlates with altered heat and cold pain thresholds, as this study seeks to investigate.

Evidence for cross-modal sensory interference

Several studies show that loss of one thermal modality can alter perception in others, indicating functional interdependence despite anatomical separation at early stages. Research has demonstrated that patients with partial warmth loss perceive cold stimuli as warm, a phenomenon known as paradoxical thermal sensation (Defrin et al., 2002). This strongly suggests that the brain relies on balanced input from both warmth and cool receptors to accurately interpret thermal stimuli—losing one side of the system disrupts the whole.

Newer research, particularly studies in mice, challenges the older assumption that warmth and cold detection rely solely on separate labeled lines. Instead, it is increasingly evident that warmth perception arises from the balance between warm-excited and cold-excited fibers, particularly through interactions between TRPV1 and TRPM8 channels (Paricio-Montesinos et al., 2020). This dual-coding mechanism suggests that any loss in warmth sensitivity could distort cold and cold pain perception, making the entire sensory balance unstable.

Further supporting this, Green et al demonstrated that prior thermal adaptation directly shifts thermal pain thresholds—showing that sensory history primes the nervous system to interpret future thermal stimuli (Green & Akirav, 2007). This reinforces the idea that the absence

of warmth input from certain skin fields (like in WIFs) could alter baseline sensory calibration, making individuals more sensitive to thermal pain in those areas.

Another research study revealed that individual sensitivity to warmth and cold are highly correlated, suggesting that these two thermal modalities are not processed entirely independently, but instead rely on overlapping central mechanisms (Green & Akirav, 2007). This interdependence implies that the absence of warmth detection, as seen in warmth-insensitive fields (WIFs), could disrupt the broader balance of thermal perception, potentially altering cold perception and pain sensitivity in these regions. These findings emphasize the importance of studying warmth detection not in isolation, but as part of a larger sensory network, which is critical for understanding how localized sensory deficits may contribute to broader sensory dysfunction.

The ability to selectively activate noxious C nociceptors also offers a controlled framework for studying the specific contributions of these fibers to pain modulation. In this context, warmth-insensitive fields (WIFs) offer a unique, naturally occurring sensory model to investigate how non-noxious thermal loss affects pain sensitivity.

Furthermore, Ossipov et al. emphasize the significance of descending pain modulation in the transition from acute to chronic pain. Their study suggests that an imbalance in these modulatory pathways—favoring pain facilitation over inhibition—may contribute to the persistence of chronic pain states (Ossipov et al., 2014). Since warmth-insensitive fields may influence pain perception, investigating their role in these dysregulated pain modulation systems could provide deeper insights into the mechanisms of chronic pain. Additionally, the effectiveness of serotonin/norepinephrine reuptake inhibitors (SNRIs) in managing chronic pain further underscores the importance of these descending modulatory processes. Understanding whether

warmth-insensitive fibers interact with these pathways could offer new perspectives on pain modulation and potential therapeutic interventions (Ossipov et al., 2014).

By studying how heat pain and cold pain thresholds shift within WIFs, researchers can directly assess the interdependence between thermal perception and nociception, providing insights that could translate into both diagnostic and therapeutic innovations. This is particularly relevant in chronic pain conditions such as fibromyalgia, where altered thermal thresholds and central sensitization are prominent features (Desmeules et al., 2003; Petzke et al., 2003). Understanding whether warmth detection correlates with sensitivity to thermal and pain thresholds could reveal valuable sensory biomarkers for altered peripheral and central processing in chronic pain.

Rationale for the Present Study

This study examines the separate yet convergent thermal processing systems to elucidate the functional interdependence of sensory pathways. By investigating whether reduced warmth detection correlates with altered cool, heat, and cold pain thresholds, the study directly explores the integration of thermal and nociceptive processing. It is predicted that warmth detection thresholds will correlate positively with heat pain thresholds in both WIFs and non-WIFs, indicating that individuals with reduced warmth sensitivity also exhibit reduced sensitivity to heat pain. Additionally, warmth detection thresholds are expected to correlate negatively with cool detection and cold pain thresholds, suggesting that individuals with higher warmth detection thresholds (reduced sensitivity to warmth) will have lower cool detection (requiring colder temperatures to perceive cool stimuli) and cold pain thresholds. These relationships would provide evidence for a shared neural basis underlying thermal and nociceptive processing.

To test these hypotheses, quantitative sensory testing (QST) was employed to map WIFs and measure the thresholds for warmth, cool, cold pain, and heat pain detection in both WIFs and non-WIFs. This approach allowed for a direct comparison between areas with only nociceptive fibers and those capable of detecting both innocuous and noxious stimuli, offering insights into the peripheral and central processing of thermal sensation. The findings from this study demonstrate that warmth insensitivity is associated with altered sensitivity to other thermal stimuli, supporting the hypothesis of shared neural mechanisms in thermal perception.

Materials and Methods

Study Design

In this study, participants were pre-screened to ensure they were healthy controls. The exclusion criteria included severe physical impairment, cardiopulmonary disorders, a history of cancer, severe psychiatric illnesses, opioid use, pregnancy, and autoimmune diseases. Those who met the eligibility requirements were asked to come for an in-person session. This study involved a total of 21 participants recruited with IRB approval, comprising healthy controls aged between 17 and 70. In total, there were 5 participants that were completely excluded due to inability to find WIFs. Additionally, only 6 of the participants had two WIFs totaling to 22 WIFs and 22 non-WIFs, among 16 participants that were included. There were 11 females and 5 males with an average of 31.5 years. During this session, the sensory testing protocol and questionnaires enquiring about previous experiences of pain, anxiety, depression were administered. This protocol included quantitative sensory testing, identifying warmth-insensitive fields (WIFs), and determining thermal thresholds. For each session, two WIFs and two non-WIFs were selected for testing. If a second WIF could not be identified, only one was tested. The total duration of the study visit was approximately 2.5 hours.

Thermal Stimulation Device

For this study we used the Medoc-TSA 2 (Medoc Ltd., 2019) thermal stimulator to deliver varying temperature simulations. The Medoc-TSA 2 utilizes a 16X16 cm square thermode that uses rapid liquid cooling to guarantee no prolonged stimulation.

Figure 1. Medoc TSA2 thermal stimulator (Medoc Ltd., 2019)

Identification of the Warmth Insensitive Fields (WIFs)

To systematically identify warmth-insensitive fields (WIFs) and assess their relationship to other thermal thresholds, we conducted sensory testing on the non-dominant forearm and lower calf. This protocol followed the approach used by Green and Cruz, ensuring consistency in methodology(Green and Cruz, 1998). The goal was to locate regions with reduced warmth sensitivity and test sensitivity thresholds to areas with normal thermal perception.

The identification process began by mapping a standardized grid onto the skin surface of the tested area using a stencil corresponding to the size of the thermode probe. On the forearm, the grid extended from the inner wrist to the bend of the elbow, aligning with the middle finger. On the leg, the grid was applied to the lower calf region. This ensured a consistent testing area among participants.

Figure 2. Thermode used 16X16 mm

Figure 3. WIF mapping grid on forearm

To assess warmth sensitivity, the Medoc thermal device delivered controlled temperature increases. The thermode was set to gradually raise the skin temperature from a baseline of 32°C to 38°C, with an increment of 0.5°C per second. This temperature was selected to activate innocuous warmth-sensitive fibers effectively without activating the nociceptors. After each temperature presentation, participants rated their warmth sensation on a 100-point scale, where 0 indicated no sensation at all and 100 represented the most intense sensation imaginable. This scale was chosen to provide a wide range for participants to express their warmth sensation, allowing for more precise data collection.

The lowest 10% of warmth ratings were marked and documented to identify potential WIFs. This threshold was chosen to ensure that only the most insensitive areas were categorized as WIFs. In these marked regions, the temperature was further increased to 40°C in increments of 0.5°C per second to confirm warmth insensitivity. This temperature was selected as it is the higher range of temperature to activate innocuous warm fibers. Participants rated their warmth sensation again using the same scale. Areas that consistently received a rating of 0 were classified as warmth-insensitive regions. Additionally, participants were asked to present sensation qualities from a list that consisted of Neutral, Burning, Cool, Stinging, Hot, Cold, Sharp, Warm, Aching, or none.

If none of the areas were found to have a zero rating, the thermode was systematically shifted in various orientations around the regions with ratings lower than 5, continuing this process until one or two complete warmth-insensitive fields (WIFs) were identified. Once the WIFs were identified, they were marked for further testing. Additionally, two regions demonstrating normal sensitivity were selected to undergo the same testing procedures for comparative analysis.

Nociceptive sensitivity testing

Several tasks were used to evaluate the sensitivity and response of mechanoreceptors. Using this method of quantitative sensory testing, the nociceptive sensitivity of different modalities, such as warm thresholds, cool thresholds, heat pain thresholds, and cold pain thresholds, were measured. These tests are performed separately in each of the marked regions, with the thresholds determined for each specific region. In total, four areas are tested in this series of tasks, with two of them being warmth-insensitive regions and the other two being normally

sensitive regions. Additionally, the stimuli presented were alternated between a WIF and a normally sensitive region to minimize possible changes in sensitivity due to repeated testing.

1. *Warm thresholds- Method of Limits*

The Medoc is used to apply the appropriate stimulus to measure the warmth thresholds in the regions of both warmth insensitivity and normal sensitivity. For this task, the method of limits was used to determine the warm thresholds. There was a gradual increase in temperature from baseline (32°C) in increments of 0.5°C per second, and the participants were given a remote control with a button that they were instructed to press when they felt a change in sensation from neutral to warm for the first time. They were also given a list of sensation qualities from which they were asked to choose as many or as few as they felt. The sensation quality list contained the following sensations- Neutral, Burning, Cool, Stinging, Hot, Cold, Sharp, Warm, and Aching. The same task is repeated three times per region, and finally, the average threshold of warmth is calculated using the Medoc program.

2. *Warm thresholds- levels*

The Levels Test was utilized to accurately determine the warmth detection threshold. Participants were presented with multiple randomized temperature trials, where the temperatures were systematically varied to refine the measurement of their thresholds. The test was conducted on four selected areas, including two WIFs and two non-WIFs, which allowed for effective comparisons. Participants were instructed to respond "Yes" when they first perceived a warm sensation, and their responses were recorded using Medoc software. The test presented temperatures close to each participant's threshold based on their responses, allowing the program to narrow down to the temperature at which the participant first felt warmth. The task continued

until the system collected sufficient responses, at which point Medoc automatically ended the test. The warmth detection threshold was then calculated based on the recorded responses.

3. *Cool thresholds- Method of Limits*

The Medoc is used to apply the appropriate stimulus to measure the cool thresholds in both warmth insensitivity and normal sensitivity regions. For this task, the method of limits is used to determine the cool thresholds. There was a gradual decrease (0.5°C per second) in temperature from baseline, and the participants were given a remote that they were instructed to press when they felt a change in sensation from neutral to cool for the first time. Participants were also given a list of sensation qualities, Burning, Cool, Stinging, Hot, Cold, Sharp, Warm, and Aching, from which they were asked to choose as many or as few as they felt. The same task is repeated three times per region, and finally, the average cool threshold was calculated using the Medoc program.

4. *Cool Thresholds- Levels*

The levels test presents multiple trials using which the threshold is calibrated to measure the cool threshold more closely to the temperature first felt by the subject. To the four selected regions, the ability to perceive the sensation of cool was measured by presenting randomly varying temperatures. The participants were asked to say “Yes” when they felt any sensation, in this case, a cool sensation. The Medoc ended the task once all the necessary responses were noted. The cool threshold was determined by looking at the values that closely matched the participants' response to first feeling a sensation.

5. *Heat Pain and Cold Pain Thresholds*

For both heat and cold pain thresholds, the Method of Limits was utilized, where the temperature increased or decreased (0.5°C per second) from the baseline (32°C) until participants

indicated the sensation had shifted to pain. This task was repeated three times per region, and the pain threshold was determined through the average of the three trials for each region.

Prolonged noxious stimulation

A noxious heat stimulus was repeatedly applied to the WIFs for this task. The temperature for this was determined by adding 1°C to the detection threshold of the subject to ensure that the stimuli is painful and activates noxious fibers for that specific region. This allows the standardized application of a stimulus that will be painful for the subject. The participants were allowed to stop the teat at any point in case they felt intolerable pain. The task began with two methods of limiting tasks before the continuous stimulation so that the baseline threshold could be determined. In the limits portion of the task, the participants are asked to press the button when they feel any sensation. Then, the noxious stimuli were applied for 10 seconds, after which a rating of their pain and sensation quality were noted. It was then followed by two methods of limits test where the participant was asked to press the button if they felt any sensation. These tasks were repeated for eight trials, and all the ratings were noted.

Analysis

After collecting all the data, analysis was conducted using SPSS (Version 29.0.2.0 (20)) to examine the correlations between the various sensory thresholds and the ability to detect different innocuous and noxious stimuli. Both Pearson and Spearman correlation tests were used to assess the strength and significance of these relationships. Pearson's correlation was used to assess the strength and direction of linear relationships, while Spearman's correlation, a non-parametric test, was also used to identify the direction of relationships and provide robustness in the presence of outliers. Using both methods allowed for a more thorough analysis, ensuring that associations were not limited to linear trends but also accounted for broader patterns in the data.

Additionally, the data was visualized through linear regression plots, allowing for the calculation of correlation values and the identification of key significant findings.

Results

Among 21 participants, there were 5 participants that were completely excluded due to inability to find WIFs. Additionally, only 6 of the participants had two WIFs totaling to 22 WIFs and 22 non-WIFs tested. Each site was analyzed individually to assess the relationships between warmth detection thresholds and other thermal sensory modalities, including heat pain thresholds, cold sensitivity, and cold pain thresholds. Correlation analyses were performed using both Pearson's correlation (Table 1) to evaluate linear relationships and Spearman's correlation (Table 1) to confirm robustness in cases of non-linear distributions**.**

Warmth Detection and Heat Pain Thresholds

A strong positive correlation was observed between warmth detection thresholds and heat pain thresholds in women with chronic conditions (WIFs), indicating that those who had higher warmth detection thresholds also displayed higher heat pain thresholds. Specifically, Pearson's correlation analysis revealed a significant positive relationship between warmth thresholds and heat pain thresholds in WIFs ($r = 0.614$, $p = 0.002$). This finding was consistent with Spearman's correlation, which showed a similar positive trend ($\rho = 0.793$, $p < 0.001$), reinforcing the notion that individuals with elevated warmth detection thresholds also tended to have increased heat pain thresholds (Figure 4).

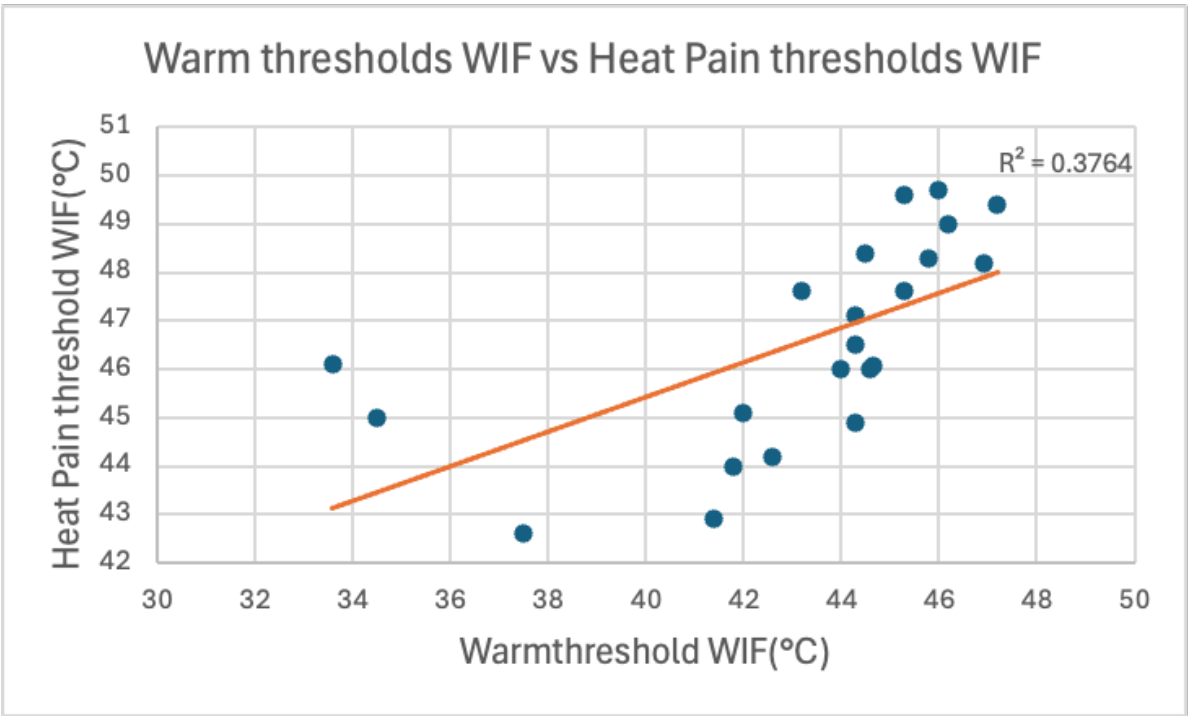

Figure 4. Correlation between Warmth thresholds in warmth insensitive fields (WIFs) and Heat pain thresholds in WIFs Pearson's Correlation ($r = 0.614$, $p = 0.002$)

A comparable trend was noted between warm levels thresholds and heat pain thresholds in WIFs, where Pearson's correlation indicated a value of ($r = 0.525$, $p = 0.012$), and Spearman's correlation yielded ($\rho = 0.456$, $p = 0.033$) (see Figure 5). Furthermore, there was a significant correlation between heat pain in WIFs and heat pain in regions with normal sensitivity, with Pearson's correlation measuring ($r = 0.658$, $p < 0.001$) and Spearman's correlation at ($\rho = 0.662$, $p < 0.001$). This suggests that heat pain thresholds are stable across different skin regions (Figure 6).

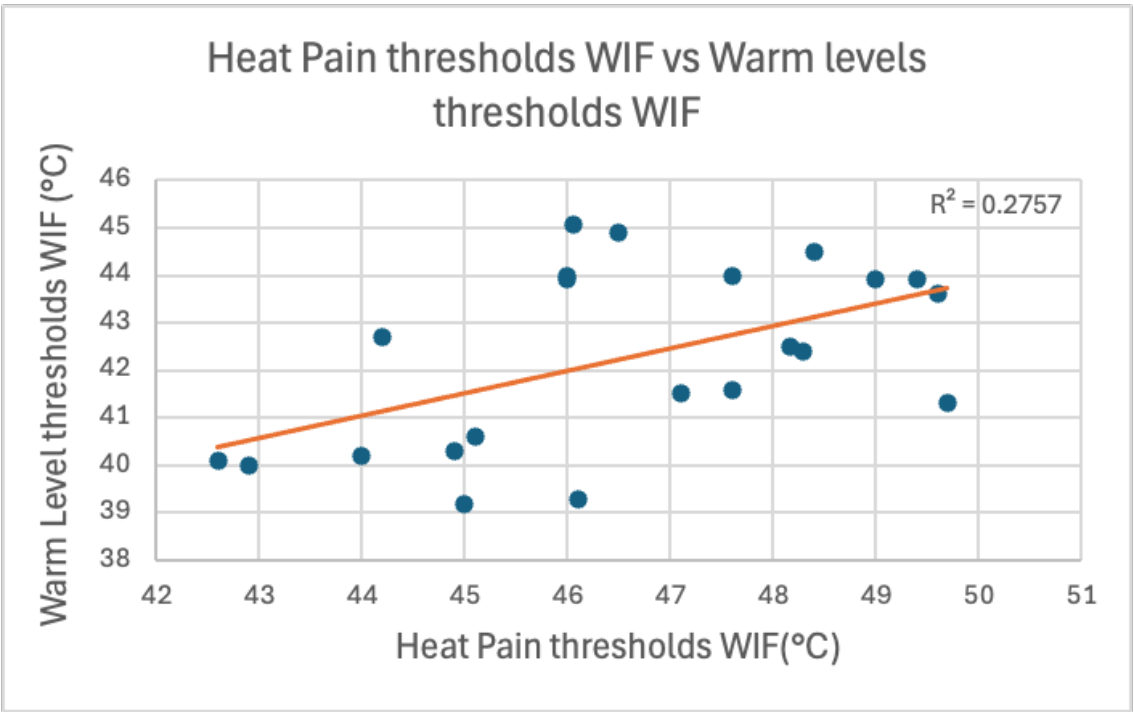

Figure 5. Correlation between Heat pain thresholds in WIFs and warm levels thresholds in WIFs Pearson's correlation (r = 0.525, p = 0.012)

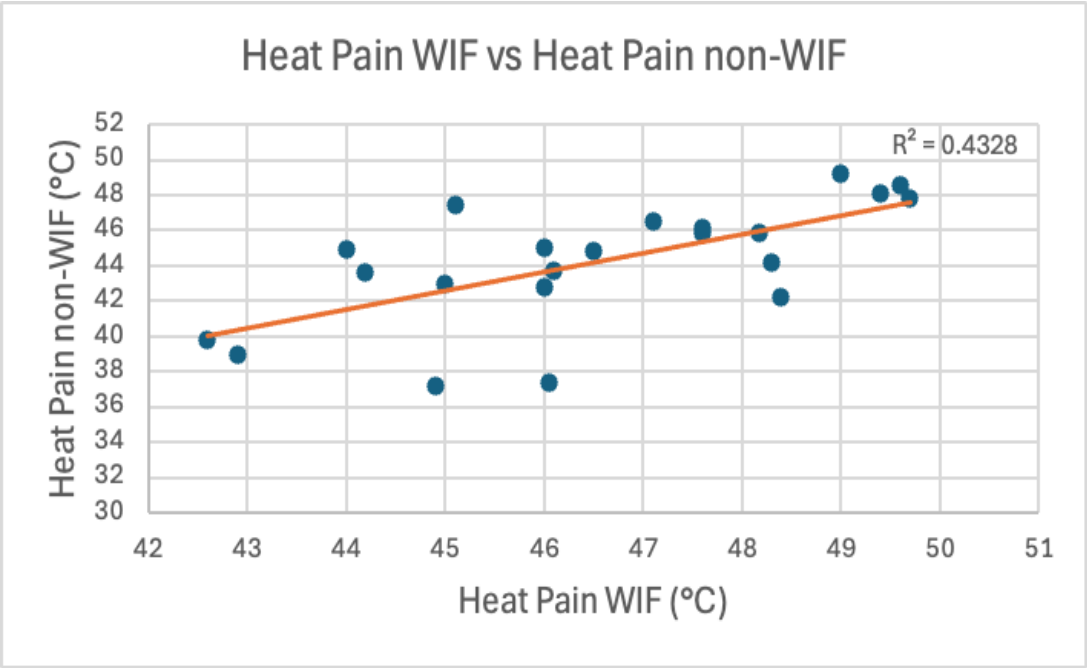

Figure 6. Correlation between Heat pain thresholds in WIFs and Heat pain in non-WIFs Pearson's correlation (r = 0.658, p < 0.001)

Additionally, a robust positive correlation was identified between warm thresholds and warm levels thresholds in WIFs ($r = 0.705$, $p < 0.001$), highlighting a significant relationship in warmth detection when using both method of limits and method of levels (Figure 7). Spearman's correlation further supported this finding with ($\rho = 0.629$, $p = 0.002$), indicating a level of consistency across different warmth detection assessment methods.

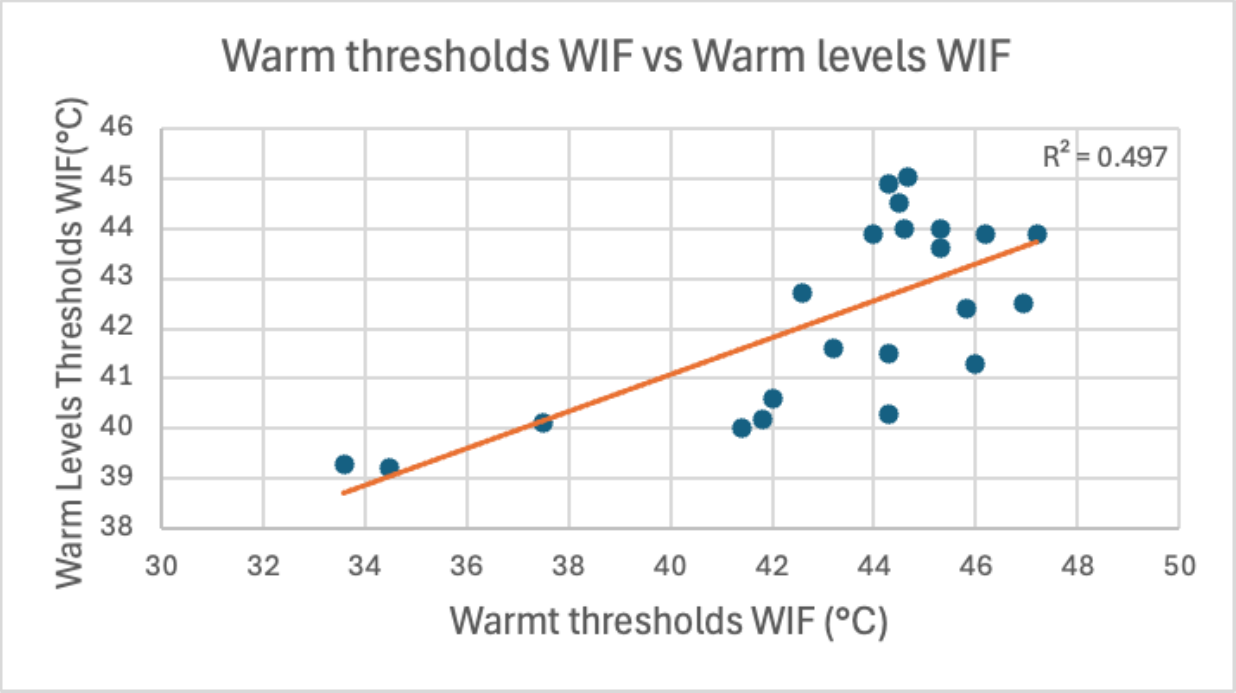

Figure 7. Correlation between Warm thresholds in WIFs and Warm levels thresholds in WIFs Pearson Correlation ($r = 0.705$. $p < 0.001$)

Warmth Detection and Cold Sensitivity

It was found that warm detection was inversely correlated with cold-related measures, suggesting that as sensitivity to heat increased, sensitivity to cold also increased. As the threshold for detecting warmth rose, the threshold for detecting cold dropped, meaning individuals required lower temperatures to perceive cool sensations, contributing to reduced overall thermal sensitivity. Pearson's correlation between warm thresholds in WIFs and cool thresholds in WIFs

was (r = –0.450, p = 0.041), while Spearman's correlation was (ρ = –0.609, p = 0.003), confirming a significant negative association (Figure 8).

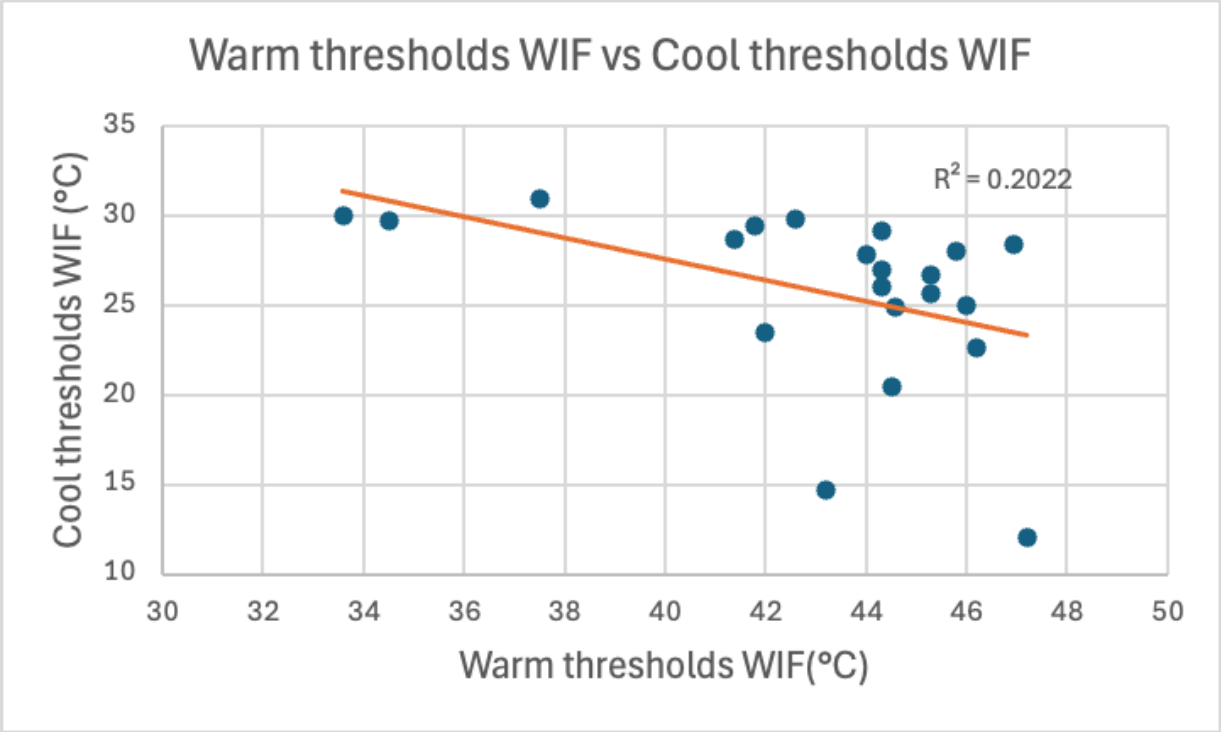

Figure 8. Correlation between Warm thresholds in WIFs and Cold thresholds in WIFs Pearson's correlation (r = –0.450, p = 0.041)

A similar trend was observed between warm thresholds in WIFs and cool thresholds in normally sensitive regions, with Pearson's correlation at (r = –0.476, p = 0.029) and Spearman's correlation at (ρ= –0.491, p = 0.024) (Figure 9).

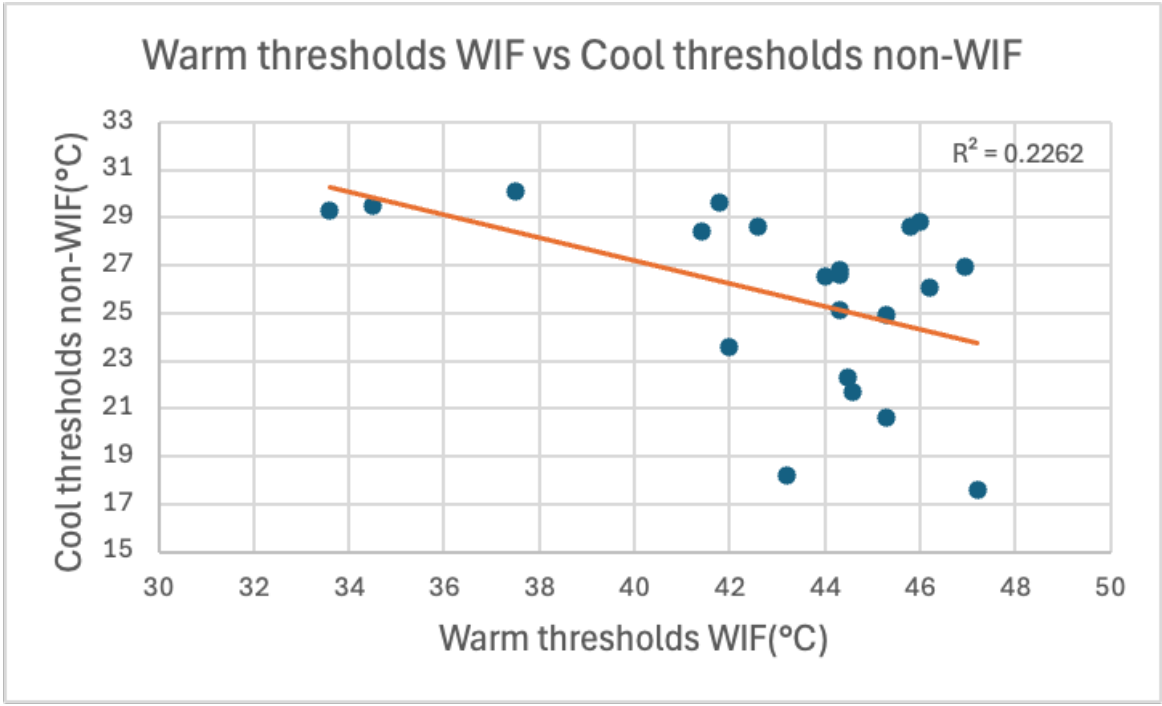

Figure 9. Correlation between Warm thresholds in WIFs and Cold thresholds in non-WIFs Pearson's correlation (r = –0.476, p = 0.029)

An inverse relationship was also identified between warmth detection and cold pain thresholds. Warm thresholds in normally sensitive regions showed a significant negative correlation with cold pain thresholds in non-WIFs, with Pearson's correlation at (r = -0.575, p = 0.006) and Spearman's correlation at (ρ = -0.473, p = 0.030) (Figure 10).

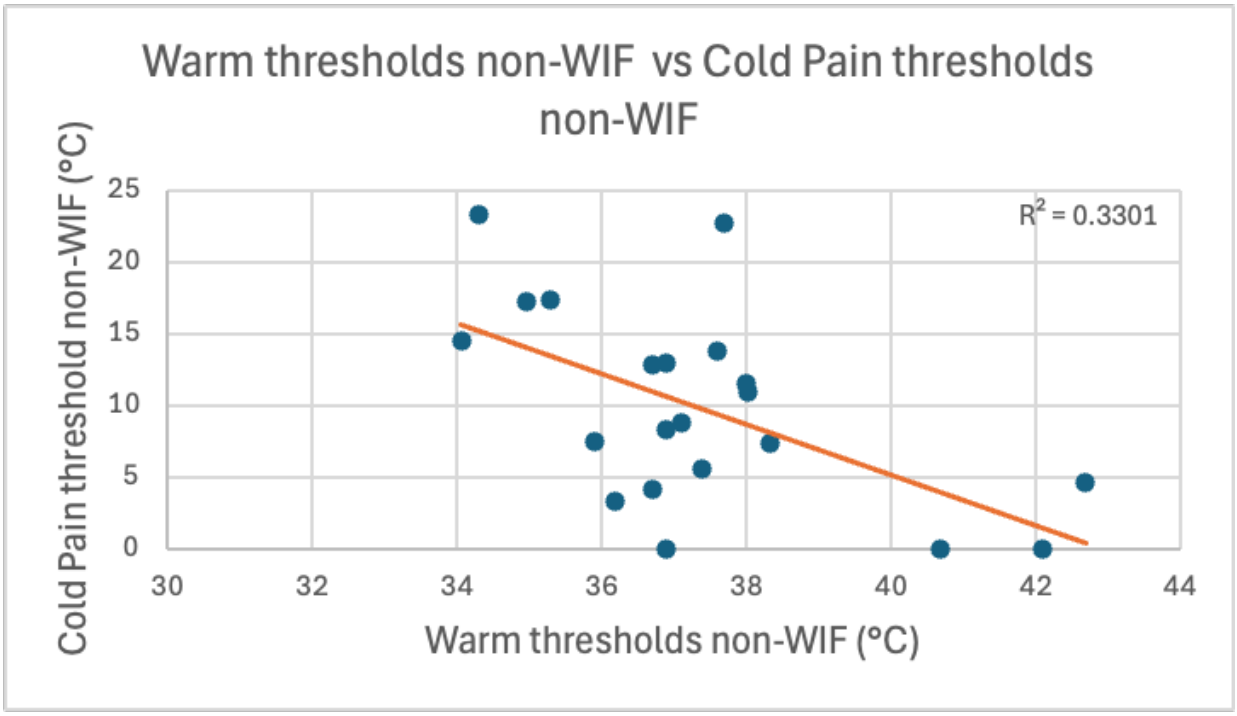

Figure 10. Correlation between Warm thresholds and Cold pain thresholds in non-WIFs Pearson's Correlation (r = -0.575, p = 0.006)

These results suggest a strong functional interplay between warmth and cold sensory processing, with inverse relationships persisting across WIFs and non-WIFs. There was also a significant negative correlation between heat pain thresholds and cool thresholds in WIFs (Figure 11) with Pearson's correlation (r=-0.556, p=0.007) and Spearman's correlation (ρ = -0.671, p <0.001).

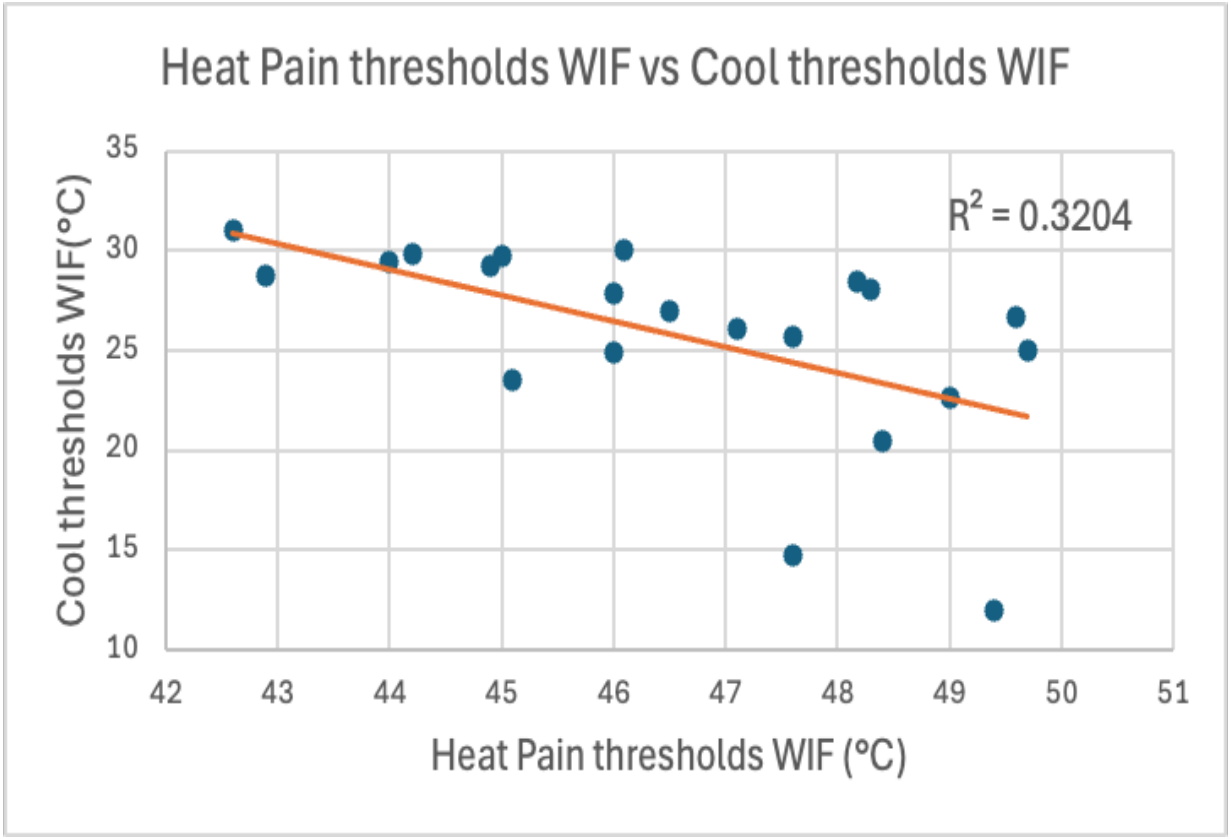

Figure 11. Correlation between Heat Pain thresholds in WIFs and Cold thresholds in WIFs Pearson's correlation (r=-0.556, p=0.007)

However, no significant correlation was found between warmth detection thresholds in normally sensitive regions and heat pain thresholds. Pearson's correlation between warm thresholds and heat pain in non-WIFs was ($r = 0.343$, $p = 0.118$), indicating that warmth detection did not strongly influence heat pain sensitivity in normally sensitive areas. Correlation analyses did not reveal significant relationships between warmth detection and cold pain thresholds in WIFs. Pearson's correlation between warm thresholds and cold pain thresholds in WIFs was ($r = -0.103$, $p = 0.655$), while Spearman's correlation was ($\rho = -0.204$, $p = 0.375$), neither of which reached statistical significance. A similar trend was observed for warm levels and cold pain thresholds in WIFs with Pearson's correlation at ($r = -0.177$, $p = 0.444$). These findings suggest

that warmth detection and cold pain thresholds are more strongly correlated in non-WIFs than in WIFs, potentially indicating distinct sensory processing within WIFs.

Lastly, among cool thresholds, the thresholds in WIFs and non-WIFs correlate positively with strong significance having Pearson values ($r=0.865$, $p<0.001$) and spearman's ($\rho=0.848$, $p<0.001$) (Figure 12). This shows that cool detection thresholds in WIFs and non-WIFs are consistent. A summary of significant correlations using both Pearson's and Spearman's analyses is presented in Table 1, confirming the robustness of key findings.

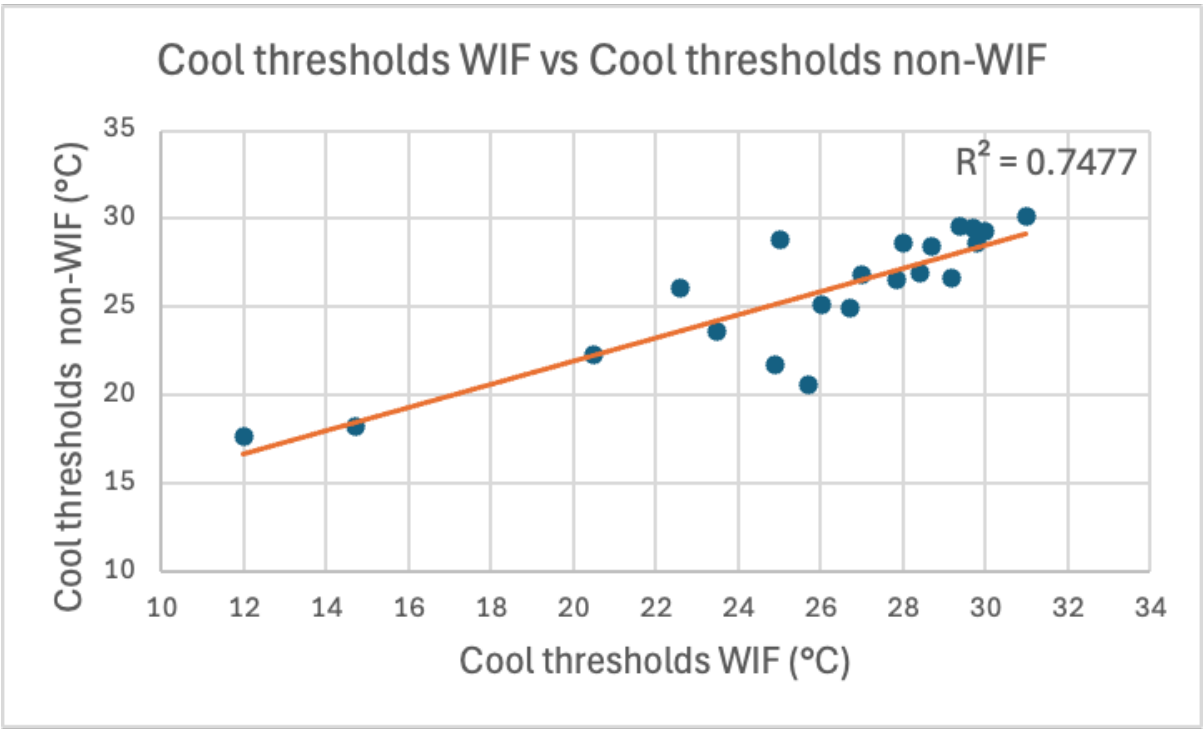

Figure 12. Correlation between Cool thresholds in WIFs and Cool thresholds in non-WIFs Pearson's correlation ($r=0.865$, $p<0.001$)

Modalities	Pearson Correlation	Two- tailed gnificance(p)	pearman orrelation	Two- tailed gnificance(p)
Warm thresholds WIF vs Heat pain thresholds WIF	0.614	0.002	0.793	<0.001
Warm levels thresholds WIF vs Heat pain thresholds WIF	0.525	0.012	0.456	0.033
Heat pain thresholds WIF vs Heat pain thresholds non-WIF	0.658	<0.001	0.662	<0.001
Warm thresholds WIF vs Warm levels thresholds WIF	0.705	<0.001	0.629	0.002
Warm thresholds WIF vs Cool thresholds WIF	-0.45	0.041	-609	0.003
Warm thresholds WIF vs Cool thresholds non-WIF	-0.476	0.029	-0.491	0.024
Warm thresholds non-WIF vs Cold pain thresholds non-WIF	-0.575	0.006	-0.473	0.03
Heat pain thresholds WIF vs Cool thresholds WIF	-0.556	0.007	-0.671	<0.001
Cool thresholds WIF vs Cool thresholds non-WIF	0.865	<0.001	0.848	<0.001

Table 1. Pearson and Spearman Correlations with the two tailed significance for different modalities

Discussion

This study investigated the relationships between warmth detection thresholds, cold sensitivity, and nociceptive processing, revealing significant correlations suggesting possible interdependent thermal and pain perception mechanisms. In line with the hypothesis, the key findings indicate that increased sensitivity to warmth corresponds with increased sensitivity to cold, cold pain, and heat pain. The results suggest the possibility that thermal sensitivity may

involve some degree of shared processing, where responsiveness to one thermal modality could be associated with sensitivity across others.

Although there has been research on the correlation between warm and cool perception, there has not been extensive research on its correlation with nociceptive pathways or the differences between warmth-insensitive regions and non-WIFs. Traditionally, each thermal modality has been considered distinct and said to have very different methods of perception and processing. However, the findings of this study provide insight into pain modulation and physiological processing of pain and contribute to our growing understanding of chronic pain pathways. The correlation between heat pain thresholds in non-WIFs and heat pain in WIFs suggests that heat pain processing remains stable across different regions of the skin (Figure 6). This indicates that, even in areas where warmth detection is impaired (WIFs), the mechanisms responsible for detecting noxious heat (heat pain) are still functional.

Since WIFs lack warmth-sensitive C fibers but retain nociceptive C fibers, this finding supports the idea that heat pain is primarily mediated by nociceptive fibers rather than warmth-sensitive ones. Since WIFs lack C fibers that sense innocuous warmth, the fibers that get activated at warmth thresholds are the nociceptive fibers that are active. Therefore, the warmth detection thresholds in WIFs refer to the detection of heating stimuli rather than the sensation of warmth. This aligns with the findings as heat pain and warmth in WIFs are dictated by nociceptive C fibers. These findings also reinforce the robustness of pain-processing pathways, which appear to function consistently regardless of the presence or absence of warmth sensitivity in a particular region. This finding aligns with research indicating that thermal pain perception can remain intact in areas lacking certain thermal sensations. For instance, a study on the sensory determinants of

pain observed that individuals with preserved warm sensations exhibited normal heat pain perception, even when other thermal sensations were absent (Defrin et al., 2002).

Furthermore, the strong positive correlation between warmth and heat pain thresholds in WIFs (Figure 4, 5) suggests that the ability to detect warmth is correlated to nociceptive heat processing, potentially implicating shared sensory pathways (Figure 4, 5). This leads to a potential understanding of pain mechanisms and distribution of nociceptive C fibers. Research suggests that regions with reduced warmth detection often have a lower density of warmth-sensitive C-fibers, which could account for the diminished thermal sensitivity observed in WIFs (Green and Cruz, 1998). The findings of Campero et al. support this idea by demonstrating that C-polymodal nociceptors, which mediate both thermal and nociceptive signals, can be differentially distributed across the skin, influencing both warmth detection and cold pain sensitivity (Campero et al., 2001; Campero et al., 1996).

This strong correlation between warmth and heat pain thresholds supports the notion that heat perception and nociceptive heat processing could rely on overlapping neural substrates. This reinforces previous findings that TRPV1 ion channels, which mediate warmth sensation and noxious heat perception, may play a central role in these interactions. Research done on TRPV1-deficient mice showed that TRPV1 was integral to detecting painful sensations and thermal hypersensitivity, as those lacking these vanilloid receptors could not detect heat pain (Caterina et al., 2000; Davis et al., 2000).

Similarly, the negative correlation between warmth detection and cold pain sensitivity (Figure 10) implies that individuals less sensitive to warmth also experience cold pain at lower temperatures (low warmth sensitivity leads to low cold pain sensitivity), reinforcing the idea of possible interdependence amongst temperature and pain related stimuli (Figure 10). This was

significant in non-WIFs, showing that in the presence of warmth insensitivity, there is no correlation between warmth detection and cold pain, suggesting that C fibers play a role in both warmth detection and cold pain processing. The lower peripheral fiber density of these fibers in WIFs might explain the weaker correlation between warmth detection and cold pain sensitivity in these regions, suggesting a distinct processing mechanism compared to non-WIF areas.

These findings provide insights into sensory integration and may have important implications for pain research and clinical applications. This correlation between warmth detection and cold pain further suggests that as an individual's ability to detect warmth increases, they feel more cold pain. This may be particularly relevant in conditions associated with chronic pain and sensory hypersensitivity. Additionally, these findings resonate with previous work that identified distinct and shared patterns of cerebral activation for innocuous heat and noxious heat (Tseng et al., 2010). Their study showed the superior role of brain regions like the inferior parietal lobe in warmth perception while highlighting the unique activation of the primary and secondary somatosensory cortices during painful stimuli (Tseng et al., 2010). Research has also shown that, with the peripheral nerve fibers terminating in the dorsal horn of the spinal cord, the majority of the A-delta and C fibers activate the laminae I and II (Todd, 2010).

It has also been found that in the cortex, no one region responds to only thermal stimulation and not noxious stimulation (Green & Akirav, 2007). The insular cortex, anterior cingulate cortex (ACC), and secondary somatosensory cortex (S2) have been shown to process both noxious and innocuous thermal stimuli (Bushnell et al., 2013; Craig et al., 2000). Past research has also shown that pain and temperature are distributed close to each other in the somatotopic map of the thalamus and insula (Hua le et al., 2005; Olausson et al., 2005; Ostrowsky et al., 2002; Patel et al., 2006). The extent and point at which thermal integration occurs is a

scarcely researched topic; it has been said that it happens in multiple different locations within the neural axis, leading to a hierarchical system with the dorsal horn being the first point of control (Pehl et al., 1997; Simon & Iriki, 1971). Therefore, understanding where the information potentially converges could help us determine the specific pathways that play a role in detecting both innocuous warmth, cool and noxious heat and cold.

Our results suggest that warmth detection might engage overlapping neural pathways mediating the perception of heat pain and cold pain, indicating potential for a more integrated thermal processing system than previously understood. Looking at the peripheral detection mechanisms, research reveals that many cold-specific receptors are located within the slow-conducting C fiber range, challenging the conventional view that cold sensation is primarily mediated by myelinated A-delta fibers. These C fibers not only exhibit steady activity at normal skin temperatures but also respond dynamically to cooling, highlighting their essential role in modulating cold sensitivity (Campero et al., 2001; Campero et al., 1996). Furthermore, the presence of these unmyelinated C fibers suggests a complex interplay in the sensory pathways for cold, potentially contributing to non-discriminatory cold sensations alongside faster conducting A delta fibers. This could explain the lack of correlation in WIFs as there are very few or no C fibers in those regions.

Underlying neural and physiological mechanisms of temperature and pain processing can also explain these correlations. Warmth detection is primarily mediated by TRPV1 receptors, which also detect noxious heat stimuli, explaining the correlation between warmth and heat pain thresholds (Caterina et al., 1997). At the same time, cold sensitivity is detected by TRPM8 receptors, while cold pain is thought to involve TRPA1 and TRPM8 receptors detected by Aδ and C-fibers nociceptive fibers (McCoy et al., 2011). The positive correlation between warmth

sensitivity and cold pain sensitivity may indicate crosstalk between TRPV1, TRPM8, and TRPA1 pathways, suggesting sensory integration between thermal perception and pain responses. Research has found that TRPA1 neurons involved in the noxious cold detection also express TRPV1, which could provide evidence for the correlation between warmth detection and cold pain (Bautista et al., 2013).

However, some past studies have suggested that thermal pain thresholds may function independently of warmth and cold detection, contrasting with the current findings. For example, it was proposed that heat pain and warmth perception rely on separate afferent pathways (Craig, 2003) . The observed correlations indicate that thermosensory and nociceptive pathways are more interdependent than previously assumed, reinforcing the need for further research to clarify their interactions.

Looking at the correlation of thresholds in WIFs, In this study the results showed that warm thresholds in WIFs negatively correlated with cool thresholds in WIFs and non-WIFs (Figure 8,9) , suggesting that whenever there is warmth insensitivity, there is also insensitivity to cooler temperatures. The correlation between warm thresholds in WIFs and cool thresholds in non-WIFs shows that warmth insensitivity correlated to cool insensitivity in both WIFs and non-WIFs, indicating more evidence for the integration of information for warm and cool stimuli. Also, the correlation between warm thresholds and warm levels thresholds in WIFs (Figure 7) presents a consistency in identifying thresholds in both the method of limits and the methods of levels used to determine thresholds. Looking within cool thresholds, cool detection within WIFs and non-WIFs correlated significantly, showing that cool sensation is conserved (Figure 12).

Additionally, the cool thresholds in WIFs correlated with heat pain thresholds in WIFs (Figure 11), indicating that as the ability to detect cool increased the ability to detect heat pain

also increased, further emphasizing the p role of C fibers in mediating both cool and noxious heat conditions.

The observed correlations in warmth-insensitive fields (WIFs) provide insight into the neural mechanisms underlying thermal sensation and its integration with pain perception. The specificity theory and across-fiber theory offer two perspectives on how thermal and nociceptive information is processed. The specificity theory states that separate, specialized receptors and pathways mediate distinct sensory modalities, such as warmth, cold, and pain (Rey, 1995). In contrast, the across-fiber theory suggests that thermal and pain perception arise from activation patterns across multiple types of sensory fibers rather than from isolated, dedicated pathways (Erickson, 1982). The results of this study align with both these ideas, suggesting that further studies are required to confirm the exact mechanisms.

Prior research has identified specific neurons responsible for thermal perception in various species. In cats, Hensel and Iggo demonstrated that C-fiber thermoreceptors selectively responded to warmth, while A-delta fibers were primarily involved in cold sensation (Hensel & Iggo, 1971). Studies in mice have further clarified the role of TRPM8-expressing neurons in cool detection and TRPV1-expressing neurons in noxious heat perception (Caterina et al., 1997; McKemy et al., 2002). In humans, microneurography studies have confirmed that C-fiber warm receptors exhibit slow conduction velocities and display spatially heterogeneous distributions across the skin, aligning with the presence of WIFs (Vallbo et al., 1995). Additionally, research by Craig has provided key insights into spinothalamic neurons mediating thermal sensation. His studies identified specific lamina I spinothalamic tract (STT) neurons that respond to thermal stimuli, including HPC (heat, pinch, cold) neurons, which integrate noxious heat, mechanical stimuli, and cold signals (Craig et al., 2001). He also characterized cooling-specific neurons that increase their

discharge rates as skin temperature decreases, further supporting the role of the spinothalamic pathway in thermal discrimination (Craig & Bushnell, 1994). These findings support the idea that C fibers and spinothalamic neurons play a crucial role in mediating both innocuous warmth and noxious heat, reinforcing the observed correlation between cool and heat pain thresholds within WIFs.

A key strength of this study is the inclusion of warmth-insensitive fields (WIFs), which provide insight into the role of nociceptive fibers in temperature-related pain sensitivity. WIFs lack typical warmth detection due to their exclusive innervation by C nociceptive fibers, allowing for a controlled comparison between nociceptive and non-nociceptive thermal processing (Green and Cruz, 1998). The findings from WIFs provide further evidence that thermal-pain interactions are not purely peripheral but involve higher-level integration in the spinal cord and brain, aligning with past research. Previous research has indicated that pain processing is uniquely influenced by central mechanisms, mainly through the phenomenon of temporal contrast enhancement (TCE)(Petre et al., 2017). Unlike other sensory modalities, where peripheral inputs predominantly determine perceptual outcomes, these findings suggest that the integration and modulation of nociceptive signals within the central nervous system play a crucial role in interpreting rapid changes in thermal stimuli.

Understanding the role of C fibers in WIFs may have important implications for chronic pain conditions such as fibromyalgia, where patients exhibit altered thermal perception alongside increased pain sensitivity (Petzke et al., 2003). Future research should explore whether nociceptive sensitization in WIFs could be a biomarker for central sensitization syndromes and chronic pain disorders. If WIFs are linked to variations in pain thresholds, they could serve as biological markers for understanding individual differences in pain perception. Further,

investigating how WIFs contribute to pain hypersensitivity in chronic conditions could offer valuable insights into the mechanisms underlying sensory dysfunction.

Future research should explore whether individuals with chronic pain exhibit a higher prevalence or altered distribution of WIFs. Understanding the neural basis of WIFs, such as whether they result from differences in peripheral receptor density, central processing, or both—could enhance our ability to diagnose and manage pain conditions. Additionally, identifying interventions that modulate WIF-related sensory differences could lead to improved pain management strategies.

The results of this study have important clinical implications, particularly for neuropathic pain conditions, fibromyalgia, and central sensitization syndromes. Many pain disorders are characterized by altered thermal perception and increased sensitivity to both innocuous and noxious stimuli, suggesting that dysfunctions in warmth and cold processing could contribute to pathological pain states. Fibromyalgia is associated with thermal hypersensitivity and central amplification of pain signals, as patients with these conditions often exhibit hyperalgesia or allodynia in response to thermal stimuli (Nijs et al., 2010). In chronic pain conditions such as fibromyalgia, multiple sclerosis, and complex regional pain syndrome, both warm and cold temperatures have been shown to influence pain sensitivity significantly, with patients reporting altered thresholds and exacerbation of symptoms in response to temperature changes (Jevotovsky et al., 2025).

In individuals with CRPS and fibromyalgia, sensitivity to both warm and cold temperatures significantly impact their pain experience, with those affected by CRPS more often reporting that warm weather intensifies their pain. In contrast, individuals with fibromyalgia typically experience discomfort (Ten Brink et al., 2020). This differential response underscores

the importance of understanding specific temperature thresholds and exploring the underlying mechanisms, as it could inform tailored management strategies to improve the quality of life for these patients. Therefore, the strong correlation observed in this study between warmth detection and pain thresholds suggests that altered thermosensory processing could serve as a biomarker for central sensitization disorders such as fibromyalgia and CRPS.

Similarly, the findings have relevance for neuropathic pain conditions, particularly diabetic neuropathy and small fiber neuropathy, which involve impairment of thinly myelinated and unmyelinated fibers responsible for thermal sensation. Prior research has shown that damage to small fibers results in decreased thermal detection but paradoxically increased pain perception (Kramer et al., 2004). The observed positive correlation between deteriorating cold detection thresholds and pain intensity in diabetic neuropathy aligns with the relationship between warmth detection and pain thresholds found in this study, suggesting that small fiber dysfunction may be a key factor underlying both sensory and pain abnormalities in these conditions. Furthermore, altered thermosensation in neuropathic pain syndromes has been linked to changes in TRP channel activity, particularly TRPV1 and TRPA1, which play an integral role in mediating noxious thermal stimuli and pain hypersensitivity (Bautista et al., 2013; McCoy et al., 2011).

Given these findings, this study highlights the potential need for thermal-based diagnostic tools to identify abnormal sensory processing in pain patients. Assessing warmth detection alongside pain thresholds could improve diagnostic precision for conditions involving sensory dysfunction and central sensitization. Additionally, pharmacological approaches targeting TRPV1 and TRPA1 channels may be explored as potential therapeutic interventions for patients experiencing thermal hyperalgesia. Research into TRP channel modulation has shown promising results, with TRPV1 and TRPA1 antagonists effectively reducing thermal hyperalgesia and

mechanical allodynia in experimental models of neuropathic pain(Koivisto et al., 2022). Future investigations should explore whether targeting these ion channels could provide effective relief for individuals with heightened thermal pain sensitivity, further advancing treatment options for chronic pain conditions.

The findings on warmth-insensitive fields (WIFs) and their correlation with cool and heat pain thresholds have significant implications for chronic pain research. Chronic pain conditions, such as fibromyalgia, neuropathic pain, and complex regional pain syndrome, often involve alterations in thermal and nociceptive processing. The observed relationship between warmth insensitivity and increased sensitivity to cool and heat pain suggests that dysfunction in C-fiber-mediated thermal perception may contribute to abnormal pain signaling in these conditions. Furthermore, the ability to selectively activate C-nociceptors in WIFs without co-activating innocuous warm fibers provides a unique opportunity to study pain processing mechanisms without confounding influences from non-nociceptive thermal pathways. This could help refine diagnostic criteria for pain disorders and inform targeted therapies aimed at modulating C-fiber activity. Understanding how these sensory pathways interact may also shed light on central sensitization, a key mechanism underlying chronic pain, and guide the development of treatments that restore normal sensory integration.

Limitations

While this study provides valuable insights, several limitations should be considered. One primary limitation is the sample size, as the study included only 22 sites each of WIFs and non-WIFs, which may restrict the generalizability of the findings. A larger sample would allow for greater statistical power and more reliable conclusions. Additionally, this study is cross-sectional, meaning it captures a single time point of sensory processing. Future longitudinal studies could

assess whether warmth detection and pain sensitivity change over time or in response to external factors such as injury, chronic pain development, or neuroplastic changes. Furthermore, individual differences such as age and sex may influence pain and thermal sensitivity. Out of the 16 included participants, 11 of them were female, accounting for about 70% of the sample size, which could have been a factor that influenced results. In the future, sample sizes that are diverse will help increase validity of the results.

Lastly, a significant limitation is the lack of neuroimaging data. While the findings suggest interactions between neural processing of warmth detection and nociception, functional neuroimaging techniques such as fMRI or EEG would be necessary to directly observe brain activation patterns associated with thermal and pain perception and to examine cortical activation patterns in response to WIF stimulation. Addressing these limitations in future research will be essential for refining the understanding of thermal nociceptive processing and improving the accuracy of sensory assessments. Additionally, pharmacological interventions targeting TRPV1 and TRPA1 receptors could provide insight into the role of these pathways in nociceptive processing. Longitudinal studies tracking individuals over time may also determine whether heightened WIF sensitivity is a predictor of chronic pain development.

Conclusion

This study provides strong evidence for a bidirectional relationship between warmth detection, cold sensitivity, and pain thresholds, highlighting the intricate link between thermal and nociceptive processing. The findings contribute to theoretical models of thermosensation, offer clinical implications for pain management, and open new avenues for research into sensory and nociceptive mechanisms. However, further investigation is needed to fully understand the effects of one modality on another. For instance, manipulating these sensory modalities and

observing responses to stimuli could help establish causal relationships. Specifically, selectively inhibiting warmth or cool detection while recording subsequent changes in sensitivity to cool, heat pain, or cold pain could provide deeper insights into whether one modality directly influences another. These experimental approaches could refine our understanding of thermal perception and its role in pain disorders, ultimately guiding the development of targeted interventions for chronic pain conditions.

Reference list

Abraira, V. E., & Ginty, D. D. (2013). The sensory neurons of touch. *Neuron*, *79*(4), 618-639. https://doi.org/10.1016/j.neuron.2013.07.051

Arcilla, C. K., & Tadi, P. (2025). Neuroanatomy, Unmyelinated Nerve Fibers. In *StatPearls*.

Arezzo, J. C., Schaumburg, H. H., & Spencer, P. S. (1982). Structure and function of the somatosensory system: a neurotoxicological perspective. *Environ Health Perspect*, *44*, 23-30. https://doi.org/10.1289/ehp.824423

Barry Green, A. C. (1998). “Warmth-insensitive fields": evidence of sparse and irregular innervation of human skin by the warmth sense. *Somatosensory & Motor Research*, *15*(4), 269-275. https://doi.org/10.1080/08990229870682

Bautista, D. M., Pellegrino, M., & Tsunozaki, M. (2013). TRPA1: A gatekeeper for inflammation. *Annu Rev Physiol*, *75*, 181-200. https://doi.org/10.1146/annurev-physiol-030212-183811

Bushnell, M. C., Ceko, M., & Low, L. A. (2013). Cognitive and emotional control of pain and its disruption in chronic pain. *Nat Rev Neurosci*, *14*(7), 502-511. https://doi.org/10.1038/nrn3516

Campero, M., Serra, J., Bostock, H., & Ochoa, J. L. (2001). Slowly conducting afferents activated by innocuous low temperature in human skin. *J Physiol*, *535*(Pt 3), 855-865. https://doi.org/10.1111/j.1469-7793.2001.t01-1-00855.x

Campero, M., Serra, J., & Ochoa, J. L. (1996). C-polymodal nociceptors activated by noxious low temperature in human skin. *J Physiol*, *497 (Pt 2)*(Pt 2), 565-572. https://doi.org/10.1113/jphysiol.1996.sp021789

Caterina, M. J., Leffler, A., Malmberg, A. B., Martin, W. J., Trafton, J., Petersen-Zeitz, K. R.,…Julius, D. (2000). Impaired nociception and pain sensation in mice lacking the capsaicin receptor. *Science*, *288*(5464), 306-313. https://doi.org/10.1126/science.288.5464.306

Caterina, M. J., Schumacher, M. A., Tominaga, M., Rosen, T. A., Levine, J. D., & Julius, D. (1997). The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature*, *389*(6653), 816-824. https://doi.org/10.1038/39807

Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci*, *3*(8), 655-666. https://doi.org/10.1038/nrn894

Craig, A. D. (2003). Pain mechanisms: labeled lines versus convergence in central processing. *Annu Rev Neurosci*, *26*, 1-30. https://doi.org/10.1146/annurev.neuro.26.041002.131022

Craig, A. D., & Bushnell, M. C. (1994). The thermal grill illusion: unmasking the burn of cold pain. *Science*, *265*(5169), 252-255. https://doi.org/10.1126/science.8023144

Craig, A. D., Bushnell, M. C., Zhang, E. T., & Blomqvist, A. (1994). A thalamic nucleus specific for pain and temperature sensation. *Nature*, *372*(6508), 770-773. https://doi.org/10.1038/372770a0

Craig, A. D., Chen, K., Bandy, D., & Reiman, E. M. (2000). Thermosensory activation of insular cortex. *Nat Neurosci*, *3*(2), 184-190. https://doi.org/10.1038/72131

Craig, A. D., Krout, K., & Andrew, D. (2001). Quantitative response characteristics of thermoreceptive and nociceptive lamina I spinothalamic neurons in the cat. *J Neurophysiol*, *86*(3), 1459-1480. https://doi.org/10.1152/jn.2001.86.3.1459

Darian-Smith, I., & Johnson, K. O. (1977). Thermal sensibility and thermoreceptors. *J Invest Dermatol*, *69*(1), 146-153. https://doi.org/10.1111/1523-1747.ep12497936

Davis, J. B., Gray, J., Gunthorpe, M. J., Hatcher, J. P., Davey, P. T., Overend, P.,…Sheardown, S. A. (2000). Vanilloid receptor-1 is essential for inflammatory thermal hyperalgesia. *Nature*, *405*(6783), 183-187. https://doi.org/10.1038/35012076

Defrin, R., Ohry, A., Blumen, N., & Urca, G. (2002). Sensory determinants of thermal pain. *Brain*, *125*(Pt 3), 501-510. https://doi.org/10.1093/brain/awf055

Desmeules, J. A., Cedraschi, C., Rapiti, E., Baumgartner, E., Finckh, A., Cohen, P.,…Vischer, T. L. (2003). Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis Rheum*, *48*(5), 1420-1429. https://doi.org/10.1002/art.10893

Dhaka, A., Viswanath, V., & Patapoutian, A. (2006). Trp ion channels and temperature sensation. *Annu Rev Neurosci*, *29*, 135-161. https://doi.org/10.1146/annurev.neuro.29.051605.112958

Erickson, R. P. (1982). The Across-Fiber Pattern Theory: An Organizing Principle for Molar Neural Function. *Contributions to Sensory Physiology*, *6*, 79-110. https://doi.org/10.1016/B978-0-12-151806-6.50009-3

Finnerup, N. B., Haroutounian, S., Kamerman, P., Baron, R., Bennett, D. L. H., Bouhassira, D.,…Jensen, T. S. (2016). Neuropathic pain: an updated grading system for research and clinical practice. *Pain*, *157*(8), 1599-1606. https://doi.org/10.1097/j.pain.0000000000000492

Geuter, S., Boll, S., Eippert, F., & Buchel, C. (2017). Functional dissociation of stimulus intensity encoding and predictive coding of pain in the insula. *Elife*, *6*. https://doi.org/10.7554/eLife.24770

Green, B. G. (2009). Temperature perception on the hand during static vs. dynamic contact with a surface. *Attention, Perception and Psychophysics*, *71(5)*, 1185. https://doi.org/https://doi.org/10.3758/APP.71.5.1185

Green, B. G., & Akirav, C. (2007). Individual differences in temperature perception: evidence of common processing of sensation intensity of warmth and cold. *Somatosens Mot Res*, *24*(1-2), 71-84. https://doi.org/10.1080/08990220701388117

Hensel, H., & Iggo, A. (1971). Analysis of cutaneous warm and cold fibres in primates. *Pflugers Arch*, *329*(1), 1-8. https://doi.org/10.1007/BF00586896

Hua le, H., Strigo, I. A., Baxter, L. C., Johnson, S. C., & Craig, A. D. (2005). Anteroposterior somatotopy of innocuous cooling activation focus in human dorsal posterior insular cortex. *Am J Physiol Regul Integr Comp Physiol*, *289*(2), R319-R325. https://doi.org/10.1152/ajpregu.00123.2005

Iggo, A. (1976). Is the physiology of cutaneous receptors determined by morphology? *Prog Brain Res*, *43*, 15-31. https://doi.org/10.1016/S0079-6123(08)64334-4

Jevotovsky, D. S., Oehlermarx, W., Chen, T., Ortiz, C. C., Liu, A., Sahni, S.,…Lau, R. (2025). Weathering the Pain: Ambient Temperature's Role in Chronic Pain Syndromes. *Curr Pain Headache Rep*, *29*(1), 31. https://doi.org/10.1007/s11916-025-01361-8

Koivisto, A. P., Belvisi, M. G., Gaudet, R., & Szallasi, A. (2022). Advances in TRP channel drug discovery: from target validation to clinical studies. *Nat Rev Drug Discov*, *21*(1), 41-59. https://doi.org/10.1038/s41573-021-00268-4

Kramer, H. H., Rolke, R., Bickel, A., & Birklein, F. (2004). Thermal thresholds predict painfulness of diabetic neuropathies. *Diabetes Care*, *27*(10), 2386-2391. https://doi.org/10.2337/diacare.27.10.2386

Latremoliere, A., & Woolf, C. J. (2009). Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain*, *10*(9), 895-926. https://doi.org/10.1016/j.jpain.2009.06.012

Liu, Z., Wu, H., Wei, Z., Wang, X., Shen, P., Wang, S.,…Lu, Y. (2016). TRPM8: a potential target for cancer treatment. *J Cancer Res Clin Oncol*, *142*(9), 1871-1881. https://doi.org/10.1007/s00432-015-2112-1

Lumpkin, E. A., & Caterina, M. J. (2007). Mechanisms of sensory transduction in the skin. *Nature*, *445*(7130), 858-865. https://doi.org/10.1038/nature05662

Medoc Ltd. (2019). TSA2 Thermal Sensory Analyzer. [apparatus and software]. https://www.medoc-web.com/tsa-2

McCoy, D. D., Knowlton, W. M., & McKemy, D. D. (2011). Scraping through the ice: uncovering the role of TRPM8 in cold transduction. *Am J Physiol Regul Integr Comp Physiol*, *300*(6), R1278-1287. https://doi.org/10.1152/ajpregu.00631.2010

McGlone, F., & Reilly, D. (2010). The cutaneous sensory system. *Neurosci Biobehav Rev*, *34*(2), 148-159. https://doi.org/10.1016/j.neubiorev.2009.08.004

McKemy, D. D., Neuhausser, W. M., & Julius, D. (2002). Identification of a cold receptor reveals a general role for TRP channels in thermosensation. *Nature*, *416*(6876), 52-58. https://doi.org/10.1038/nature719

Nijs, J., Van Houdenhove, B., & Oostendorp, R. A. (2010). Recognition of central sensitization in patients with musculoskeletal pain: Application of pain neurophysiology in manual therapy practice. *Man Ther*, *15*(2), 135-141. https://doi.org/10.1016/j.math.2009.12.001

Olausson, H., Charron, J., Marchand, S., Villemure, C., Strigo, I. A., & Bushnell, M. C. (2005). Feelings of warmth correlate with neural activity in right anterior insular cortex. *Neurosci Lett*, *389*(1), 1-5. https://doi.org/10.1016/j.neulet.2005.06.065

Ossipov, M. H., Morimura, K., & Porreca, F. (2014). Descending pain modulation and chronification of pain. *Curr Opin Support Palliat Care*, *8*(2), 143-151. https://doi.org/10.1097/SPC.0000000000000055

Ostrowsky, K., Magnin, M., Ryvlin, P., Isnard, J., Guenot, M., & Mauguiere, F. (2002). Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. *Cereb Cortex*, *12*(4), 376-385. https://doi.org/10.1093/cercor/12.4.376

Paricio-Montesinos, R., Schwaller, F., Udhayachandran, A., Rau, F., Walcher, J., Evangelista, R.,…Lewin, G. R. (2020). The Sensory Coding of Warm Perception. *Neuron*, *106*(5), 830-841.e833. https://doi.org/10.1016/j.neuron.2020.02.035

Patel, S., Ohara, S., Dougherty, P. M., Gracely, R. H., & Lenz, F. A. (2006). Psychophysical elements of place and modality specificity in the thalamic somatic sensory nucleus (ventral caudal, vc) of awake humans. *J Neurophysiol*, *95*(2), 646-659. https://doi.org/10.1152/jn.00756.2005

Pehl, U., Schmid, H. A., & Simon, E. (1997). Temperature sensitivity of neurones in slices of the rat spinal cord. *J Physiol*, *498 (Pt 2)*(Pt 2), 483-495. https://doi.org/10.1113/jphysiol.1997.sp021874

Peier, A. M., Reeve, A. J., Andersson, D. A., Moqrich, A., Earley, T. J., Hergarden, A. C.,…Patapoutian, A. (2002). A heat-sensitive TRP channel expressed in keratinocytes. *Science*, *296*(5575), 2046-2049. https://doi.org/10.1126/science.1073140

Peirs, C., & Seal, R. P. (2016). Neural circuits for pain: Recent advances and current views. *Science*, *354*(6312), 578-584. https://doi.org/10.1126/science.aaf8933

Petre, B., Tetreault, P., Mathur, V. A., Schurgin, M. W., Chiao, J. Y., Huang, L., & Apkarian, A. V. (2017). A central mechanism enhances pain perception of noxious thermal stimulus changes. *Sci Rep*, *7*(1), 3894. https://doi.org/10.1038/s41598-017-04009-9

Petzke, F., Clauw, D. J., Ambrose, K., Khine, A., & Gracely, R. H. (2003). Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation. *Pain*, *105*(3), 403-413. https://doi.org/10.1016/S0304-3959(03)00204-5

Proksch, E., Brandner, J. M., & Jensen, J. M. (2008). The skin: an indispensable barrier. *Exp Dermatol*, *17*(12), 1063-1072. https://doi.org/10.1111/j.1600-0625.2008.00786.x

Purves, D., Augustine, G. J., Fitzpatrick, D., Katz, L. C., Lamantia, A.-S., McNamara, J. O., & Williams, S. M. (2001). Neuroscience. 2nd. *Sunderland. MA: Sinauer Associates*.

Rey, R. (1995). *The history of pain*. Harvard University Press.

Rosenbaum, T., & Simon, S. A. (2007). TRPV1 Receptors and Signal Transduction. In W. B. Liedtke & S. Heller (Eds.), *TRP Ion Channel Function in Sensory Transduction and Cellular Signaling Cascades*.

Samanta, A., Hughes, T. E. T., & Moiseenkova-Bell, V. Y. (2018). Transient Receptor Potential (TRP) Channels. *Subcell Biochem*, *87*, 141-165. https://doi.org/10.1007/978-981-10-7757-9_6

Simon, E., & Iriki, M. (1971). Sensory transmission of spinal heat and cold sensitivity in ascending spinal neurons. *Pflugers Arch*, *328*(2), 103-120. https://doi.org/10.1007/BF00592439

Ten Brink, A. F., Goebel, A., Berwick, R., McCabe, C. S., & Bultitude, J. H. (2020). Sensitivity to Ambient Temperature Increases in Fibromyalgia and CRPS. *Pain Med*, *21*(12), 3726-3729. https://doi.org/10.1093/pm/pnaa074

Todd, A. J. (2010). Neuronal circuitry for pain processing in the dorsal horn. *Nat Rev Neurosci*, *11*(12), 823-836. https://doi.org/10.1038/nrn2947

Treede, R. D., Meyer, R. A., Raja, S. N., & Campbell, J. N. (1992). Peripheral and central mechanisms of cutaneous hyperalgesia. *Prog Neurobiol*, *38*(4), 397-421. https://doi.org/10.1016/0301-0082(92)90027-c

Tseng, M. T., Tseng, W. Y., Chao, C. C., Lin, H. E., & Hsieh, S. T. (2010). Distinct and shared cerebral activations in processing innocuous versus noxious contact heat revealed by functional magnetic resonance imaging. *Hum Brain Mapp*, *31*(5), 743-757. https://doi.org/10.1002/hbm.20902

Vallbo, A. B., Olausson, H., Wessberg, J., & Kakuda, N. (1995). Receptive field characteristics of tactile units with myelinated afferents in hairy skin of human subjects. *J Physiol*, *483 (Pt 3)*(Pt 3), 783-795. https://doi.org/10.1113/jphysiol.1995.sp020622