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# Quantitative sensory testing for evaluation chronic arthritis or local anesthesia

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BOSTON UNIVERSITY  
SCHOOL OF MEDICINE

Thesis

**QUANTITATIVE SENSORY TESTING FOR EVALUATION CHRONIC  
ARTHRITIS OR LOCAL ANESTHESIA**

by

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Submitted in partial fulfillment of the  
requirements for the degree of  
Master of Arts

2013

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ARTHRITIS OR LOCAL ANESTHESIA**

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Boston University School of Medicine, 2013

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**ABSTRACT**

**Background**

Properly functioning sensory systems are crucial in perception of external stimuli. Different modalities such as touch, temperature, and pain can only be appreciated with intact sensory pathways from the peripheral receptors to the cerebral cortex via the spinal cord. Pain is a sensory response to noxious, tissue damaging stimuli. It is an essential protective response for survival. However, abnormalities in sensory function may lead to hyposensitization or hypersensitization to a stimulus, which may cause numbness or pain respectively.

Juvenile Idiopathic Arthritis (JIA) is a condition characterized by inflammation of the joints, resulting in stiffness and pain. The etiology of JIA is not well known, and little is understood about the associated changes in sensory function that may be present. In this study, we use quantitative sensory testing

(QST) as a validated measure to assess local and global changes in sensory function in JIA patients.

### **Objective**

The aim of the study is to use quantitative sensory testing (QST) to assess sensory function in patients with JIA. Collecting quantitative data, we hypothesize that JIA patients will exhibit a hypersensitivity to noxious stimuli when compared to healthy, age-matched reference values.

### **Methods**

Pediatric JIA patients 7-17 years of age will be recruited. Mechanical and thermal sensory function will be tested using Quantitative Sensory Testing (QST). For each JIA patient, two skin sites will be tested: (1) the inflamed joint, and (2) the thenar eminence (a non-inflamed control). Eight different tests will be given: Mechanical detection threshold and mechanical pain threshold tests will be tested using von Frey monofilaments. Dynamic allodynia will be tested using a soft brush. Pressure Pain thresholds will be tested using a digital algometer. Cool detection, warm detection, cold pain threshold, and hot pain thresholds will be tested using a TSA-II sensory device.

### **Results**

QST data was collected from twelve JIA patients and an interim analysis performed. Compared to reference values from previously published data, JIA patients were hypersensitive to noxious mechanical and thermal stimuli at the thenar eminence. To test if these changes were local to the site of inflammation

in JIA patients, noxious sensory thresholds were compared between the thenar eminence and inflamed joint for each subject; Noxious sensory thresholds were not significantly different between the thenar eminence and inflamed joint, and suggest a global decrease in sensitivity to noxious stimuli that extend beyond the site of inflammation.

### **Conclusions**

Results from this interim analysis indicate that JIA patients are hypersensitive to noxious stimuli. The underlying mechanisms involved may lie at the level of the periphery – due to peripheral sensitization of the sensory receptors and increased neuronal excitability, or at the level of the spinal cord and higher centers – reflecting central sensitization. Although this is an interim analysis, these preliminary results show, quantitative sensory testing (QST) is a useful measure to assess sensory function in JIA patients. While QST is not a substitute for other diagnostic exams, it is a useful support tool to gather quantitative measures evaluating different modalities. Future work will include correlating skin sensory responses with objective inflammatory markers indicating the severity of JIA, and psychological assessment of pain perception.

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## LIST OF ABBREVIATIONS

CDT	Cool Detection Threshold
CPT	Cold Pain Threshold
CT	Computed Tomography
df	degrees of freedom
EMG	Electromyography
HPT	Hot Pain Threshold
IJ	Injured Joint
JIA	Juvenile Idiopathic Arthritis
MDT	Mechanical Detection Threshold
MPT	Mechanical Pain Threshold
MRI	Magnetic Resonance Imaging
PPT	Pressure Pain Threshold
QST	Quantitative Sensory Testing
SD	Standard Deviation
SE	Standard Error of Mean
TE	Thenar Eminence
TST	Thermoregulatory Sweat Testing
WDT	Warm Detection Threshold

## **1. Introduction**

Maintenance of sensory function is important for daily activity. Properly functioning sensory systems are needed to perceive the outside environment and external stimuli. Different types of touch stimuli are transduced by peripheral skin receptors into electrical signals at the peripheral level and sent towards the spinal cord, brain stem, thalamus, and the cerebral cortex where they are processed into perception of valuable, sensory events (McGlone & Reilly, 2010). For example, a stimulus, that may potentially be or is harmful and damaging, will activate a free nerve ending, conduct an action potential across a C-fiber, travel to the cerebral cortex via the spinal cord, and be perceived as being painful. Specifically, these responses are necessary to ensure survival by associating noxious stimuli with unpleasant sensation, pain, and avoidance of tissue-damaging sensation. (Woolf et al., 2004). However, when a sensory system malfunctions, alterations in the perception of stimuli may occur.

For example, when the nociceptive system becomes pathological, it may be characterized by hyposensitivity or hypersensitivity to external stimuli. Some of the underlying mechanisms of alterations in nociception involve peripheral and central sensitization (Woolf et al., 2004). In brief, these mechanisms attempt to explain neurophysiological changes that affect the pathways that mediate sensation.

Although these proposed mechanisms explain the alterations in sensory processing, many mechanisms of sensitization from pathologies and diseases

are not well known. For example, rheumatoid arthritis is a condition that is characterized by joint inflammation with ongoing pain (Meeus et al., 2012). Increased pain can be evoked spontaneously, with joint movement, or from light, touch stimulation in inflamed areas. The mechanism of peripheral sensitization, which will be explained further, may account for localized pain sensation through local, inflammatory mediators. However, many patients with rheumatoid arthritis also feel increased pain in non-inflamed areas. Central sensitization, which involves areas of the central nervous system, is a proposed mechanism to explain this phenomenon (Meeus et al., 2012).

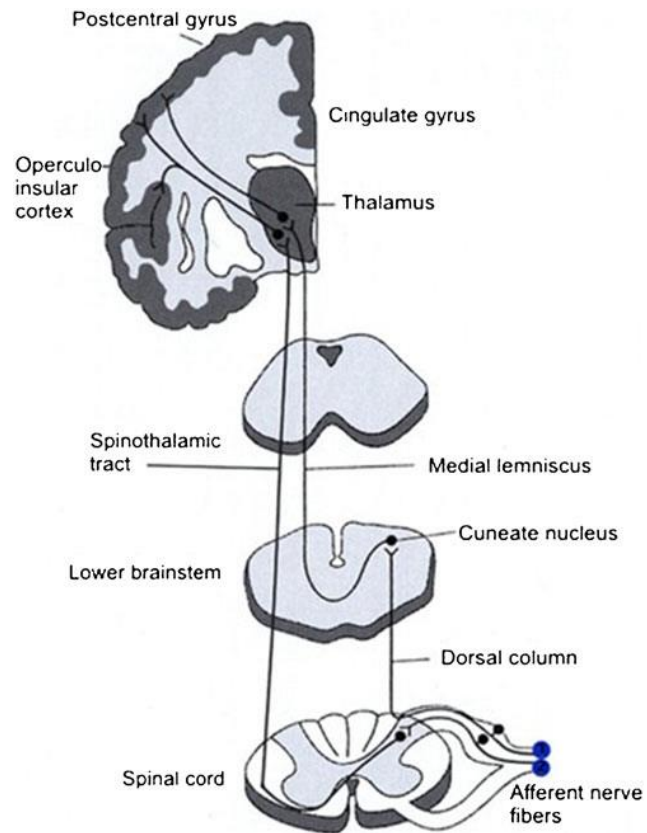
Many pathologies and diseases exhibit abnormal, sensory responses due to disruptions within the sensory circuitry, and the mechanisms of these responses are not well known. It is important to note that other sensory modalities, such as light touch and temperature, may become sensitized in these pathologies. A brief, general overview of sensory processing will be presented.

## **1.1 Processing of Somatosensory Information**

Different pathways exist to convey information from the submodalities of the somatosensory system. Mechanoreceptive and proprioceptive information is transduced from the periphery by mechanoreceptors and conducted to the spinal cord via large, A $\beta$  fibers (Pfau et al., 2012). First order axons form the dorsal column and synapse on the lower medulla. Subsequently, axons from second

order neurons project axons that form the medial lemniscus, which ascend to the brainstem, thalamus, and higher-order processing areas of the cortex.

Similarly, peripheral information of thermoreception is transduced by a set of thermoreceptors that lie at the nerve terminals of A $\delta$  and C-fibers. The information is conducted via these afferent fibers to the spinal cord. From the spinal cord, the secondary neurons project fibers to form the spinothalamic tract and ascend towards the brain, reaching the thalamus. Awareness becomes relevant once the information is relayed to and processed in higher-order cortical areas (Pfau et al., 2012).



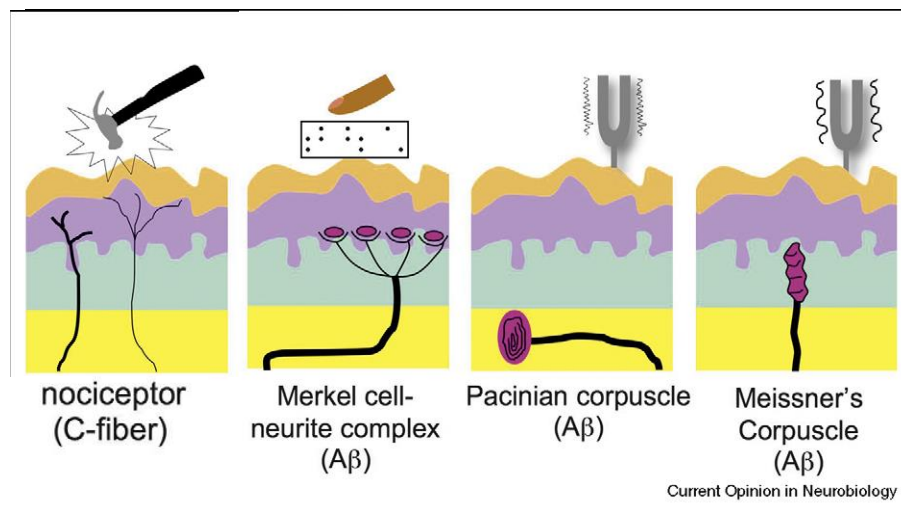
**Figure 1: Schematic Outline of Somatosensory Pathways.**

Schematic outline of the pathways that conduct somatosensory information from the periphery to the higher-order areas of cortical processing. The medial lemniscus tract conveys mechanoreception such as touch and vibration. The spinothalamic tract conveys nociceptive and thermoreceptive information (Figure taken from Pfau et al., 2012).

## 1.2 Receptors in the Skin

Biologically, there are specific types of fibers that convey distinct types of information. Stimulation of these receptors located in the skin allows transduction of external stimuli information into electrical signals conveyed to the brain. These different types of sensory receptors will respond to specific stimuli and will send information across a specific fiber. Different types of receptors are linked to different fibers, which have varying amounts of myelination between specific types. Sensory information can be transmitted at different conduction speeds depending on the type of afferent fiber involved.

In brief, touch is encapsulated by several different submodalities: vibration, pressure, and texture are mediated by different types of receptors that are specific to those stimuli. These mechanoreceptors include Pacinian, Meissner, and Ruffini corpuscles and Merkel disks, and they are primarily mediated by A $\beta$  fibers (McGlone & Reilly, 2010). Thermoreceptors respond to temperature via free nerve endings and are mediated by A $\delta$  and C-fibers. Similarly, nociceptors mediate perception of pain via C-fibers.



**Figure 2: Schematic Drawing of Somatosensory Receptors.**

Schematic drawing of a cross section of the skin outlines the various sensory receptors located in the periphery with their respective, conducting fibers. Layers of the skin are noted: epidermis (orange and purple), dermis (green), and subcutaneous (yellow). Thickness of the fiber is proportional to the amount of myelination, with the exception of the C-fiber. From left to right, the indicated sensations include: nociception, light deflections of hair, touch, rapid vibrations, and slower vibrations (Figure modified from Tsunozaki & Bautista, 2009).

### 1.2.1 Touch

Mechanical stimulation of the skin activates mechanoreceptors via skin displacement with Ruffini endings or Meissner corpuscles (Walk et al., 2009). This type of stimuli involves displacement of the skin with light touch and

activates specific receptors that transduce the information across A $\beta$  nerve fibers. The A $\beta$  nerve fibers are largely myelinated and can conduct information rapidly from 35 – 70 m/s (Yarnitsky, 1997). Low-threshold receptors respond to stimuli, which invokes perception to light-touch. These receptors can be further divided into two classifications: slowly-adapting and rapidly-adapting. Slowly-adapting receptors are constantly active during constant stimulus application. In contrast, rapidly-adapting receptors only respond to the onset and offset of a stimulus (McGlone & Reilly, 2010). A combination of activity from these low-threshold receptors mediates specific information about the innocuous stimulus. In contrast, high-threshold mechanoreceptors can be stimulated by high-intensity stimuli in order to evoke sharp, often painful-like sensations (Walk et al., 2009).

Abnormal responses to light-touch stimuli include decreased or increased sensitivity to the stimuli. The increased sensitivity to the innocuous stimuli can include the perception of pain and is referred to mechanical allodynia. Two types of mechanical allodynia involve static and dynamic allodynia. Static allodynia is tested using a static force such as applied pressure, while dynamic allodynia is tested using a moving, light-touch stimulus across an area of skin. Typically, a soft tool, such as a brush, can be used over an area of interest to simulate the touch.

### **1.2.2 Pressure**

Both slowly-adapting and rapidly-adapting mechanoreceptors exist in the skin to mediate pressure in the skin. This function is mediated by mechanoreceptors that are located deeper in the tissue. Merkel cells, which are located near the surface of the skin, and Ruffini endings, located deeper in the tissue, connect with both A $\beta$  and C-fibers (Walk et al., 2009). These receptors' primary function is to mediate pressure information.

### **1.2.3 Vibration**

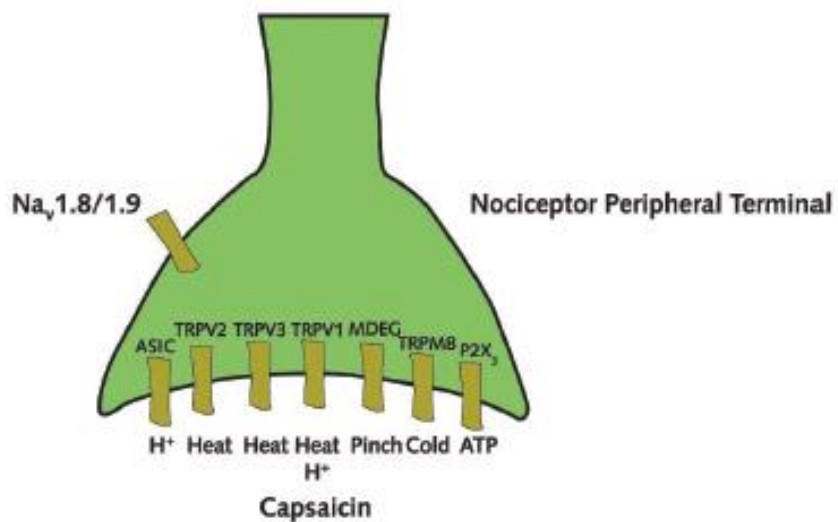
Located deep in the tissue, the Pacinian corpuscle primarily functions to mediate the sensation of vibration via A $\beta$  fibers. As it is classified as a rapidly adapting stimulus, the receptor is able to respond to varying amounts of stimuli that have a range of 40-500Hz (McGlone & Reilly, 2010).

### **1.2.4 Temperature**

Thermal stimuli can be used to test for A $\delta$  and C-fiber linked thermoreceptors. While both peripheral sensory fibers are able to mediate cold and hot temperature pain information, the C-fiber mediates warm temperature sensation, and the A $\delta$  mediates the cool temperature pain (Greenspan, 2001).

### 1.3 Processing of Noxious Stimuli

Peripheral receptors of nociceptor neurons are able to respond to a wide range of noxious thermal, chemical, and mechanical stimuli (Woolf et al., 2004). Different types of stimulus modality will activate a specific receptor that transduces the signal into electrical activity, as illustrated in Figure 3.



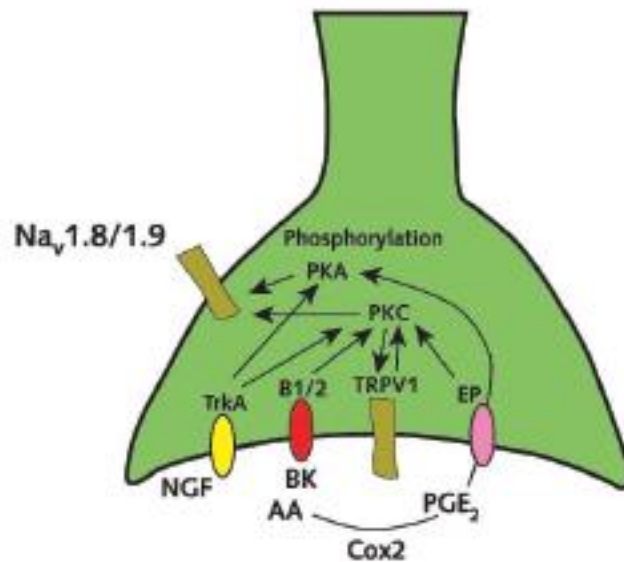
**Figure 3: Ion Channels in the Peripheral Receptor.**

This figure shows various ion channels that mediate and transduce different sources of chemical, mechanical, and thermal stimuli (Figure adapted from Woolf et al., 2004).

#### 1.3.1 Peripheral Sensitization

As mentioned earlier, damaging or noxious stimuli result in tissue injury and inflammation. The damage results in many changes to the chemical environment of the peripheral terminal of nociceptors (Woolf et al., 2004). The

damaged area undergoes peripheral sensitization, where local inflammatory mediators such as prostaglandin, cytokines, chemokines, and bradykinin are released. Under normal conditions, peripheral receptors, that are linked to A $\delta$  and C-fibers, are activated by noxious stimuli under noninflamed conditions (Meeus et al., 2012). These inflammatory factors from damaged cells can directly activate these peripheral receptors that mediate pain sensation and can also sensitize the terminal to evoke much larger responses than under normal conditions. For example, sunburn will ultimately lead to the production of prostaglandin E, which is able to bind to specific receptors on the membrane of nociceptors. After activation of adenylyl cyclase and several downstream processes, post-translational modifications of proteins, such as phosphorylation of amino acids, take place. This modification will alter activity of receptors and ion channels. Specifically, the heat-sensitive V1 channel that normally is activated at 46°C now responds at 26°C. This sensitization is responsible feeling pain towards normally innocuous stimuli with a sunburn condition (Woolf et al., 2004).



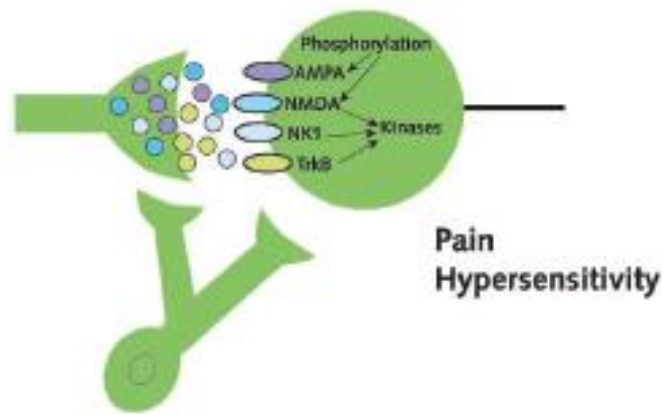
**Figure 4: Peripheral Sensitization.**

This diagram shows inflammatory mediators activating proteins that phosphorylate and alter the activity of ion channels and receptors (Figure adapted from Woolf et al., 2004).

### 1.3.2 Central Sensitization

The peripheral sensitization mechanism explains the sensitization that occurs over inflamed areas. However, sensitization also occurs in areas that are non-inflamed. It is thought that the central nervous system can be sensitized. One proposed mechanism explains that the central sensitization can amplify signals from the nociceptors to the dorsal horn neurons of the spinal cord, triggering changes in intracellular phosphorylation of proteins and modifications

of ion channels and receptors. The dorsal horn neurons will become sensitized to subsequent stimuli that may normally be undetectable and innocuous. The increase in sensitivity in non-inflamed areas may also be a consequence of central sensitization. Alterations in the NMDA channel play a primary role in mediating this phenomenon. As the channel becomes more sensitive to respond to lower concentrations of glutamate and stays open longer, the channel will respond to subthreshold stimuli and amplify noxious stimuli (Woolf et al., 2004).



**Figure 5: Central Sensitization.**

This diagram shows changes in gene expression via phosphorylation of ion channels and receptors that result in the sensitization of the dorsal horn neuron. Easier activation of the neuron plays a key role in mediating painful sensations from innocuous and noxious stimuli (Figure adapted from Woolf et al., 2004).

#### **1.4 Ambiguity of Pain Scores**

In a clinical setting, it may be difficult to assess patient's pain in order to accurately understand what a patient is experiencing. Due to the general variability of pain responses, using verbal descriptions to assess pain may be difficult. Because these scores carry a qualitative factor, it may be helpful to use and have a quantifiable measure in addition to verbal ratings to support a diagnosis of a disorder.

#### **1.5 Methods of Assessing Peripheral Nerve Function**

There are many tools used to assess the integrity of peripheral nerve function. These tools include electromyography (EMG), thermoregulatory sweat testing (TST), and skin biopsies. Each test has its advantages and drawbacks. Electromyography (EMG) is used to evaluate electrical activity within muscles. Although it is a useful tool to measure nerve conduction in the muscle, usually after an injury, it cannot assess activity originating from A $\delta$  and C-fibers (Whittaker, 2012). Thermoregulatory Sweat Testing (TST) is another tool to measure the integrity of the central and peripheral sympathetic system (Illigens & Gibbons, 2009). Because sweating is mediated by the autonomic nervous system, any dysfunction could indicate possible pathology and abnormalities in distal small fibers. Although it can localize specific areas of sensory dysfunction, it cannot discern between a pre-ganglionic and post-ganglionic abnormality (Illigens & Gibbons, 2009). A skin biopsy is a useful tool to analyze small-nerve

fiber activity, such as unmyelinated and thinly myelinated fibers, that may not be evaluated using other nerve conduction tests (Lauria & Devigili, 2007).

### **1.6 Quantitative Sensory Testing (QST)**

Quantitative sensory testing was developed to obtain quantifiable measures of sensory responses from A $\delta$  and C-fibers. Along with other available clinical tools such as the EMG and TST, QST is another support tool used to provide more information of the disorder. Even though QST is fundamentally subjective, it is a support measure that can be used to test for peripheral nerve disorders that result in a loss or gain of sensation in conjunction with other diagnostic tests (Zaslansky & Yarnitsky, 1998).

QST allows for the quantifiable assessment of the complete sensory neural axis (Zaslansky & Yarnitsky, 1998). As noted before, perception of a sensory stimulus takes a defined path from the beginning of the stimulation of the peripheral receptors located in the skin to the higher cortical areas. Testing for different modalities allows the clinician to evaluate sensory fibers respective to each modality. For example, touch and vibration modalities activate larger, myelinated A $\beta$  fibers that form the medial lemniscus pathway. Other modalities, such as nociception and thermoreception, activate smaller, less myelinated A $\delta$  and C-fibers that form the spinothalamic tract. In the case where abnormal responses are reported, it is possible to locate the possible areas of interest.

Various equipment is used to assess each modality. For example, tactile responses are evaluated and quantified using graded, von frey monofilaments. The monofilaments each deliver constant, graded amount of force on a specific area on the skin, activating the A $\beta$  fibers. To measure pressure, an algometer is a device that reports that measures the amount of force that is applied on the area of interest. Thermal sensation is tested using a computer-controlled device that delivers different temperature. Responses from the activation of the A $\delta$  and C-fibers are measured.

QST can be used to test for dysfunction at all levels of the nervous system (Yarnitsky, 1997). Recent research has focused more on using QST to test for peripheral neuropathy, while more refined imaging techniques are used to investigate central nervous system disorders (Yarnitsky, 1997). Diabetes is an active area of research where QST can be used to test for peripheral neuropathy, one of the common causes of neuropathy. It is proposed that degeneration of both the smaller and larger fibers are the main causes (Yarnitsky, 1997). Sensitivities to mechanoreception and nociception can be tested using QST. Another area of interest is testing sensory function on patients with cerebral lesions resulting from stroke. Testing has shown that patients who experience central post-stroke pain (CPSP) had deficits in thermal sensation (Yarnitsky, 1997). Using QST as a tool to measure sensory responses, it was proposed that there was damage to the spino-thalamo-cortical pathway that led to hyperexcitability in cortical neurons and enhanced sensitivity to thermal stimuli.

**Table 1: Overview of Sensory Modalities.**

The table shows an overview of different types of stimuli with their respective peripheral sensory fibers and central pathways. The listed QST methods are sensory exam designed to specifically test that modality.

(Table amended from Hansson et al., 2007)

Type of Stimulus	Peripheral Sensory Fiber	Central Pathway	QST Methods
<u>Thermal</u>			
Cold	A $\delta$	Spinothalamic	Computer Controlled Thermal Testing Device
Warmth	C	Spinothalamic	Computer Controlled Thermal Testing Device
Cold Pain	A $\delta$ , C	Spinothalamic	Computer Controlled Thermal Testing Device
Heat Pain	A $\delta$ , C	Spinothalamic	Computer Controlled Thermal Testing Device
<u>Mechanical</u>			
Static light touch	A $\beta$	Medial Lemniscus	Monofilament Von Frey Hairs
Vibration	A $\beta$	Medial Lemniscus	Computer Controlled Vibration Testing Device
Brushing	A $\beta$	Medial Lemniscus	Brush
Blunt Pressure	A $\delta$ , C	Spinothalamic	Algometer

Use of neurobiological, sensory mechanisms allows us to utilize quantitative sensory testing (QST) as a method to test for different submodalities of the sensory system. By exploring the neurobiological mechanisms, QST is used to actively test areas such as touch, pressure, vibration, temperature, and pain sensation. Quantitative sensory testing can be used as an effective, diagnostic tool to evaluate different disorders and to support a clinician's sensory examination (Hansson et al., 2007). For example, juvenile idiopathic arthritis (JIA) is an important area for research, as the etiology of it is not well understood. It is possible to explore QST as an applicable means to understand pain mechanisms in JIA patients.

### **1.7 Juvenile Idiopathic Arthritis (JIA)**

JIA is an uncommon condition that affects children; however, it is the most commonly occurring, childhood rheumatological disease (Boros & Whitehead, 2010; Espinosa & Gottlieb, 2012). It is reported that JIA may occur from 2-20 cases per 10,000 people (Prakken et al., 2011) and even as frequent as 1-4 cases per 500 children (Boros & Whitehead, 2010). A comprehensive analysis of 34 epidemiological studies indicated JIA having a prevalence rate of 0.07 to 4.01 per 1000 children and an incidence rate of 0.008 to 0.226 per 1000 children (Manners & Bower, 2002).

JIA is not a single disorder but is a complex group of disorders that broadly describes various forms of chronic arthritis that are characterized

commonly with arthritis (Gowdie & Tse, 2012). Each disease contains a different presentation, course, and effect that are different from others, yet still have that defining commonality of arthritis (Espinosa & Gottlieb, 2012). Table 2 represents the different classifications of JIA that are set by the International League of Associations for Rheumatology.

**Table 2: Classifications of Juvenile Idiopathic Arthritis.**

This figure presents a brief overview of currently classified, different types of juvenile idiopathic arthritis and their respective diagnostic criteria. (Table edited from Boros & Whitehead, 2010).

Category	Diagnostic criteria
Systemic arthritis (10–20%)	Fever of at least 2 weeks duration (daily for at least 3 days) and arthritis in one or more joints, plus one of the following: <ul style="list-style-type: none"> <li>• erythematous rash</li> <li>• generalised lymph node enlargement</li> <li>• hepatomegaly and/or splenomegaly</li> <li>• serositis</li> </ul>
Oligoarthritis (50–60%)	Arthritis affecting $\leq$ four joints during the first 6 months of the disease. If after 6 months more than four joints are involved the term extended oligoarthritis is used
Polyarthritis (20–30%) (rheumatoid factor negative)	Arthritis affecting $\geq$ five joints during the first 6 months of the disease with rheumatoid factor negative
Polyarthritis (5–10%) (rheumatoid factor positive)	Arthritis affecting $\geq$ five joints during the first 6 months of disease with rheumatoid factor positive on at least two occasions at least 3 months apart
Psoriatic arthritis (2–15%)	Arthritis and psoriasis or arthritis and at least two of the following: <ul style="list-style-type: none"> <li>• dactylitis</li> <li>• nail pitting or onycholysis</li> <li>• psoriasis in a first degree relative</li> </ul>
Enthesitis related arthritis (1–7%)	Arthritis and enthesitis or arthritis or enthesitis with at least two of the following: <ul style="list-style-type: none"> <li>• presence/history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain and HLA-B27 positive</li> <li>• onset of arthritis in a male over 6 years of age</li> <li>• acute (symptomatic) anterior uveitis</li> <li>• history of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease or acute anterior uveitis in a first degree relative</li> </ul>
Undifferentiated arthritis	Arthritis that fulfils criteria in no category or in two or more of the above categories

## **1.8 Pain in JIA**

One of the symptoms that may occur in JIA patients is pain. It is interesting to note that JIA patients may present clinically significant pain while some patients do not undergo the same type of pain. There has been some published literature that focused on the evaluation of JIA patients' pain. Schanberg et. al. described that children experienced pain on an average of 73% of days in a two-month period, and a 76% of the children reported pain on over 60% of all days (Schanberg et al., 2003). However, McGhee et. al. found that 16% of children diagnosed with JIA reported musculoskeletal pain as their chief complaint, while the latter 84% of children did not report pain (McGhee et al., 2002).

There have also been discrepancies in the patients' psychological reports. Aasland et. al. described that the severity of JIA did not negatively impact psychosocial functioning (Aasland et al., 1997). However, Billings et. al. found that those with a more severe form of JIA showed more psychological and physical problems than those without the disease, and those with a milder form of JIA (Billings et al., 1987). Both the physical and psychological discrepancies in published literature prompts for a more complete understanding of pain in JIA patients.

## **1.9 Current JIA Research**

One of the largest problems obstacles of treating JIA patients is the need for effective communication for precise treatment. While there may be several biological markers that may be used to support a diagnosis, none of these values correlate with the experience of pain. Proper care and treatment is needed to tend to a subjective value of pain, and without a systematic way of evaluating, treatment will be varied and challenging.

## **1.10 Specific Aim of This Study**

The aim of the study is to characterize sensory function on JIA patients using QST. We hypothesize that JIA patients will exhibit lower sensory thresholds, i.e. increased sensitivity, to multiple sensory modalities, compared to age-matched controls.

## **2. Methods**

### **2.1 JIA Study Criteria**

The JIA study was conducted at the rheumatology clinic located at Boston Children's Hospital. The study was approved by the Boston Children's Hospital Institutional Review Board. We recruited children ages 7-17 years. The children were scheduled to visit the rheumatology clinic, located at Boston Children's Hospital in Boston, MA. Scheduled patients were screened and selected for our patient population. Existing medical records of the subjects were used to

determine the patients' eligibility for the study. Eligible subjects included those with polyarticular JIA with previous or active inflammation of the small joints of the hands. Other forms of JIA, such as systemic JIA, were excluded. Patients with neurological disorders were not included.

After the appointment with the clinician, both the patient and parents were approached and informed of the study by a member of the research team. Both the patient and his or her parent received a consent form detailing the description of the study and experimental test procedure. The patients were consented after their appointment with the rheumatologist, and voluntarily agreed to participate in the study.

## **2.2 QST Site Simulation**

Two sites were tested on each patient:

- Site 1: a joint with active arthritis/history of arthritis
- Site 2: the control site (no-joint, no history of inflammation).

Site 1 included one of the following: the proximal interphalangeal (PIP) joint or the distal interphalangeal (DIP) joint. Site 2 was located contralateral to the inflamed site and included the thenar eminence. Both the inflamed and uninflamed testing sites were selected based on the clinical judgment of the treating rheumatologist.

### 2.3 QST Procedure

The QST procedure consists of eight different sensory tests. The tests are comprised of: mechanical detection threshold (MDT), mechanical pain threshold (MPT), brush test, vibration detection threshold (VDT), pressure detection threshold (PDT), cool detection threshold (CDT), warm detection threshold (WDT), cold pain detection (CPT), and hot pain detection (HPT).

### 2.4 Innocuous Stimuli Tests

The MDT tests were conducted using a set of monofilament von Frey Hairs. The von Frey hairs have a uniform contact area, and each hair is calibrated to apply a fixed amount of force when pressed upon a surface. The hair is applied perpendicularly to the area of skin interest until it bends, and the nylon hair will consistently apply the same amount of force (Figure 3).



**Figure 6: Von Frey Monofilament Hair.**

Each von Frey monofilament hair applies a specific, constant force (Figure downloaded from DocCheck Shop at <https://dccdn.de/shop.doccheck.com/>).

#### **2.4.1 Mechanical Detection Threshold (MDT) Test**

During the MDT test, the patient is asked to sit in a comfortable position. The von Frey hairs are applied using the method of limits. The procedure involves gradually increasing the amount of force until the subject verbally reports that the sensation is felt. Three trials were conducted for each site. The average of the three trials were used and calculated.

#### **2.4.2 Brush-evoked Allodynia Test**

The Brush-evoked pain test was conducted to test for dynamic hyperalgesia. A soft brush, weighing 5 grams, was stroked across the area of stimulus at a rate of 1 cm per second. The subject was then asked to report whether the sensation felt “soft” or “harsh.” The test involved three trials per area. Response that was recorded two times out of the three trials was recorded to be the perceived sensation.

#### **2.4.3 Vibration Detection Threshold (VDT) Test**

The vibration test involved using a TSA II (MEDOC, Israel) thermal sensory device with a vibration unit (Figure 5). A vibration-stimulating probe has a contact area measuring 1.2 cm<sup>2</sup>. It is attached to the TSA-II unit and applied directly on the area of interest. The strength of the vibration was gradually increased at 0.1 μm/s at a fixed amplitude of 100Hz until the patient felt the sensation. The patient used a computer mouse to indicate that the sensation was

felt. The test consisted of eight trials for each site. The average of the eight trials were used and calculated.



**Figure 7: TSA-II Vibration Unit.**

Vibration unit attaches to the TSA-II unit. The white tip of the device applies graded and varying amounts of frequency to the site of interest.

(Figure downloaded from Biolink at

[http://www.biolinkbr.com/tsa\\_accessories/index.htm](http://www.biolinkbr.com/tsa_accessories/index.htm))

#### **2.4.4 Cool Detection Threshold (CDT) Test**

The temperature tests included cool and warm threshold detection and cold and hot pain temperature detection. The testing was done via the Thermal and Vibratory Quantitative Sensory Testing Analyzer (TSA-II, MEDOC, Israel). The device attached a thermode that was 16x16mm in size and was placed directly over the area of interest. Temperature was gradually decreased at a rate of 1.0°C, starting from a baseline temperature of 32°C. The subject was then

asked to click, using a computer mouse, to signal when the sensation was felt. Four trials per stimulation site were conducted. The average of the four trials were used.



**Figure 8: Thermode Unit**

A 16x16mm thermode connects to a TSA-II Thermal and Vibratory Quantitative Sensory Testing Analyzer. The specific area will be applied to the area of interest and change in specific temperature increments.

(Figure downloaded from Biolink at

[http://www.biolinkbr.com/tsa\\_accessories/index.htm](http://www.biolinkbr.com/tsa_accessories/index.htm)).

#### **2.4.5 Warm Detection Threshold (WDT) Test**

In the warm detection test, the patient was asked to respond when warmth was detected. Temperature was gradually increased at a rate of 1.0°C, starting from a baseline temperature of 32°C. The subject was then asked to click, using a computer mouse, to signal when the sensation was felt. Four trials per stimulation site were conducted and the average of the four trials were used.

## **2.5 Noxious Stimuli Tests**

### **2.5.1 Mechanical Pain Threshold (MPT) Test**

The MPT test consisted of a protocol similar to the MDT test. The amount of force was increased from a light force until the subject was able to verbally report that the sensation felt sharp. The subject was asked to verbally report when the von Frey hair stimulation felt “like a sharp sensation like a pin-prick.” Two trials were conducted for each site. The average of the two trials were used and calculated.

### **2.5.2 Pressure Pain Threshold (PPT) Test**

The pressure threshold test involved using a hand-held Pressure Algometer (Wagner Inc., USA). It was used to quantify pressure sensation. The device was fit with a 1cm<sup>2</sup> rubber tip that is applied over the area of interest. The pressure was increased at a rate of 1 N/sec. The patient was instructed to respond when he or she felt discomfort in the area. Three trials were performed for each site of stimulation. The average of the three trials were used and calculated.



**Figure 9: Pressure Algometer Device**

The handheld device calculates the specific amount of pressure applied at the rubber tip. Different units can be selected for measurement. (Figure downloaded from Wagner Instruments at [http://www.wagnerinstruments.com/force\\_gauges/fdx\\_digital\\_force\\_gauge.php](http://www.wagnerinstruments.com/force_gauges/fdx_digital_force_gauge.php))

### **2.5.3 Cold Pain Threshold (CPT) Test**

In the cold pain threshold test, the temperature was gradually decreased at a rate of 1.5°C, starting from a baseline temperature of 32°C. The subject was then asked to click, using a computer mouse, to signal when the sensation felt cold, as if one was “holding a popsicle.” three trials per stimulation site were conducted and the average of the three trials were used.

#### **2.5.4 Hot Pain Threshold (HPT) Test**

In the hot pain threshold test, the temperature was gradually increased at a rate of 1.5°C, starting from a baseline temperature of 32°C. The subject was then asked to click, using a computer mouse, to signal when the sensation felt hot, as if one was “holding a hot cup of coffee.” three trials per stimulation site were conducted and the average of the three trials were used.

#### **2.6 Statistical Analysis**

All data are reported as mean  $\pm$  SD. To test for differences in sensory function between JIA patients (data collected from this study) and healthy age-matched controls, the data are compared to a previously published work (Blankenburg et al., 2010; Meier et al., 2001). A Wilcoxon matched-paired signed rank test was done between the thenar eminence and the inflamed joint within the same JIA group. An unpaired, t-test was performed for comparison between the reference value group and JIA patients. All data were plotted and analyzed with GraphPad Prism statistical software (GraphPad, CA). A P-value  $<0.05$  was considered to be statistically significant. Respective T-values and degrees of freedom (df) are indicated in parentheses in the main of the text.

### **3. Results**

This is an interim report from an ongoing study. A total of 12 patients are included in this interim analysis. The mean age was  $11.9 \pm 3.1$  years. All subjects were females. No subjects withdrew from the study or reported severe pain or distress. The following sections describe the results of each sensory modality, and are summarized on Table 3 on page 46.

#### **3.1 Innocuous Stimuli**

Innocuous stimuli tests included sensory tests that did not involve any stimuli that required the patients to report a painful sensation. This category included the following tests: Mechanical Detection Threshold, Cool Detection Threshold, Warm Detection Threshold, Vibration Detection Threshold, and brush allodynia tests.

##### **3.1.1 Mechanical Detection Threshold (MDT) Test**

Mechanical detection threshold was compared between a reference cohort and JIA patients on the thenar eminence. The reference cohort data were taken from a previously published data set (Blankenburg et al., 2010).

For the reference cohort, the mean mechanical detection threshold was  $0.03 \pm 0.03$ g (n=32). The JIA patients had a significantly higher threshold for mechanical detection, mean mechanical detection threshold was  $0.06 \pm 0.005$ g

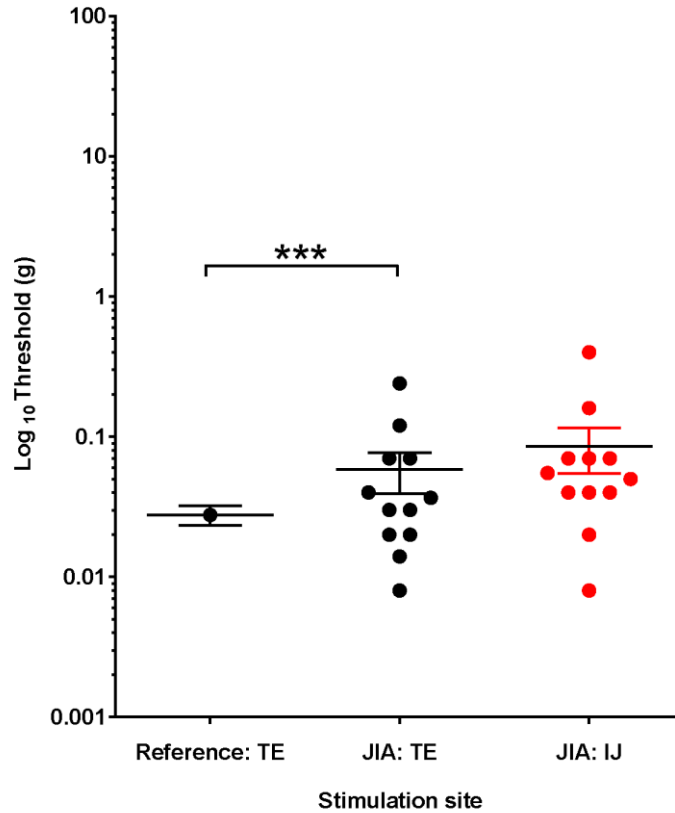
(unpaired t-test,  $p \leq 0.0002$ ;  $t$ , 4.12;  $df$ , 42). Figure 10 shows JIA patients had a decreased sensitivity to mechanical detection thresholds at the thenar eminence.

Mechanical detection threshold was tested in JIA patients at the thenar eminence and compared to the inflamed joint. The aim of this was to test for globalized changes in sensory function. We used within-subject comparison. There were no significant differences in cool detection threshold at the thenar eminence compared to the inflamed joint (Wilcoxon matched-pairs test,  $p=0.46$ ), Figure 10.

### **3.1.2 Brush-evoked Allodynia Test**

Brush-evoked allodynia responses were compared between a reference cohort and JIA patients on the thenar eminence. The reference cohort data were taken from a previously published data set (Blankenburg et al., 2010).

All responses from the reference cohort reported a soft and innocuous sensation (Blankenburg et al., 2010). In our study, all JIA patients reported a “soft” sensation in both the thenar eminence and the inflamed joint.



**Figure 10: JIA patients had a decreased sensitivity to mechanical detection thresholds at the thenar eminence compared to reference cohort.**

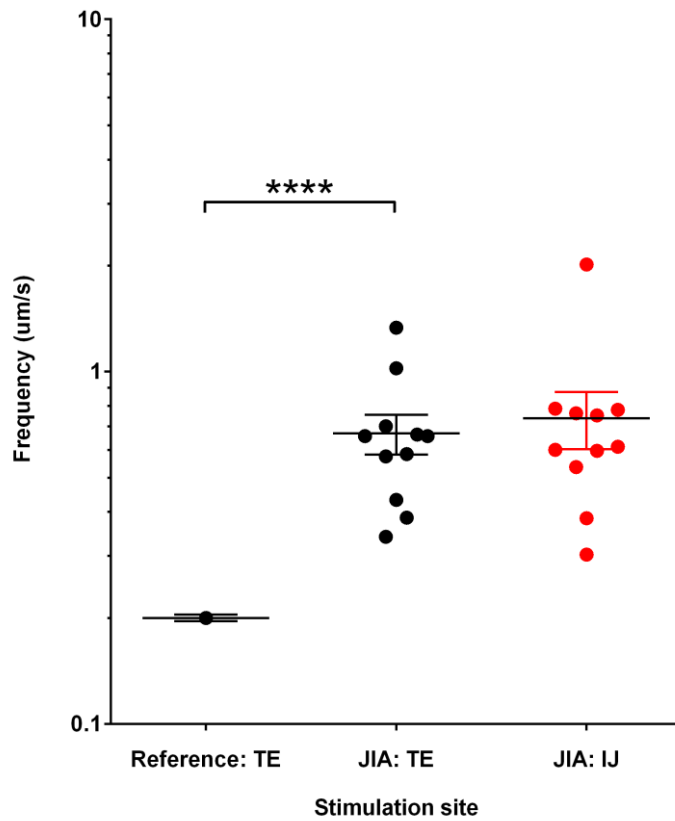
JIA patients had no differences in mechanical detection threshold at the thenar eminence (TE) and the inflamed joint (IJ), suggesting a globalized change in mechanosensory function. Each dot represents an individual patient for the JIA patient group. Horizontal bar represents the mean for each group. Vertical bar represents the standard deviation. \*\*\*p=0.0002, unpaired Student's T-Test

### **3.1.3 Vibration Detection Threshold (VDT) Test**

Vibration detection threshold was compared between a reference cohort and JIA patients on the thenar eminence. The reference cohort data were taken from a previously published data set (Meier et al., 2001).

For the reference cohort, the mean vibration detection threshold was  $0.2 \pm 0.04\text{g}$  ( $n=101$ ). The JIA patients had a significantly higher threshold for vibration detection. The mean vibration detection threshold was  $0.67 \pm 0.03\text{g}$  (unpaired t-test,  $p \leq 0.0001$ ;  $t, 35.89$ ;  $df, 110$ ). Figure 11 shows JIA patients had a decreased sensitivity to vibration detection thresholds at the thenar eminence.

Vibration detection threshold was tested in JIA patients at the thenar eminence and compared to the inflamed joint. The aim of this was to test for globalized changes in sensory function. We used within-subject comparison. There were no significant differences in cool detection threshold at the thenar eminence compared to the inflamed joint (Wilcoxon matched-pairs test,  $p=0.9658$ ), Figure 11.



**Figure 11: JIA patients had a decreased sensitivity to vibration detection thresholds at the thenar eminence compared to reference cohort.**

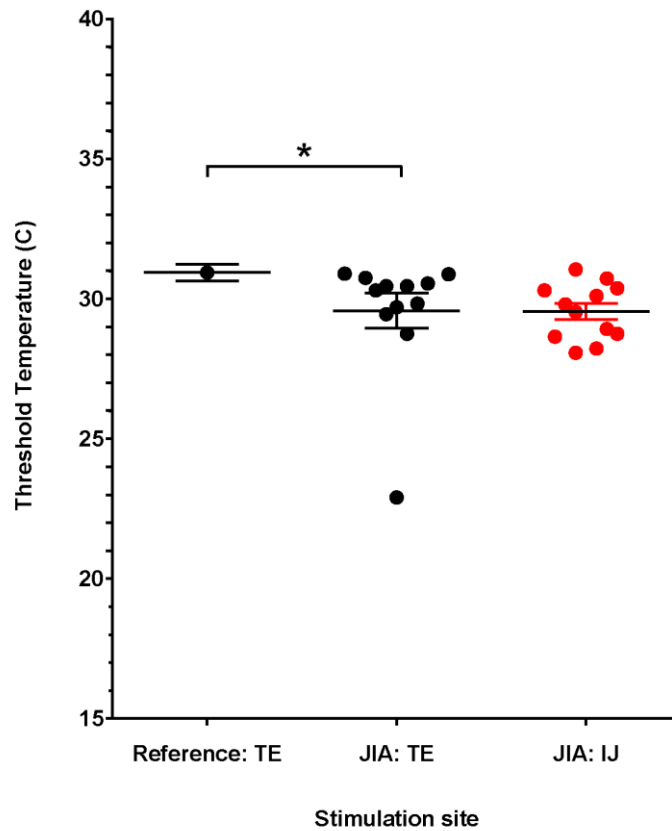
JIA patients had no differences in vibration detection threshold at the thenar eminence and the inflamed joint, suggesting a globalized change in mechanoreceptive sensory function. Each dot represents an individual patient for the JIA patient group. Horizontal bar represents the mean for each group. Vertical bar represents the standard deviation. \*\*\*\*p=0.0001, unpaired Student's T-Test.

### 3.1.4 Cool Detection Threshold (CDT) Test

Cool detection threshold was compared between a reference cohort and JIA patients on the thenar eminence. The reference cohort data were taken from a previously published data set (Blankenburg et al., 2010).

For the reference cohort, the mean cool detection threshold was  $30.94 \pm 1.68^{\circ}\text{C}$  (n=32). The JIA patients had a significantly higher threshold for cool detection, mean cool detection threshold was  $29.58 \pm 2.20^{\circ}\text{C}$  (unpaired t-test,  $p=0.03$ ; t, 2.20; df, 42). Figure 12 shows JIA patients had a decreased sensitivity to cool temperatures at the thenar eminence compared to the reference cohort.

Cool detection threshold was tested in JIA patients at the thenar eminence and compared to the inflamed joint. The aim of this was to test for globalized changes in sensory function. We used within-subject comparison. There were no significant differences in cool detection threshold at the thenar eminence compared to the inflamed joint (Wilcoxon matched-pairs test,  $p=0.26$ ), Figure 12.



**Figure 12: JIA patients had a decreased sensitivity to cool temperature detection at the thenar eminence compared to reference cohort.**

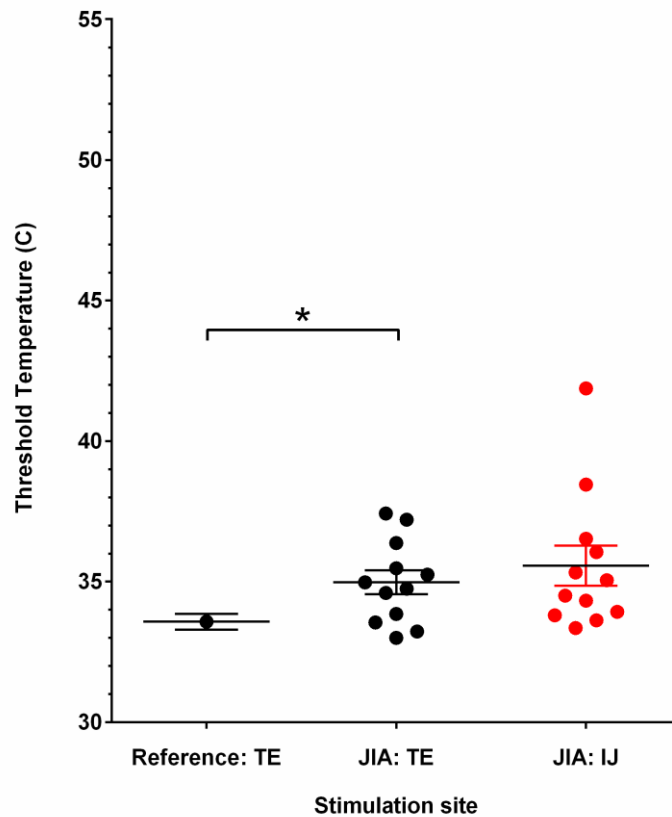
JIA patients had no differences in cool detection threshold at the thenar eminence and the inflamed joint, suggesting a globalized change in thermal sensory function. Each dot represents an individual patient for the JIA patient group. Horizontal bar represents the mean for each group. Vertical bar represents the standard deviation. \*p <0.05, unpaired Student's T-Test

### 3.1.5 Warm Detection Threshold (WDT) Test

Warm detection threshold was compared between a reference cohort and JIA patients on the thenar eminence. The reference cohort data were taken from a previously published data set (Blankenburg et al., 2010).

For the reference cohort, the mean warm detection threshold was  $33.58 \pm 1.58^{\circ}\text{C}$  (n=32). The JIA patients had a significantly higher threshold for warm detection, mean warm detection threshold was  $34.97 \pm 1.47^{\circ}\text{C}$  (unpaired t-test,  $p=0.01$ ;  $t, 2.65$ ;  $df, 42$ ). Figure 13 shows JIA patients had a decreased sensitivity to warm temperatures at the thenar eminence compared to the reference cohort.

Warm detection threshold was tested in JIA patients at the thenar eminence and compared to the inflamed joint. The aim of this was to test for globalized changes in sensory function. We used within-subject comparison. There were no significant differences in warm detection threshold at the thenar eminence compared to the inflamed joint (Wilcoxon matched-pairs test,  $p=0.38$ ), Figure 13.



**Figure 13: JIA patients had a decreased sensitivity to warm temperature detection at the thenar eminence compared to reference cohort.**

JIA patients had no differences in warm detection threshold at the thenar eminence and the inflamed joint, suggesting a globalized change in thermal sensory function. Each dot represents an individual patient for the JIA patient group. Horizontal bar represents the mean for each group. Vertical bar represents the standard deviation. \*p =0.01, Unpaired Student's T-Test

## **3.2 Noxious Stimuli**

Noxious stimuli tests include sensory tests that involve stimuli that may require patients to report uncomfortable sensations. The following tests are considered to involve noxious stimuli: Mechanical Pain Threshold, Pressure Detection Threshold, Cold Pain Threshold, and Hot Pain Threshold.

### **3.2.1 Mechanical Pain Threshold (MPT) Test**

Mechanical pain threshold was compared between a reference cohort and JIA patients on the thenar eminence. The reference cohort data were taken from a previously published data set (Blankenburg et al., 2010).

For the reference cohort, the mean mechanical pain threshold was  $1.69 \pm 0.04$ g (n=32). The JIA patients had a significantly lower threshold for mechanical pain. The mean mechanical pain threshold was  $1.19 \pm 0.14$ g (unpaired t-test,  $p < 0.0001$ ;  $t, 7.45$ ;  $df, 42$ ). Figure 14 shows JIA patients had an increased sensitivity to mechanical pain at the thenar eminence.

Mechanical pain threshold test was tested in JIA patients at the thenar eminence and compared to the inflamed joint. The aim of this was to test for globalized changes in sensory function. We used within-subject comparison. There were no significant differences in mechanical pain detection threshold at the thenar eminence compared to the inflamed joint (Wilcoxon matched-pairs test,  $p=0.18$ ), Figure 14.

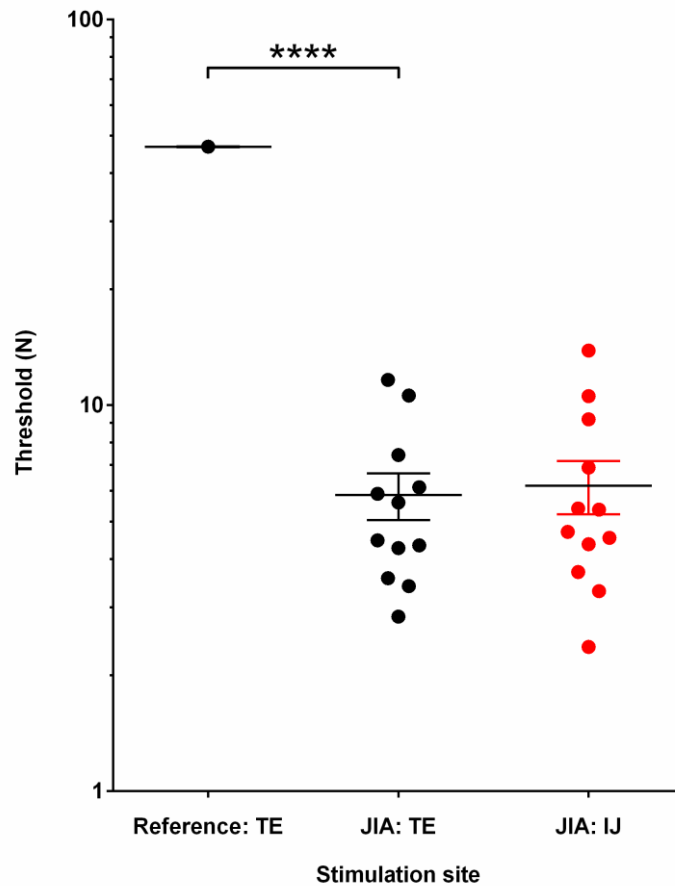


### **3.2.2 Pressure Pain Threshold (PPT) Test**

Pressure pain threshold was compared between a reference cohort and JIA patients on the thenar eminence. The reference cohort data were taken from a previously published data set (Blankenburg et al., 2010).

For the reference cohort, the mean pressure pain threshold was  $46.77 \pm 0.14\text{N}$  ( $n=32$ ). The JIA patients had a significantly lower threshold for pressure pain. The mean pain pressure threshold was  $5.85 \pm 0.81\text{N}$  (unpaired t-test,  $p<0.0001$ ;  $t$ , 281;  $df$ , 42). Figure 15 shows JIA patients had an increased sensitivity to pressure pain threshold at the thenar eminence.

Pressure pain threshold was tested in JIA patients at the thenar eminence and compared to the inflamed joint. The aim of this was to test for globalized changes in sensory function. We used within-subject comparison. There were no significant differences in pressure pain threshold at the thenar eminence compared to the inflamed joint (Wilcoxon matched-pairs test,  $p=0.86$ ), Figure 15.



**Figure 15: JIA patients had an increased sensitivity to pressure pain threshold at the thenar eminence compared to reference cohort.**

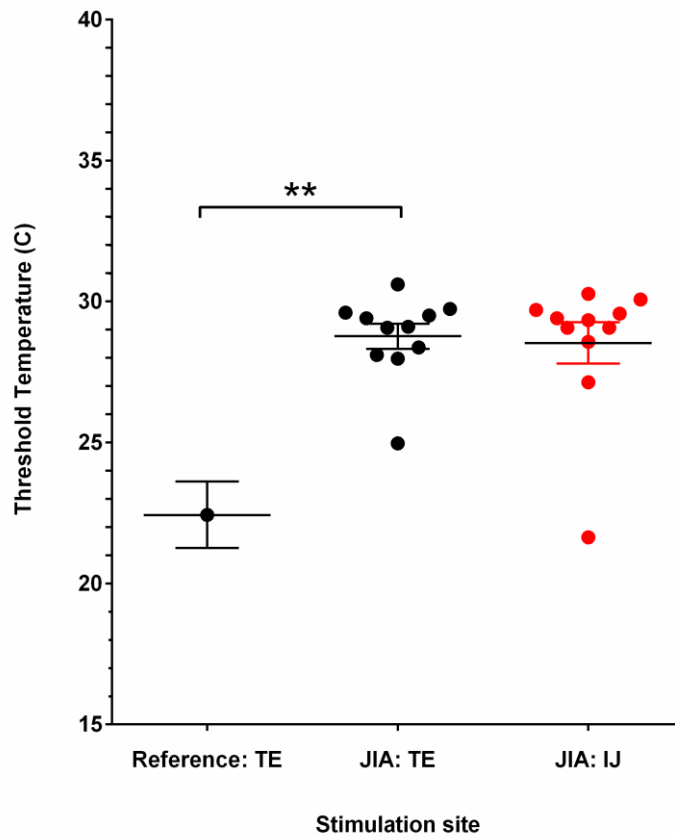
JIA patients had no differences in pressure pain threshold at the thenar eminence and the inflamed joint, suggesting a globalized change in sensory function. Each dot represents an individual patient for the JIA patient group. Horizontal bar represents the mean for each group. Vertical bar represents the standard deviation. \*\*\*\*p <0.0001 Unpaired Student's T-Test.

### 3.2.3 Cold Pain Threshold (CPT) Test

Cold pain threshold was compared between a reference cohort and JIA patients on the thenar eminence. The reference cohort data were taken from a previously published data set (Blankenburg et al., 2010).

For the reference cohort, the mean cold pain threshold was  $22.43 \pm 6.65^{\circ}\text{C}$  (n=32). The JIA patients had a significantly lower threshold for cold pain, mean cold pain threshold was  $28.76 \pm 1.48^{\circ}\text{C}$  (unpaired t-test,  $p=0.0023$ ;  $t, 3.25$ ;  $df, 42$ ). Figure 16 shows JIA patients had an increased sensitivity to cold pain at the thenar eminence.

Cold pain threshold was tested in JIA patients at the thenar eminence and compared to the inflamed joint. The aim of this was to test for globalized changes in sensory function. We used within-subject comparison. There were no significant differences in cold pain threshold at the thenar eminence compared to the inflamed joint (Wilcoxon matched-pairs test,  $p=0.90$ ), Figure 16.



**Figure 16: JIA patients had an increased sensitivity to cold pain at the thenar eminence compared to reference cohort.**

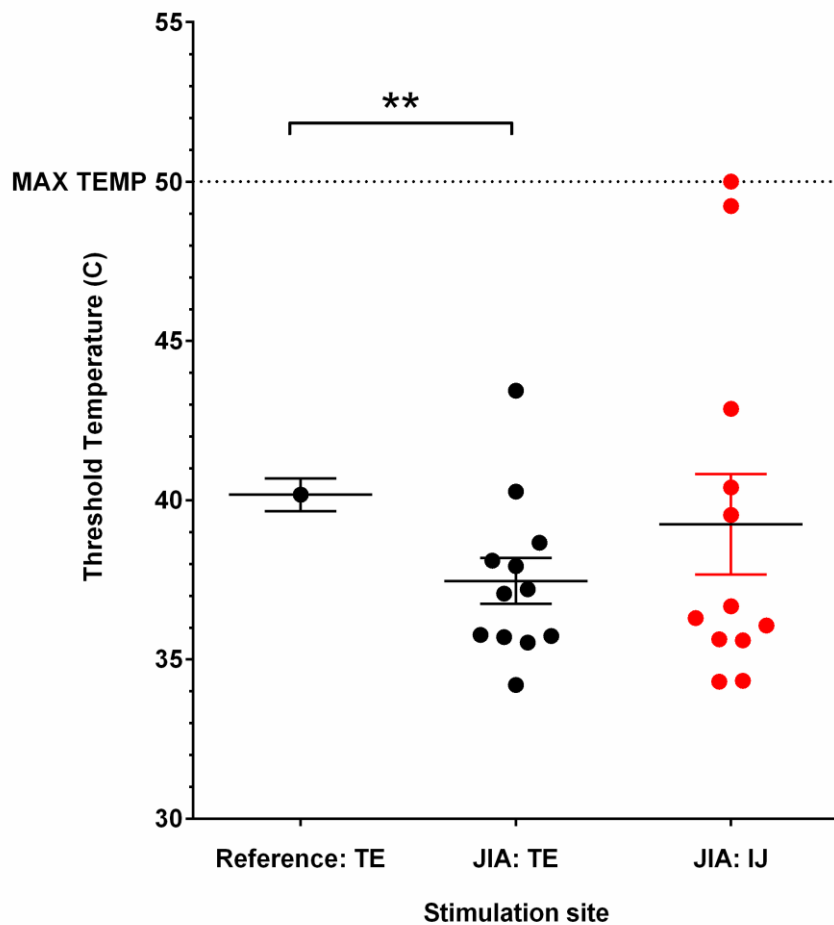
JIA patients had no differences in cold pain threshold at the thenar eminence and the inflamed joint, suggesting a globalized change in sensory function. Each dot represents an individual patient for the JIA patient group. Horizontal bar represents the mean for each group. Vertical bar represents the standard deviation. \*\*p=0.0023, Unpaired Student's T-Test.

### 3.2.4 Hot Pain Threshold (HPT) Test

Hot pain threshold was compared between a reference cohort and JIA patients on the thenar eminence. The reference cohort data were taken from a previously published data set (Blankenburg et al., 2010).

For the reference cohort, the mean hot pain threshold was  $40.17 \pm 2.93^{\circ}\text{C}$  (n=32). The JIA patients had a significantly lower threshold for hot pain, mean hot pain threshold was  $37.47 \pm 2.51^{\circ}\text{C}$  (unpaired t-test,  $p=0.0072$ ;  $t$ , 2.82;  $df$ , 42). Figure 17 shows JIA patients had an increased sensitivity to hot pain at the thenar eminence.

Hot pain threshold was tested in JIA patients at the thenar eminence and compared to the inflamed joint. The aim of this was to test for globalized changes in sensory function. We used within-subject comparison. There were no significant differences in hot pain threshold at the thenar eminence compared to the inflamed joint (Wilcoxon matched-pairs test,  $p=0.18$ ), Figure 17.



**Figure 17: JIA patients had an increased sensitivity to hot pain at the thenar eminence compared to reference cohort.**

JIA patients had no differences in hot pain threshold at the thenar eminence and the inflamed joint, suggesting a globalized change in sensory function. Each dot represents an individual patient for the JIA patient group. Horizontal bar represents the mean for each group. Vertical bar represents the standard deviation. \*\*p=0.0072 Unpaired Student's T-Test.

**Table 3: Means, SD, P-values of Raw Values.**

Table of the means, SD, and p-values of the raw values are listed. Reference values are tabulated from different sources. Comparisons between the Reference cohort and JIA patients in the TE were performed. JIA Patient within-subject comparisons were not significant and are not tabulated.

MDT, MPT, Brush Test, CDT, WDT, PPT, CPT, HPT Reference values are taken from Blankenburg et. al. study. VDT Reference values are taken from Meier et. al. study.

QST Parameter	Reference: Thenar Eminence <sup>1</sup>		JIA: Thenar Eminence (n=12)	JIA: Inflamed Joint (n=12)	P-value	JIA No Difference	JIA Increased Sensitivity	JIA Decreased Sensitivity
	MDT (g)	0.02 ± 0.001	0.06 ± 0.019	0.08 ± 0.02	0.08 ± 0.02	0.0002		
Vibration Test (µm/s)	0.2 ± 0.04	0.67 ± 0.090	0.74 ± 0.14	0.74 ± 0.14	< 0.0001			✓
Brush Allodynia (%)	0	0	0	0	0	✓		
CDT (°C)	30.94 ± 1.68	29.58 ± 2.20	29.54 ± 1	29.54 ± 1	0.03			✓
WDT (°C)	33.58 ± 1.59	34.97 ± 1.47	35.57 ± 2.46	35.57 ± 2.46	0.01			✓
MPT (g)	13.87 ± 2.04	1.19 ± 0.47	1.42 ± 0.70	1.42 ± 0.70	< 0.0001		✓	
PPT (N)	46.77 ± 0.14	5.85 ± 0.81	6.19 ± 0.98	6.19 ± 0.98	< 0.0001		✓	
CPT (°C)	22.43 ± 6.65	28.76 ± 1.48	28.53 ± 2.44	28.53 ± 2.44	0.0023		✓	
HPT (°C)	40.17 ± 2.93	37.47 ± 2.51	39.24 ± 5.48	39.24 ± 5.48	0.0072		✓	

#### **4. Discussion**

JIA patients exhibited increased sensitivity to noxious stimuli (Table 3). . The underlying mechanisms involved may lie at the level of the periphery – due to peripheral sensitization of the sensory receptors and increased neuronal excitability, or at the level of the spinal cord and higher centers – reflecting central sensitization.

In the MDT test, the recorded values from the TE of the reference groups were significantly lower from the values of the TE and inflamed joint of the JIA group. This marked the JIA patients to be less sensitive to light touch compared to the reference groups taken from other literature. A higher force was applied to the skin before stimulus detection. However, the MPT test, which tests for sensitivity to mechanical pain, showed that the JIA patient was more sensitive than the reference cohort. The threshold level, which the JIA patients were able to sense the sharp and painful stimulus, was lower than that of the reference cohort.

The brush allodynia test showed that JIA patients were not allodynic. Almost all the patients reported a feeling of “soft” when the brush was applied over the skin. There was no significant difference between the two groups’ response to the stimulus.

JIA patients also experienced a lower threshold to pressure-induced pain in both the thenar eminence and the inflamed joint when compared to the normal controls experienced in the thenar eminence. While the reference cohort showed

an increased sensitivity in detecting vibrating stimuli, significantly smaller amounts of applied pressure were recorded to detect pressure pain for the JIA patients. Both stimulation sites in JIA patients showed similar values, indicating a non-local effect.

In the temperature tests, JIA patients had different responses than the normal controls did. JIA patients were more insensitive to changes in cool temperature than that of the normal controls. Similarly, the JIA patients showed a lower sensitivity in detecting a change in warm temperature than that of the normal controls.

JIA patients were unable to detect the cold pain temperatures as well as the normal controls. The reference cohort detected pain when there was about a 10°C decrease, while the JIA group detected a change in 3°C to be painful. Interestingly, the JIA group expressed a similar increase in sensitivity to hot temperatures that were painful in the thenar eminence. However, the same phenomenon was not seen in the inflamed joint, denoting that there was no difference from the threshold of the control group.

Analysis showed that skin sensation responses recorded at different locations within the same JIA group showed no significant difference for the eight sensory tests. The increased sensitivity in noxious stimuli of the JIA patients indicated possible pathology that may exist within the pain processing pathways. Some of the points of interest may be at the peripheral receptors level or at the fiber level such as the A $\delta$  or C-fibers. It also appeared to be a globalized change

in sensitivity as opposed to a localized change. JIA patients did not experience an increased sensitivity in the inflamed joints. Non-inflamed and other non-affected areas are also characterized by similar changes in sensitivities.

## **5. Study Limitations**

Although there may be a rationale of inflamed areas being more sensitized than non-inflamed areas, the results of the sensory exams show that JIA does not result in a localized change in sensory responses. It is difficult to interpret whether the JIA condition carries a local or systemic effect on responses to different types of stimuli. With a limited sample number, the range of responses is high.

It is also important to note that testing procedures can be viewed as subjective. The concept of a sensation being “painful” will be highly variable. Some patients may have a higher threshold to painful stimuli, while others may not have a high tolerance.

Study procedures across all subjects were conducted as closely and identically as possible. Parents were allowed to be present with the child in the same examination room. According to Zohsel et. al’s study, it was found that when a mother was present, the child consistently reported higher, heat pain thresholds (Zohsel et al., 2006). It may be possible that the lab values collected in our current study may be higher than normal.

## **6. Future Studies**

Further work is needed in this area of sensory testing. Although results showed differences in sensory physiological responses between healthy controls and JIA patients, this was a pilot study with a limited number of recruited patients. More patients will need to be recruited in order to help strengthen and clarify the relationships of sensitivities in responses. After a bigger database of patients is collected, these QST values will then be correlated with objective, laboratory markers that may be indicative of disease. Expansion of other stimulation sites, such as the wrist, ankle, and knees, will be considered in future studies in order to increase our population criteria.

It is also possible to use QST in other applications, such as measuring sensory responses in patients who have undergone local anesthesia. One of our future studies will involve testing the efficacy of a novel, local anesthetic. QST may have an applicable use in assessing the duration of the anesthetic's effects and the need for additional anesthetics administration for patients post-surgery. Determining the state of the patient's sensory functions will be necessary for treatment and adequate patient care. It will also be a useful tool in development and research of new, local anesthetics. In order to assess and test for the efficacy of the drug, QST can be a useful tool to determine the duration of the drug's effects and the physiological responses of the sensory systems.

## **7. Conclusion**

This study demonstrated that QST is an applicable means of gathering sensory data from JIA patients. However, more information and research is needed to build a closer picture to understand the etiology of JIA. It is even suggested that children who are diagnosed with JIA earlier than those diagnosed later in life may have better psychosocial functioning skills (April et al., 2012). QST may be useful when used in conjunction with other diagnostic tools to assess sensory function. Further research could be extended to discover pain mechanisms in JIA.

## LIST OF JOURNAL ABBREVIATIONS

Ann Intern Med	Annals of Internal Medicine
Arthritis Rheum	Arthritis and Rheumatism
Aust Fam Physician	Australian Family physician
Child Care Health Dev	Child: Care, Health and Development
Clin Auton Res	Clinical Autonomic Research : Official Journal of the Clinical Autonomic Research Society
Clin Exp Rheumatol	Clinical and Experimental Rheumatology
Clin J Pain	The Clinical Journal of Pain
Curr Opin Neurobiol	Current Opinion in Neurobiology
Curr Pain Headache Rep	Current Pain and Headache Reports
Health Psychol	Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association
J Neurol Sci	Journal of the Neurological Sciences
J Rheumatol	The Journal of Rheumatology
Muscle Nerve	Muscle & Nerve
Nat Clin Pract Neurol	Nature Clinical Practice. Neurology
Neurosci Biobehav Rev	Neuroscience and Biobehavioral Reviews
Pediatr Clin North Am	Pediatric Clinics of North America

Pediatr Rev

Pediatrics in Review / American Academy of

Pediatrics

Pract Neurol

Practical Neurology

Semin Arthritis Rheum

Seminars in Arthritis and Rheumatism

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