COMPARISON BETWEEN THE TSA2 AND THE MEDOC PATHWAY IN ASSESSING THERMAL LEG SENSITIVITY

by

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Chapter 1

ABSTRACT

Quantitative Sensory Testing (QST) is a method used to quantify somatosensory function in large and small nerve fibers to detect sensory loss (i.e., hypoesthesia, hypoalgesia) or sensory gain (i.e., hyperesthesia, hyperalgesia, allodynia) that may be associated with acute and chronic pain. A set of objective testing procedures that include both thermal and mechanical test stimuli are administered based on a protocol. Thermal stimuli are administered with the gold standard Medoc Pathway, a stationary and heavy piece of equipment, however, a new to the market portable Advanced Thermosensory Stimulator (TSA2) is now available for testing with many of the same functions as the pathway; however, it has not been tested in the lower extremity. The aim of this study is to evaluate the agreement in thermal testing between the two machines. This is a repeated-measures two group study with two test sessions one day apart (N=20). Thermal testing consisted of warm/cold detection and heat/cold pain. Statistical analyses include paired t-test for mean differences, Pearson's correlation for agreement, intraclass correlation and coefficient alpha values, and Bland-Altman's plots for differences between the measurements. Mean age for participants was 32 years (SD=14.3) and evenly split between men and women. The paired t-test revealed no significant differences between the TSA2 and Medoc Pathway. Pearson correlations show strong correlations for thermal pain on the TSA2 and Medoc Pathway. High alpha values were revealed on all tests conducted, except for warm detection. Bland-Altman plots reveal agreeable data for cold detection, cold pain, and warm pain. Warm detection displayed a distinct pattern where there were differences between the Medoc Pathway and TSA2 when temperature rose, which might account for the low alpha value for warm detection.

Chapter 2

BACKGROUND

PAIN

Chronic pain is a significant problem reported by 50 million U.S adults r which contributes to morbidity and mortality, disability, healthcare demands, and economic burdens (National Institutes of Health [NIH], 2020). The total financial cost of pain to society combining the cost of healthcare is estimated to range from around $560 to $635 billion per year (National Institutes of Health [NIH], 2020). In addition to extensive healthcare costs, the loss of productivity and employment due to pain additionally has a negative societal economic impact on individual's lives. Pain will cause individuals to achieve lower economic productivity associated with lost wages, missed workdays, and fewer hours worked (Gaskin & Richard, 2018).

Chronic pain has a negative impact on overall patient health and quality of life as it can impact sleep, cognitive processes (i.e., impairment of memory and attention), brain function (i.e., abnormal brain chemistry and loss of gray matter which can decrease cognitive and motor function), mental health (i.e., mood and anxiety disorders), cardiovascular health (i.e., hypertension), and impaired sexual function (Fine, 2011). Chronic pain is associated with increased rates of depression, suicidal ideation, and the prevalence of psychological disorders ranges from 33%-46% amongst individuals with pain compared to only 10% in individuals not reporting pain (Fine, 2011). Pain has been shown to negatively affect biological, psychological, and social aspects of health, therefore pain research may improve the lives of individuals and reduce healthcare costs.

Pain is defined as "unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Treede, 2018). Acute pain serves

a biological purpose and is provoked by specific disease and/or injury and is associated with sympathetic nervous system activation and skeletal muscle spasm and is self-limiting (Grichnik KP;Ferrante FM, 2022).

Chronic pain is defined as, “pain which has persisted beyond normal tissue healing time, which, in the absence of other factors, is generally taken to be 3 months (Grichnik KP;Ferrante FM, 2022). Chronic pain does not serve a biological purpose, may arise from psychological states, and has no recognizable endpoint. In general, pain is described to have three major dimensions: sensory (discriminative), motivational (affective), and cognitive (evaluative) with many different categories of pain, such as acute pain, chronic pain, nociceptive, neuropathic, or by site (i.e., back, leg) (Bendinger & Plunkett, 2016).

Sensory-discriminative pain describes the intensity, location, quality, and duration of the pain. Affective-motivational pain describes the emotional responses to pain such as anxiety and fear, while cognitive-evaluative pain describes thoughts of pain influenced by experiences and knowledge (*Psychological Basis of Pain*, 2018). The interaction of these dimensions contributes to the complexity of the pain experience. Treatment of chronic pain is recommended to rely on multidisciplinary approaches and involve more than one treatment modality (Grichnik KP;Ferrante FM, 2022). Some factors of chronic pain that can greatly affect one’s quality of life includes physical, psychological, social, and emotional states and often arises from a combination of multiple events (Mills et al., 2019). Both chronic and acute pain can influence an individual’s way of living and require treatment before leading to complications.

PATHOPHYSIOLOGY OF PAIN

To properly diagnose and treat pain, it is important to understand the underlying pathophysiology on pain. Pain is an unpleasant experience resulting from physical and psychological responses to injury through a pathway that transmits pain messages from the periphery to the central nervous system (Steeds, 2016). This pain pathway includes the process of 1) transduction, 2) transmission, 3) modulation, and 4) perception. *Transduction* begins when damaged cells release nociceptors, free nerve endings, and nociceptor-sensitizing substances such as bradykinins, histamines, prostaglandins, and substance P in response to external stimuli, such as thermal, mechanical, and chemical signals (Rodriguez, 2015). Three kinds of nociceptors include fast myelinated A-delta fibers that respond to pinprick and mechanical (pressure) stimuli, A-beta fibers that carry vibratory signals and produce deep and stabbing sensations, and unmyelinated slow C-fibers that respond to thermal and chemical stimuli, which creates an action potential (Schug et al., 2011, Woessner, 2011).

Transmission occurs following a stimulus, when the signal travels to the dorsal horn in the spinal cord where primary afferent pain fibers synapse with second-order neurons and then bifurcate and ascend via the spinothalamic and spinoreticular tracts to the thalamus and brain stem (Steeds, 2016). Transmission continues when the signal travels across the synaptic cleft of one neuron to the next and neurotransmitters are released to bind to specific receptors on receptive neurons where pain is then perceived (Rodriguez, 2015).

Perception of pain is an important component of the pain experienced as it integrates cognitive and affective (emotional) responses, playing a role in the pain pathway (Cohen & Mao, 2014). Perception of pain occurs after stimuli reaches the thalamus via the spinothalamic tract

(Kübler, 2009). The thalamus is the key area for processing somatosensory information and its areas play various roles in pain perception by serving sensory information to the cerebral cortex and it interacts with other parts of the brain to create somatosensory input and output neural impulses (Kübler, 2009).

Structures in the dorsal area horn of the spinal cord *modulate* (alters pain signals) on ascending nociceptive transmission while neurons located in the lower brain stem regulate this modulation. During modulation, nociceptive impulses transmit through dorsal horn projections which releases substances such as serotonin, endorphins, and norepinephrine, which serve to decrease the pain response when it is perceived. Pain response is interrupted through the process of facilitation and inhibition. Facilitation is an unconscious act that warns the individual of tissue injury and encourages "fight or flight" reactions, while inhibition is the hypothesis that during threatening periods, pain is numbed so function is not compromised (Rodriguez, 2015).

To prevent damage to the body and its function, it's important to measure and monitor pain to prevent the progression and decrease the complications resulting from the pain process. The assessment of pain is essential to provide safe and effective pain management, interpret prevalence rates to direct further treatment, and reduce the risk of pain development chronically (Bendinger & Plunkett, 2016). Pain assessment should focus on measuring the type of pain, intensity, location, duration, and aggravating or alleviating factors of pain (Fink, 2000). It's important to use scientifically valid tools to assess these measurements, so these tools should be measured subjectively through patient-reported outcomes and objectively through quantitative sensory testing.

Pain sensitivity measurement scales are important to understand proper pain treatment protocols. As pain is a part of the somatosensory system, it's important to understand somatosensory function and its relation to pain to properly diagnose pain. *Hyperalgesia* is defined as "the enhanced sensitivity and responsivity to stimulation of the area around the damaged tissue. Therefore, in areas around an injury, the stimuli that causes pain are significantly more painful (Purves et al., 2012). The sensitization of nociceptors by the substances released when the tissue is damaged causes this phenomenon as these substances enhances the responsiveness of nociceptive endings (Purves et al., 2012).

Hypoalgesia is the decreased sensitivity to a stimulus that should be perceived as painful. This phenomenon indicates a decrease in function because of neurological disease or injury affecting thermonociceptive pathways, such as diabetic neuropathies (Backonja, 2013). This is also caused by exogenous chemicals such as opioids, psychological responses such as fear, and exercise ("Manipulation: Theory, Practice, and Education," 2009).

Allodynia is defined as "pain due to a stimulus that does not normally provoke pain," such as pain when lightly touching a feather (Yusi He & Kim, 2021). While allodynia is different from hyperalgesia, both often co-exist. With allodynia, the pain response to stimuli differs from individuals who have a normal pain sensation, while hyperalgesia is the same response to those with normal sensation, however the response is exaggerated. Usually, allodynia is caused by an underlying disease and presents as a symptom of a disease. It is mediated by inflammation, so NSAIDs and antiepileptic calcium channel blockers, such has gabapentin, have been shown to slow of prevent allodynia. (Yusi He & Kim, 2021).

The minimum intensity of a stimulus that can be perceived as painful is pain threshold (Kato et al., 2017). Individuals experience different levels of tolerance and threshold in relation to physical and psychological factors. Factors associated with low pain thresholds include physical variables, such as the pain severity/duration and decreased autonomic function. On the other hand, pain thresholds increase in association with psychological disorders, such as depression (Kato et al., 2017).

The first line therapy in the treatment of pain and reduction of pain sensitivity is multidisciplinary conservative care and nonopioid medications such as tricyclic antidepressants (TCA) and serotonin norepinephrine reuptake inhibitors (SNRI) (Bates et al., 2019). Multidisciplinary conversative care encompasses nonpharmacological interventions such as psychology, physiotherapy, exercise, and massage (Bates et al., 2019). These noninterventional therapies will also treat issues like depression, anxiety, pain catastrophizing, and sleep disturbance, which all contributes to increased pain sensitivity and perception.

PAIN PERCEPTION

Pain perception relates to the perception or psychological pain that is evoked by stimuli and can perceived as both a sensory and emotional experience (cite). The perception of pain is complex and multifactorial and includes the subjective experience of pain intensity and its interference with daily life (Afolalu et. Al, 2018). Pain perception is measured through pain reactivity, sensory threshold, and pain tolerance (Sandy, 2013). Pain reactivity refers to the change in behaviors following a painful experience. Sensory threshold is the weakest stimulus intensity that produces a response in an individual (Bi & Ennis, 1998). While pain tolerance is the maximum level of pain that an individual is prepared to endure (Martin, 2007).

Psychological factors can profoundly alter the strength of painful perceptions. The focus on the pain, stress, and negative perception are included with cognitive factors which can contribute to a more intense pain perception. Lastly, negative emotional factors such as depression, anger, or anxiety can predict chronicity and intensity of pain. Stress and anxiety both increase muscle contraction and sympathetic outflow which exacerbates any ongoing pain problem (Institute of Medicine (US) Committee on Pain, Disability, and Chronic Illness Behavior et al., 2014).

Positive psychological factors can have the opposite effect on pain perception. There is a benefit of high levels of positive personality traits such as optimism, hope, and self-efficacy, as these traits provide a protective influence on pain perception. Individuals with lower optimism levels have lower pain tolerance times and higher biomarkers of the stress response as compared to individuals with higher optimism levels (Pulvers & Hood, 2013). It is speculated that these individuals with higher optimism levels are inclined to respond to positive placebo expectations. Higher levels of hope have also been seen to lower pain symptoms and fatigue (Pulvers & Hood, 2013).

Pain catastrophizing is another cognitive factor that heightens pain perception. This is a negative amplification of pain-related thoughts through rumination (repetitive thoughts about pain), magnification (exaggerated concern about negative consequences of pain), and helplessness (believing nothing will change the pain) (Pulvers & Hood, 2013). Pain catastrophizing has been shown to be the strongest predictor of pain and has proven the relationship that catastrophizing precedes an increased pain response (Pulvers & Hood, 2013). An inverse relationship also exists between positive psychological thoughts and pain catastrophizing. This means that those who experience higher levels of positive traits are less likely to engage in pain catastrophizing and that positive emotions and resiliency are associated with lower pain catastrophizing. (Pulvers & Hood,

2013). Effective implications on reducing pain perception include focus on cognitive behavioral strategies for improving levels of hope, optimism, self-efficacy, and reducing pain catastrophizing.

PATIENT REPORTED OUTCOME: PAIN

Self-reporting pain is the gold-standard to quantify pain subjectively. A common pain-reporting scale is known as PQRST mnemonic. This stands for provocation (what caused it and relieves it), quality (what does it feel like), region/radiation (where is it located and does it radiate), severity (how severe is the pain), and timing (is it constant or intermittent) (Ferrell et al., 2015). This scale is used for patients to quantify and self-report their pain so that the pain intensity can be measured and assessed. Examples of self-reported pain measures are the numeric rating scale, the Short-Form McGill Pain Questionnaire v2, and the Brief Pain Inventory.

Pain scales are designed for the assessment of pain intensity, degree of pain relief. The most used pain scales when assessing acute pain are the numeric rating scale (NRS) and the visual analogue scale (VAS) (Bendinger & Plunkett, 2016). These unidimensional scales are reliable, valid, sensitive to change and easy to administer (Bendinger & Plunkett, 2016). The NRS uses an 11-point scale between 0 to 10 (0 meaning no pain while 10 meaning worst pain) for patients to rate their pain and this scale is often preferred due to the simplicity of administration. The VAS is the gold-standard technique in pain measurement in pain-related research. This scale consists of a 100mm unmarked line with wording stating “no pain” on the left the line and “worst pain imaginable” on the right and the patient places a mark on the spot on the line that corresponds with their pain (Bendinger & Plunkett, 2016).

A pain questionnaire that can be used to assess different dimension of acute and chronic pain is the Short-Form McGill Pain Questionnaire v2 (SF-MPQ-II) (Hawker, 2011). This

multidimensional questionnaire consists of 20 subgroups of words that describe sensory, evaluative, and miscellaneous components of pain. Each subgroup contains a list of words with a given ranking (0-10) and the word that is chosen by the patient is used for scoring. For example, when assessing thermal properties of perceived pain, describing the pain as "searing" is a higher score than choosing the word "hot" (Bendinger & Plunkett, 2016).

Another multidimensional tool is the Brief Pain Inventory (BPI) which has been validated for assessment of pain with a wide range of acute and chronic pain). The scale is a 17-item self-rating scale. It has the patient indicate the site(s) of pain by shading a body diagram and uses two 11-point numeric rating scales to assess pain intensity in the past 24 hours and to assess pain interference in usual activities, functions, and mood (Bendinger & Plunkett, 2016). Table 5 in the appendix summarizes these pain scales.

QUANTATIVE SENSORY TESTING

To better understand the underlying biological mechanism associated with pain, the German Research Network on Neuropathic Pain developed a quantitative sensory testing (QST) protocol to examine thermal and mechanical sensory function in relation to pain (Rolke, et al., 2006). QST refers to the use of a set of objective testing procedures (thermal and mechanical test stimuli) that allow the examiner to measure and quantify somatosensory function in large (Aβ-fibers) and small sensory nerve fibers (Aδ- and C-fibers) with an aim to detect sensory loss (i.e., hypoesthesia, hypoalgesia) or sensory gain (i.e., hyperesthesia, hyperalgesia, allodynia) (Mücke et al., 2016). Damage to small nerve fibers can manifest in thermal hypoalgesia or hyperalgesia (Medoc, 2020). QST can be suggestive to central pain sensitization through lowered pain thresholds found from affected body areas (Medoc, 2020). A total of 13 individual parameters are assessed to determine and quantify the

function of the somatosensory nervous system and these tests evaluate the function of the unmyelinated C-fibers, myelinated A fibers including their projection pathways to the brain (Mücke et al., 2016).

The Medoc Pathway (MP), a pain & sensory evaluation system used for QST, currently serves as the gold standard for assessing changes in thermal thresholds associated with pain (Medoc Advanced Medical Systems, 2009). The Medoc Pathway uses two types of thermodes, contact heat evoked potential stimulator (CHEPS) and advanced thermal sensory (ATS), to deliver thermal stimuli. The CHEPS thermode delivers a rapid heating rate of 70°C/sec and cooling rate of 40°C/sec within a temperature range of 30°C to 55°C (Medoc, 2015). While the ATS thermode has a heating and cooling rate of up to 8°C/sec within a temperature range of 0°C to 55°C (however can be expanded to -10°C.) (Medoc, 2015).

This machine is not portable (~160 pounds) and cannot be transported to sites in the community where people may be able to participate in studies. Given that quantifying somatosensory function when measuring the sensory component of pain is important to understanding biological mechanisms associated with pain, the emergent Advanced Thermosensory Stimulator (TSA2) may be a good option for pain assessment in the community.

The same company, Medoc, who also invented the Pathway, has recently developed a new QST device, the Advanced Thermosensory Stimulator. The TSA2 delivers excellent temperature control and precise thermal pain stimulation temperature control in a robust, portable device. The device delivers thermal stimulation rates up to 13°C/sec within a temperature range of 0°C to 55°C (Medoc, 2020). The TSA2 has a CHEPS thermode which deploys a fast-heating rate of 70°C/sec and cooling rate of 40°C/sec (Medoc, 2020). This device is important to consider for future QST testing

as it functions like the Medoc Pathway, except it is portable, lighter (~25 pounds), and easier to transport to different testing sites.

However, this portable machine has not been examined for reliability and validity in the lower extremity. This study will focus on examining the level of agreement between thermal sensitivity as a part of the QST protocol using the TSA2 and Medoc Pathway in the lower extremity. This work is relevant as it can reveal similarities and differences between the two devices and validate the TSA2 for sensory testing.

Chapter 3

METHODS

Design, setting, and participants

This is a repeated-measures two group study with two test sessions one day apart. Following university and institutional review board approval, participants were enrolled via advertisement at the university. Inclusion criteria included age 18 or older, ability to speak and read English. Exclusion criteria was history of chronic pain, injury, surgery, or peripheral neuropathies Potential participants were screened using the inclusion and exclusion criteria, and if eligible, scheduled for two in-person visits at the University. A total of 29 participants were screened over the phone. Five of these participants were ineligible and 20 participants were enrolled. Participants that reported pain or consumed any pain medications within 24 hours of testing were rescheduled.

Participants were randomized into two groups at the time of enrollment (5 men and 5 women in each group). Group 1 consisted of participants who had test session 1 with the Medoc Pathway and test session 2 with the TSA2. Group 2 consisted of the participants who had test session 1 with TSA2 and test session 2 with the Medoc Pathway. The study time for participants lasted approximately 2 hours on the first visit and 1.5 hours on the second visit, totaling approximately 3.5 hours. Participants received a $25 gift card for each visit.

Study Measures

Primary outcome measures were participants response to thermal stimuli on the TSA2 and Medoc Pathway. A detailed description of these outcome measures is presented in Table 1. Secondary outcomes included mechanical measures used in QST. Questionnaires asking about current health, thoughts and fears associated with pain, depression and anxiety questionnaire were

also administered as they have been associated with QST results in healthy populations. A detailed description of the patient reported outcome measures are provided in Table 2.

Quantitative sensory testing

QST consisted of assessing participants' (1) thermal detection thresholds for the perception of cold and warm stimuli, (2) thermal pain thresholds for cold and heat stimuli, (3) mechanical detection thresholds for vibration and touch, (4) ability to perceive and differentiate between pinprick and blunt pressure, and (5) pressure pain threshold. Testing was conducted on two consecutive days on both legs on the inner center of the calf at midpoint between the knee and ankle.

Thermal detection and pain thresholds We conducted thermal threshold testing using the Medoc Pathway Pain and Sensory Evaluation System and Advanced Thermosensory Stimulator. For this test, a 30mm x 30mm surface area thermode was placed on the test site. The baseline temperature of the thermode was set to 32°C with safety cutoff temperatures at 0°C and 50°C. The temperature was increased or decreased from the baseline with a 1°C/sec ramp. The first thermal test measured cold and warm detection thresholds in which the participant was instructed to press the stop button at the first sensation of cold or heat. Finally, the pain threshold for cold and heat pain is determined. The participant will press the stop button the moment the cold or hot stimuli becomes painful. The test was conducted three times and the mean was used as the detection thresholds and was calculated by averaging the three consecutive measurements.

Mechanical detection threshold. We tested mechanical touch thresholds using a standard set of 20 Semmes-Weinstein monofilaments, calibrated to bend at a specific amount of force (0.008gm – 300gm). The fibers were applied perpendicular to the testing site just until they were bent. Each fiber was applied in ascending order by force calibration and held in place for one second until they were

removed. Each force calibration is repeated 3 times with one second break between stimuli. We recorded the mechanical detection threshold at the point in which the participant reported the ability to detect the fiber at least two times out of the three applications.

Pinprick Detection We completed pinprick detection using a Neuropen that has a sharp tip and a monofilament. After a light application of the stimulus, the participant was asked to identify whether the sensation perceived was sharp or dull. A total of six random applications, three sharp and three dull, was administered and the percentage of correct responses out of the total was the pinprick detection threshold.

Vibration Detection We used a graduated tuning fork (Rydel-Seiffer, US Neurologicals) fitted with calibrated weights at the ends which vibrate at 64 Hz to detect vibration in the lower extremities. With the markings facing away from the participants, the base of the tuning fork was placed on the skin overlying the tibia midway between the knee and the ankle. The participants were asked to report when they no longer felt the vibration and the number on the calibrated weight nearest to intersection of triangles was recorded as the vibration detection threshold. This test was performed three times and the final variable was the mean score of the three trials.

Questionnaires

Pain Catastrophizing Scale (PCS) To examine the psychological thoughts when experiencing pain, we administered the Pain Catastrophizing Scale (PCS). The PCS measures thoughts and feelings experienced when the participant is in pain (Meyer et al., 2008). The scale consists of 13 items in which the respondent catastrophizes their emotions when they are in pain on a scale of 0 (not at all) to 4 (all the time). The total score is a mean of all the PCS item ratings, with lower levels

indicating less pain catastrophizing. We also calculated the mean scores for rumination, magnification, and helplessness.

Fear of Pain To examine fear towards pain, we administered the Fear of Pain Questionnaire III (FPQ-III). The FPQ-III measures the participants actual or anticipated fear towards a painful event (Di Tella et al., 2019). The 30 items measure minor, severe, and medical pain categories. Participants will rank fear responses on a scale of 0 (not at all) to 5 (extreme). The total score is a mean of all the FPQ-III item ratings, with lower scores indicating lower levels of fear towards pain. We also calculated the mean scores for minor, severe, and medical pain. To determine the fear of pain most frequently reported by a participant, we calculated the frequency of each descriptor.

Kohn Reactivity Scale So that we could evaluate experiences in everyday situations, we administered the Kohn Reactivity Scale (KRS) (Veldhuijzen et al., 2012). The 24-item questionnaire asks participants to select one of the five possible responses: 1 = *strongly disagree*, 2= *somewhat disagree*, 3= *neither agree nor disagree*, 4= *somewhat agree*, 5= *strongly agree*. Item scores are calculated to obtain total scores.

Anxiety We administered the PROMIS anxiety questionnaire in order to evaluate participants current state of anxiety. This was done to understand any subjective feelings, such as nervousness, that may influence the participants autonomic nervous system. It includes 29 items measuring trait anxiety feelings within the past 7 days in which the respondent chooses amongst five responses: 1= *never*, 2= *rarely*, 3=*sometimes*, 4=*often*, 5= *always* (Quach et al., 2016). The anxiety score calculated is the T score of the 29 items, with higher scores indicating higher levels of anxiety.

Depressive symptoms We administered the PROMIS Depression questionnaire to determine depressive symptoms and severity at the time of testing. It includes 28 items measuring traits and

symptoms of depression experienced within the past 7 days (Quach et al., 2016). Respondents are asked to choose amongst five responses: 1= *never*, 2= *rarely*, 3=*sometimes*, 4=*often*, 5= *always*. The depressive score calculated is the T score of the 28 items, with higher score indicating higher levels of depression. A T-score of 50 indicates a raw score equal to the mean.

Sleep Disturbance We administered the PROMIS sleep disturbance questionnaire to evaluate quality of sleep and its disturbance within the past 7 days. The 27-item questionnaire asked respondents to rate the quality of their sleep between five responses: 1= *not at all*, 2= *a little bit*, 3=*somewhat*, 4=*quite a bit*, 5= *very much* (Quach et al., 2016). The questionnaire also asked respondents to rate their sleep patterns between five responses: 1=*never*, 2= *rarely*, 3=*sometimes*, 4= *often*, 5= *always*. The sleep disturbance score calculation is the T score of the 27 items, with higher scores indicating higher sleep disturbance and poor sleep quality.

Data Analysis

We conducted analyses using SPSS 2.0 (IBM Statistics for Windows, Version 22.0). Descriptive statistics included the mean and standard deviation (SD) for continuous variables. A paired t-test between devices was conducted to compare the means of the dependent variables. Additionally, Pearson's correlation coefficients and significance was found between left and right legs on both devices and the tests between devices. Significance level of alpha = 0.05, unless data was indicated with **, in which case significance level of alpha = 0.01. Intraclass correlation analyses were run to determine how strongly the data between devices resembled each other. The higher the correlation value, the stronger the reliability between the data values are. Bland-Altman Plots were created to display the relationship and difference between the Pathway and TSA2. These plots can identify systematic differences between measurements and/or possible outliers.

CHAPTER 3

RESULTS

Participant Characteristics

The demographic characteristics of the participants enrolled in this are presented in Table 3. The mean age group was 31.58 years old (SD= 14.3, range = 18-61). As each experiment group contained five men and five women, gender was equally divided with half the participants being males and half being females. Most participants were white (75%), while the remaining participants were Asian. Most participants report being students and never married (60%), while 35% of participants report working and being in a partnership. Regarding highest education status, 30% of participants equally reported receiving doctorate degrees, master's degrees, and some college or no degree. The other 10% of participants reported achieving associate degrees with 5% being an educational degree and the other 5% being occupational/vocational/technical degree.

Because a priority characteristic including perception and fears of pain or depression or anxiety could impact peoples' perception of pain, it was important to ensure that our group 1 and group 2 were equal. To test this, we examined the differences on our series of questionnaire data (patient-reported data) to see if there were differences. We used a t-test to examine differences between the groups and those results are reported in Table 4.

Quantitative Sensory Testing

Nineteen of the twenty participants yielded valid data. One participant did not record the three thresholds. For thermal detection, one participant tested on the TSA2 device did not record responses for these thresholds and therefore was excluded from analysis with this device.

The descriptive statistics (i.e., means and standard deviations) for the QST results for thermal detection thresholds for both the Medoc Pathway and TSA2 are presented in Table 5. The data in this chart shows alike means between both devices, revealing data values that found on the devices were similar. Differences between the means of the Medoc Pathway and TSA2 devices were tested in a paired sample t-test and the significance value (i.e., p value) is provided for all the comparisons between the devices. None of the tests are significant at the 0.05 (or .01 level when indicated). This data is outlined in Table 5.

A central aim of this research is to see if the TSA2 device affords accurate quantitative sensory testing. This will be demonstrated by examining the correlations of the different tests between the Medoc Pathway (gold standard test) and TSA2 device (portable device). These correlations are shown in Table 7. The tests with the highest correlations are the thermal pain tests. Left cold pain has highest correlation of 0.85 ($p = <.001$) while the right leg pain has a high correlation of 0.70 ($p = <.001$). Left heat pain has the second highest correlation of 0.75 ($p = <.001$) and right leg heat pain is 0.69 ($p = <0.001$). Cold detection correlation on the right leg is 0.67 ($p = 0.002$) and warm detection on the right leg is 0.72 ($p = <0.001$).

A goal of this research is to investigate the reliability of the TSA2 and see if it compares with the reliability of the Medoc Pathway. One way to determine the stability of the measurement is to determine if the sensory perception of the right and left legs is similar. Pearson correlation coefficient analyses were used to examine the relationship between left and right legs on both the Pathway and TSA2 devices. Table 8 shows the correlations between right and left legs on both devices. The strongest correlations were with cold and heat pain. The correlation for cold pain on the Pathway was

0.81 (p= <.001) and the correlation on TSA2 was 0.79 (p= <.001). Heat pain correlation on the Pathway was .50 (p= 0.025) and the correlation on the TSA2 was .78 (p= <.001).

Reliability is an important determinant of this study to make comparisons between the two devices. Intraclass correlations show the proportion of the variability in the TSA2 that is due to the 'normal' variability between the individuals while coefficient alphas measure the internal consistency. Intraclass Correlations and coefficient alphas (α) between the Pathway and TSA2 are outlined in Table 9. Cold detection in the left leg was .61 (α = .61) while detection in the right leg was .56 (α = .55). Warm detection correlations are the lowest correlations with .34 (α = .33) in the left leg and .33 (α = .32) on the right leg. Cold pain in the left leg was .88 (α = .89) and cold pain in the right leg was .88 (α = .88). Left leg heat pain was .64 (α = .66) and heat pain on the right leg was .88 (α = .87).

Bland-Altman plots were created for every test conducted on the Pathway and TSA2. These plots include all the average data values on the left and right legs for every participant on both the Pathway and the TSA2. The difference from both devices was then calculated to find the average difference and upper and lower limits for cold detection, warm detection, cold pain, and warm pain. Cold detection has the most agreeable data with minimal outliers, while warm detection reveals the most variability with outliers.

CHAPTER 4

DISCUSSION

The data reveals no significant differences between the Medoc Pathway and TSA2. The paired sample t-test shows there were no significantly different values and this lack of significant differences between the two devices suggests that we cannot conclude that there are differences between the two devices. In the absence of discernable differences, we have no evidence to reject the notion that the TSA2 and the Medoc Pathway are performing differently.

Pearson correlations between the Medoc Pathway and TSA2 show similarity between the two devices. The high and moderate correlations between the Medoc Pathway and the TSA2 provide evidence that the devices are yielding comparable results, especially for the right leg. The results of detection of hot or cold stimuli on the left leg yielded some differences between the two devices as the correlations were only in the moderate range (e.g., r=0.42) but collectively, these data suggest that the TSA2 will provide similar readings. This is important because the TSA2 is portable and can facilitate testing in the community.

Reliability of the TSA2 was determined by the Intraclass correlations between the two devices and generally shows strong coefficients, indicating reliability. Cronbach's alpha of the TSA2 provides an index of the internal consistency of the measurement. When Cronbach's alpha coefficients are high, we can conclude that the scores obtained are similar and that the measurements are reliable and free from error. For the most part, the Coefficient alpha coefficients were high with the exception of alpha for warm detection on both the right and left leg. Further examination of scatterplots of the data (e.g., the Bland-Altman plot) suggest that there are a few outliers for warm

detection and may be contributing to the low alpha level coefficients for warm detection on both the right and left legs.

The QST results for thermal detection thresholds were similar between left and right legs on both the Medoc Pathway and the TSA2 for hot and cold detection, pain threshold, and thermal sensory limen. Overall, there was a strong positive correlation between left and right legs on both devices. Between all found correlations, it is shown that cold pain has the highest correlation between both legs and between both devices. Additionally, all the thermal pain values are proven to be statistically significant which means there is no difference between the means. This shows accuracy of the machines, and that the data is consistent across both devices.

As you can see on the Bland-Altman plot, any values above the upper and lower limits are considered to be outliers. These plots describe the agreement between both devices and as most of the data values fell in between the upper and lower limits, it can be assumed that the data in the Pathway and TSA2 agree with each other. This study suggests that the TSA2 device is valid and reliable in comparison to the Pathway device and the TSA2 can be used in future quantitative sensory testing.

Based off the evidence, we can interpret these results to mean that the TSA2 performs similarly to the Medoc Pathway. This suggests that the portal TSA2 device can be used in future quantitative sensory testing and expand the opportunities for testing sites. This is beneficial to future research as this device can be used in new settings and incorporate a wider range of participants and study demographics will include a more diverse group of populations. In addition to expanding research sites, this device can be used in healthcare settings and brought to communities in which chronic pain is prevalent and allow healthcare providers and researchers to gain a deeper understanding of sensory function in relation to pain. The biggest study limitation is specific to the

sample size. With a small sample size of 20 participants, the data is limited as smaller samples can affect the accuracy of results and become less representative of the entire population. For all future studies, larger sample sizes could be recorded.

CHAPTER 5

TABLE OF FIGURES

TABLE 1. QUANTATIVE SENSORY TESTING

Measure	Equipment	How it's administered
Thermal detection - Detection and pain thresholds	Tested with Medoc Pathway Pain and Sensory Evaluation System and Advanced Thermosensory Stimulator.	9cm^2 surface area thermode with baseline temperature of 32°C and temperature increasing or decreasing 1°C/sec ramp
Mechanical detection	20 Semmes-Weinstein monofilaments	Calibrated to bend at a specific amount of force (0.008gm – 300gm) and is applied to skin to determine hypoalgesia or hyperalgesia.
Pinprick Detection	Neuropen with a sharp tip and a monofilament	Monofilament randomly applies sharp and dull stimuli to assess sensory function.
Vibration Detection	Graduated tuning fork (Rydel-Seiffer, US Neurologicals) with calibrated weights	Vibrates at 64 Hz and is placed on the skin.
Pressure Pain Threshold	Medoc Pressure Algometer application surface (flat rubber tip 1cm^2)	Increasing force at 30kPa/sec until onset of pain is reached.

TABLE 2. PAIN METRICS

Metric	Purpose	Scoring	Reliability/Validity
Visual Analog Scale [a] (VAS)	Acute pain unidimensional measure of pain intensity used to help a person rate the intensity and sensation of pain.	Unmarked line (100mm) stating "no pain" on the left side and "worst pain imaginable" on right side	$\alpha = 0.94$
Numeric Rating Scale (NRS)[a]	Acute pain unidimensional measure of pain intensity used to help a person rate the intensity and sensation of pain.	11-point scale ranking pain from 0 (no pain) through 10 (worst pain)	$\alpha = 0.96$
McGill Pain Questionnaire[a] (MPQ-II)	Multidimensional pain questionnaire that measures sensory, affective, and evaluative aspects of pain and intensity	20 subgroups of words describing sensory, evaluative, miscellaneous components of pain	$\alpha = 0.96$
Brief Pain Inventory[b] (BPI)	Multidimensional pain questionnaire used to rate pain severity and degree of pain interference	Uses 17-item body diagram to locate site of pain and uses NRS to assess pain intensity	0.84-0.90 ($\alpha = 0.91$)
Pain Catastrophizing Scale[c]	Measures psychological thoughts and feelings experienced during pain	Consists of 13 items catastrophizes emotions when in pain on a Likert scale of 0 (not at all) to 4 (all the time).	0.80 ($\alpha = 0.92$)

Fear of Pain[d]	Measures actual or anticipated fear towards a painful event	Consists of 30 items measuring minor, severe, and medical pain categories on a Likert scale of 0 (not at all) to 5 (extreme)	0.81 ($\alpha = 0.91$)
Kohn Reactivity Scale[e]	Evaluate experiences in everyday situations	A 24-item Likert scale of 1 (strongly disagree) to 5 (strongly agree)	0.95 ($\alpha = \geq 0.77$)
PROMIS Anxiety Scale[f]	Evaluate current state of anxiety within the past 7 days	29-items measuring trait anxiety feelings on a Likert scale of 1 (never) to 5 (always)	$\alpha = 0.90$
PROMIS Depression Scale[f]	Determine depressive symptoms and severity within the past 7 days	28 items measuring traits and symptoms of depression on a Likert scale of 1 (never) to 5 (always)	$\alpha = 0.91$
PROMIS Sleep Disturbance[f]	Evaluate quality of sleep and its disturbance within the past 7 days	27-items asking respondents to rate the quality of their sleep between five responses	$\alpha = 0.86$

Note: [a]Information reported by Hawker et al., 2011, [b] Information reported by Jelsness-Jorgensen et al., 2016, [c] Information reported by Meyer et. al., 2008, [d] Information reported by Di Tella et al., 2019, [e] Information reported by from Veldhuijzen et al., 2012, [f] Information reported by Quach et al., 20

TABLE 3. PARTICIPANT CHARACTERISTICS

Characteristic	Total (N=20)	Group 1 (n=10)	Group 2 (n=10)	Test statistic (p-value)
Age, M (SD) Range	31.58 (14.3) (18-61)	34.7 (15.8)	49.5 (13.01)	.89 (.387)
Gender, n (%) Male Female	 10 (50) 10 (50)	 5 (50) 5 (50)	 5 (50) 5 (50)	.00 (1.000) [c]
Race, n (%) White Asian	 15 (75) 5 (25)	 7 (70) 3 (30)	 8 (80) 2 (20)	.00 (1.000) [c]
Ethnicity, n (%) Not Hispanic Hispanic Not reported	 18 (90) 1 (5) 1 (5)	 9 (90) 1 (10)	 9 (90) 1 (10) 	2.00 (.368)
Education, n (%) High school Associates Doctoral	 2 (10) 12 (60) 6 (30)	 1 (10) 4 (40) 5 (50)	 1 (10) 8 (80) 1 (10)	4.00 (.135)
Employment, n (%) Keeping house Student Working	 1 (5) 12 (60) 7 (35)	 4 (40) 6 (60)	 1 (10) 8 (80) 1 (10)	5.91 (.052)
Marital/partner status, n (%) Divorced Domestic partnership Married Never married	 1 (5) 1 (5) 6 (30) 12 (60)	 **1 (10)** 5 (50) 4 (40)	 1 (10) 1 (10) 8 (80)	6.00 (.112)

Note. Group 1= Pathway test first, Group 2=TSA2 test first.

TABLE 4. SAMPLE CHARACTERISTICS AND PERSONALITY FACTORS

Characteristic	Total (N=20)	Group 1 (n=10)	Group 2 (n=10)	Test statistic (p-value)
Fear of pain, M (SD) (Range)	69.5 (28.8) (18-61)	74.0 (18.4)	64.1 (18.8)	1.19 (.249)
Kohn Reactivity Scale, M (SD)	68.9 (14.3) (42-95)	74.9 (11.5)	62.8 (14.7)	2.05 (.055)
Pain Catastrophizing Scale, M (SD)	5.0 (6.4) (0-17)	6.4 (6.6)	3.5 (6.2)	1.02 (.324)
Anxiety, M (SD) (PROMIS)	49.2 (8.5) (32.9-66.9)	51.1 (9.8)	47.2 (7.0)	1.03 (.317)

Depression, M (SD)	44.5 (6.1) (34.2-55.4)	45.7 (7.7)	43.3 (4.0)	.90 (.383)
Sleep, M (SD)	48.3 (10.3) (26.3-64.1)	49.8 (11.4)	46.7 (9.3)	.67 (.511)

Note. Group 1= Pathway test first, Group 2=TSA2 test first.

TABLE 5. DESCRIPTIVE STATISTICS OF THE MEDOC PATHWAY & TSA2

Variable	**Pathway (n=20)**	**TSA2 (n=19)**
Cold detection left leg, M (SD)	28.2 (1.70)	28.3 (1.7)
Cold detection right leg, M (SD)	28.4 (1.55)	28.4 (1.6)
Warm detection left leg, M (SD)	36.9 (2.48)	36.5 (1.91)
Warm detection right leg, M (SD)	36.5 (2.20)	36.2 (2.14)
Cold pain left leg, M (SD)	10.7 (10.37)	10.4 (10.1)
Cold pain right leg, M (SD)	13.8 (10.38)	11.9 (11.5)
Heat pain left leg, M (SD)	44.3 (2.16)	44.0 (3.02)
Heat pain right leg, M (SD)	43.5 (22.55)	43.8 (3.6)

TABLE 6. PAIRED SAMPLES T-TEST BETWEEN MEDOC PATHWAY AND TSA2

Variable	**t**	**Two-Sided p-value**
Cold detection left leg	-0.78	0.44
Cold detection right leg	-0.64	0.53
Warm detection left leg	0.56	0.58
Warm detection right leg	0.48	0.64
Cold pain left leg	-2.1	0.48
Cold pain right leg	-0.87	0.40
Heat pain left leg	1.56	0.14

Heat pain right leg	.29	.78

TABLE 7. PEARSONS CORRELATIONS BETWEEN PATHWAY AND TSA2

TSA and Pathway Correlations	**Pearson Correlation (p-value)**
Cold detection	
Left leg	0.42 (0.077)
Right leg	0.67** (0.002)
Warm detection	
Left leg	0.42 (0.075)
Right leg	0.72** (<0.001)
Cold pain	
Left leg	0.85** (<0.001)
Right leg	0.70** (<0.001)
Heat pain	
Left leg	0.75** (<0.001)
Right leg	0.69** (<0.001)

**. Correlation is significant at the 0.01 level (2-tailed).

TABLE 8. PEARSONS CORRELATIONS BETWEEN LEGS ON MEDOC PATHWAY & TSA2

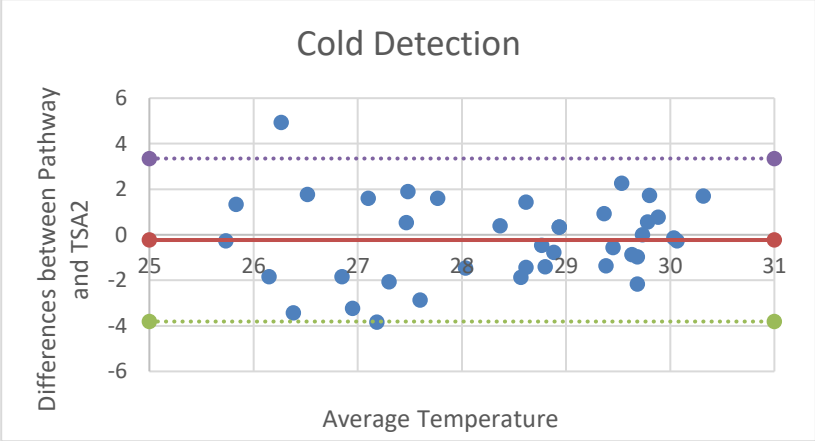
Left and Right Leg	**Pathway, Correlation (p-value)**	**TSA2, Correlation (p-value)**
Cold detection	0.43 (0.056)	0.32 (0.177)
Warm detection	0.20 (0.396)	0.20 (0.424)
Cold pain	0.81** (<0.001)	0.79** (<0.001)
Heat pain	0.50* (0.025)	0.78** (<0.001)

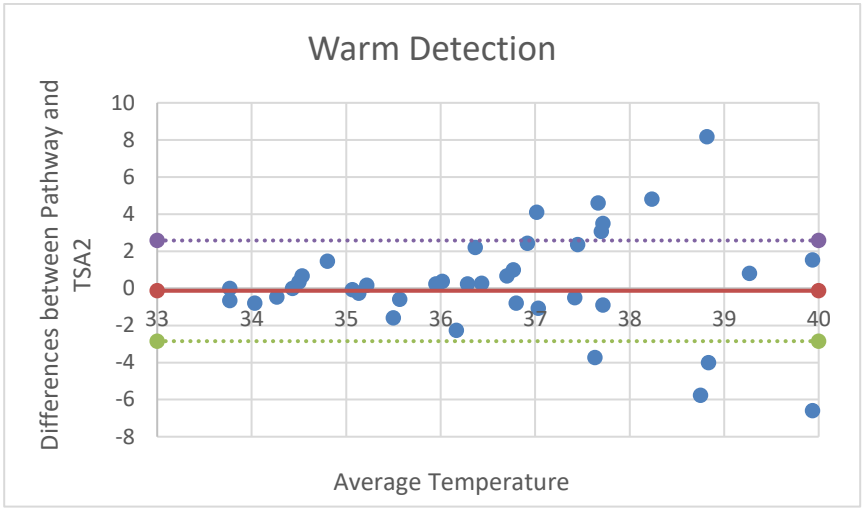
*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

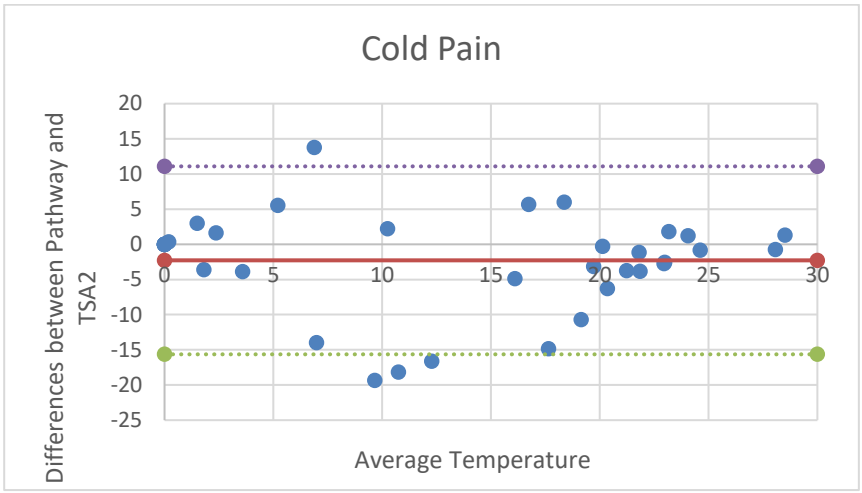
TABLE 9. RELIABILITY BETWEEN PATHWAY AND TSA2

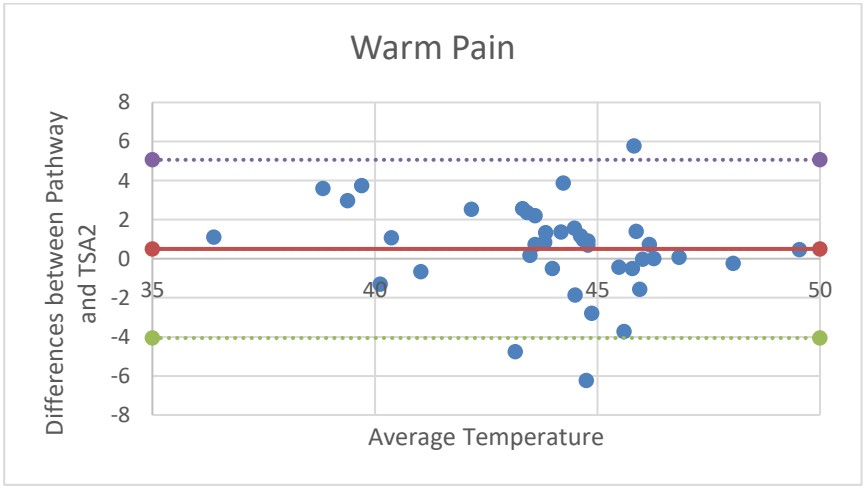
Variables	Intraclass Correlation	Cronbach's Alpha
Cold detection left leg	0.61	0.61
Cold detection right leg	0.56	0.55
Warm detection left leg	0.34	0.33
Warm detection right leg	0.33	0.32
Cold pain left leg	0.88	0.89
Cold pain right leg	0.88	0.88
Heat pain left leg	0.64	0.66
Heat pain right leg	0.88	0.87

TABLE 10. BLAND ALTMAN PLOTS




Warm Detection
Differences between Pathway and TSA2
10
8
6
4
2
0
-2
-4
-6
-8
33
34
35
36
37
38
39
40
Average Temperature


Cold Pain
Differences between Pathway and TSA2
20
15
10
5
0
-5
-10
-15
-20
-25
0
5
10
15
20
25
30
Average Temperature


Warm Pain
Differences between Pathway and TSA2
8
6
4
2
0
-2
-4
-6
-8
35
40
45
50
Average Temperature

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