

QUANTITATIVE SENSORY TESTING

QUANTITATIVE SENSORY TESTING IN MUSCULOSKELETAL PAIN DISORDERS

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for the Degree Doctor of Philosophy, Rehabilitation Science

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ABSTRACT

Altered nociceptive processing can give rise to an array of sensory findings that can be assessed non-invasively using Quantitative Sensory Testing (QST). Due to the diverse etiopathogenetic basis of musculoskeletal pain disorders, a broad range of reliable and valid QST tests may be needed to analyze the various disease entities. QST evaluated in thesis included different modalities (electrical, vibration, touch, pressure), protocols and test devices. This thesis includes five studies and has evaluated measurement issues of QST (such as reliability and validity) in clinical context and purposes were targeting discrimination, evaluation and prediction in deferent musculoskeletal pain conditions.

Study 1 demonstrated that Current Perception Threshold (CPT) is reliable (consistent across occasions) and valid (associated with neck disability) for assessment of sensory detection threshold in patients with Mechanical Neck Disorder (MND). Study 2 demonstrated that CPT testing has moderate discriminatory accuracy, specificity, and sensitivity for classification of MND categories into neck pain with or without neurological signs. CPT might be useful for screening to classify patients with MND into clinically relevant subgroups. It may play a role in establishing different prognostic or diagnostic subgroups and specifically in assessing prognosis or mechanistic studies that target neurological focused therapy interventions.

Study 3 found that more than 90% of the tests with healthy young participants were reliable and valid in relation to their ability to detect a normal Weinstein Enhanced Sensory Test (WEST) or Pressure Specified Sensory Device (PSSD) within a normal force range. This study supports the reliability and specificity of these 2 QSTs (WEST and PSSD).

Study 4 demonstrated that psychophysical dimensions (QSTs) and patient factors (gender, age and comorbidity) affect self-reported and performance-based outcome measures in shoulder disorder. Study 5 suggests that pressure pain sensitivity may play a role in the self-reported outcome measures (e.g. pain and disability) of neck pain. Study 4 and 5 also indicated that gender and comorbidity were covariants in the relationship between pain detection threshold based QST and disability.

Future research should focus on longitudinal prospective studies with a large cohort of patients are required to justify the prognostic and evaluative properties of different sensory modalities, and to compare different sensory modalities, assessment protocols, indicators, and decision rules.

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PREFACE

Below is the description of student's contribution to each of the manuscripts.

For the 6 manuscripts (1 review and 5 research papers): Zakir Uddin conceptualized the research questions, study designs, data collection (where applicable), data analyses and writing the drafts of manuscripts.

Dr. Joy MacDermid provided required expertise, assisted with refining objectives and designs for each of the studies, assisted with establishing data collection and editing the manuscripts.

Dr. Victoria Galea and Dr. Michael R Pierrynowski assisted with reviewing the study objectives, providing their content expertise, and editing the manuscripts. Ms. Anita R Gross assisted with data collecting and editing the manuscripts.

Dr. Jaydeep Moro, Dr. Linda Woodhouse, Dr. John Triano and Hyungjoo Ham assisted with data collection.

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CHAPTER 1: **Background**

Up to the “Conclusion” section of this background chapter was submitted as a review paper in a peer-reviewed journal (*Pain Medicine*) and it is currently *under revision*.

QUANTITATIVE SENSORY TESTING IN CHRONIC MUSCULOSKELETAL PAIN

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Abstract

Background: In recent years, several published articles have demonstrated that quantitative sensory testing (QST) is useful in the analysis of musculoskeletal pain disorders. Based on the evidence from these studies, it is assumed that QST might be a useful tool in the analysis of pathogenesis, classification, differential diagnosis, and prognosis of musculoskeletal pain.

Objectives: The objective of this paper is to highlight measurement properties QST and its clinical benefits in the light of mechanism based concepts of musculoskeletal pain.

Methods: This is a narrative review of the impact of QST on musculoskeletal pain disorders. We used Ovid MEDLINE (1946 to present) including EMBASE, AMED, PsycINFO databases to search for all published literature focused on QST and musculoskeletal pain. We included hand searched bibliographies and key papers from leaders in pain research as highlighted in recent pain conferences.

Results: The impact of QST on musculoskeletal pain disorders is discussed. QST has been shown to be related to pain or neural sensitivity in musculoskeletal pain. QST measurement properties have been evaluated for multiple sensory evaluation modalities and protocols. The evidence is incomplete, but suggests potential clinical benefits. Threshold detection testing is commonly used to quantify sensory loss or gain, and it is considered as a stable endpoint for clinical application. However, intensity/magnitude rating has some flexibility of scoring on a wide range of rating scales and may be more useful for pain rating in a clinical context.

Threshold detection testing and intensity/magnitude rating of pain can be combined to determine pain threshold.

Conclusions: Musculoskeletal pain management may benefit from treatment algorithms that consider mechanism, pain quality or neurophysiological correlates. Altered nociceptive processing can give rise to an array of sensory findings that can be assessed non-invasively using QST. Due to the diverse etiopathogenetic basis of musculoskeletal pain disorders, a broad range of reliable and valid QST tests may be needed to analyze the various disease entities.

Keywords: central sensitization, hyperesthesia, hypoesthesia, chronic pain, maladaptive pain, nociception, sensory measurement

Introduction

Almost all adults have an episode of musculoskeletal pain from injury or overuse during their lifetime, and recurrent or chronic problems are common.¹⁻³ Recurrent or chronic problems affect 33% of adults and account for 29% of lost workdays due to musculoskeletal pain.^{1,4} Chronic musculoskeletal pain is a global health problem with significant economic impact,⁵ second only to cardiovascular disease.⁴

The need for quantification of clinical phenomena is a central issue of any scientific or clinical process since it is difficult to make valid conclusions about a disease mechanism, epidemiology, natural history or therapy response without quantifying the relevant parameters. Pain is now considered as the 5th vital sign,⁶ so accurate measurement of pain sensitivity can be considered an essential part of the clinical assessment. Quantitative sensory testing (QST) is a feasible clinical method to measure responses to sensory stimuli and may be used as an indicator of neural function or pain sensitivity.^{19,20}

The International Association for the Study of Pain (IASP) has defined “chronic pain” as a pain syndrome lasting more than 3 months,⁷ although it is a complex phenomenon and is considered a disease of the nervous system.^{8,9} Systematic reviews indicate strong evidence for central hypersensitivity (abnormal pain response) as a prognostic factor for poor outcomes in chronic musculoskeletal pain.^{10,11} The evolution of pain theory (Figure 1) and evidence of a central component of post-injury pain hypersensitivity,¹² implicate central sensitivity in musculoskeletal pain mechanisms. Involvement of the central nervous system in musculoskeletal pain mechanisms (specifically in chronic or maladaptive pain) is emerging as a new target area for rehabilitation. Central mechanisms have been implicated in the transition from acute to

chronic pain (Figure 2 is a depiction of the stages of neurophysiologic mechanisms) suggesting that early detection of this involvement might allow clinicians to make more accurate prognosis for their patients. In addition to identifying risk, it is possible that early identification would assist in allocating patients to the appropriate management strategies to alter this risk at an earlier stage, when they are more likely to be effective. The aim of this paper is to 1) provide the rationale for research in QST measures with musculoskeletal pain populations, 2) discuss the measurement properties of QST considering psychophysical principles that affect testing, and 3) provide the rationale for using QST in clinical and research situations.

Rationale for research in QST measures

QST can be defined as “the determination of thresholds or stimulus response curves for sensory processing under normal and pathological conditions”.²⁰ It is a psychophysical testing approach where the stimulus is quantified and used to measure perception.^{19,23} The test protocol and interpretation can focus on the minimum threshold perceived, localization, threshold perceived as painful, tolerance, or differentiation of different sensory inputs.^{18-20,23} For example, pain hypersensitivity can be detected by threshold tests that assess the least amount of sensory input required that is experienced as pain. By selecting different sensory inputs using QST technique, it is possible to evaluate the sensory processing of both large and small afferent nerve fibers^{20,24}, or different afferent pathways. QST is semi-subjective as it assesses the subjective responses (within a psychophysical parameter by measuring perception magnitude) to a controlled stimulus (quantitative stimulus intensity) and hence is under voluntary control unlike nerve conduction measures.

QST demonstrates potential benefits when compared to traditional neurological diagnostic tools. For example, around 80% of the peripheral nervous system consists of small nerve fibers,²⁵ but traditional diagnostic methods for the peripheral nervous system (e.g. electromyography, nerve conduction velocity, and evoked potential) primarily focus on the large fibers.^{24,25} Nociception (pain sensation) transmits through small calibre A-delta and C fibers. QST can target these fibers by using frequencies that target small fibers or sensory stimuli (e.g. pain and temperature) that are preferential to these fibers. The potential disadvantages are that the specificity of these responses has not been adequately demonstrated and that testing is not completely objective since the patient provides a voluntary response.

There are many challenges in quantifying pain since it is inherently a subjective experience. A direct record of nociception from the muscle is not clinically measurable.²⁶ It can be difficult to separate the peripheral and central components of pain and to differentiate sensory amplification and inhibition of pain. QST can provide information about processing of sensory inputs and can detect both amplification (hyperesthesia) and inhibition (hypoesthesia) of nerve function (see Figure 3). Hyperesthesia and hypoesthesia (hypo and hyper sensory function) are fundamental features of neuropathic or maladaptive pain.²⁰

Table 1 shows the comparisons of different diagnostic methods in small-fiber neuropathy. Cardio-vagal testing focuses on autonomic function rather distal small fiber function.²⁷ The epidermal nerve fiber density test provides only histological information,²⁵ and is not correlated to features of neuropathic pain.²⁸ QST of cold threshold (ICC=0.80) and vibration threshold (ICC=0.75) has been demonstrated as more reproducible than the quantitative sudomotor axon reflex test (ICC=0.52) in neuropathic conditions.²⁹ Table 2 contrasts an overview of bedside

(clinical) examination and QST for evaluating small fiber function linked to spinal pathways. Bedside examinations are based on examiner interpretations of a qualitative nature and QST is based on patients' interpretation employing a more quantitative approach: these are methodologically quite different and incomparable each other. Current evidence suggests that QST may be a superior tool for small fiber assessment, although the evidence is weak and further research is needed to define the assessment dynamics of different methods of QST.

QST measurement principles

Weber–Fechner's psychophysical law explains the logarithmic relationship between stimulus (physical magnitudes of stimuli) and perception (subjective sensation/perceived intensity of the stimuli).³⁰ Since the 19th century, classical psychophysicists formulated the basic concepts of threshold, tolerance and stimulus-response relationships without applying these concepts specifically to assessment of pain. Measures in QST such as threshold, tolerance, and supra-threshold stimulus-response relationships were developed and investigated by many scientists including Frey, Head, Homer and Stevens.^{31,32,33} They developed concepts of the mechanism underlying sensation, the nature of sensory damage following neural lesions, simple tests to analyse the loss of sensation and were pioneers in the journey to quantify sensation.

Modern QST is based on the stimulus properties (e.g. stimulus modality, intensity of the stimulus, spatial and temporal summation of the stimulus), quality of evoked sensation and intensity quantification.³⁴ QST includes assessment of sensory threshold (detection threshold for innocuous stimuli and pain threshold) and sensations evoked by suprathreshold stimuli.^{35,36} Tests are divided into two categories based on the endpoint (response): *static* and *dynamic*. Static QST measures are: a) threshold determination (e.g. pain detection, tolerance and threshold) and b)

stimulus intensity rating or pain magnitude rating (e.g. for a given stimulus by visual analogue scale). Static QST measures are limited to identify one point on a scale of sensation within a complex pain processing system. To overcome this limitation, dynamic QST measures are suggested.²⁶ Dynamic QST measures are: tests of central integration (e.g. temporal and spatial summation) and tests of descending control (e.g. diffuse noxious inhibitory control paradigm).²⁶ These relatively new dynamic measures are still being evolved and refined. Examples of test parameters for different QST are contained in Table 3.

Threshold detection and stimulus intensity rating (pain magnitude rating) are two commonly used paradigms of QST measures. A pain magnitude rating paradigm is used in both static and dynamic QST. Stimulus intensity/magnitude rating is measured by providing a standard stimulus of fixed intensity/magnitude and instructing the subject to provide a quantitative rating of its intensity/magnitude (usually 0-10). This paradigm is used to evaluate positive or negative sensory phenomena (hyperesthesia or hypoesthesia). Conceptually, a valid way to apply stimulus intensity rating is to use a reference point (unaffected site) against which stimulus in the affected site is rated. To determine the pain threshold, threshold testing and intensity/magnitude rating can be combined.³⁷ Threshold detection testing is the most commonly used paradigm to quantify sensory loss (elevated sensory detection threshold) or gain (reduced pain threshold). A graded series of stimuli is used to establish sensory thresholds. Stimuli can be pressure (touch threshold via Semmes Weinstein Monofilaments), vibration, electrical (Current perception threshold), thermal or others.

Each psychophysical measure (QST), including threshold, employs the whole sensory axis (i.e. transduction, transmission, modulation and perception) or nociceptive/pain pathways.

Psychophysical or sensory threshold is a core measure in QST. Empirically, a sensory threshold is the stimulus level (minimum energy) to achieve perception. Theoretically, a sensory threshold is a property of the signal detection (a sensory process of the model/theory).³⁸

Two distinct threshold measuring paradigms/methods (e.g. method of limits and levels, examples in Table 4) have been developed based on the empirical and theoretical concepts of sensory threshold. The *method of limits* approach is an empirically developed method and the *method of levels* is a signal detection theory based method. In the method of limits, the intensity of an applied stimulus (to the skin) is increased or decreased until the subject perceives or feels it as painful and stops the stimulus by a button/controller (thereby involving reaction time). The threshold values are determined by calculating mean values during a series of stimuli. The major limitations of this technique are that it is highly dependent on the subjects' motor ability and attention. In the method of levels, a series of predetermined stimuli are applied (to the skin), and the subject has to report whether the stimulus is perceived or not or whether it is painful or not (by responding yes or no) for each stimulus (a forced choice option). The intensity of the next stimulus (in any series of stimuli) is systematically increased or decreased based on the subject's response (does not rely on reaction time). This method may provide more stable responses, but it is a relatively time-consuming procedure.

For clinical purposes, sensory threshold is a function of the nervous system. Threshold detection is commonly used to assess nerve function in diseases of the peripheral nervous system. Threshold determination is an indicator of basal sensitivity, which is easily defined and identifiable (stable endpoint for clinical application).²⁰ Abnormal pain can be predicted by evaluating basal pain sensitivity based on threshold measurement (Figure 5).

Rationale for using QST in clinic

There is a complexity in the classification system of pain, and it has an effect on clinical assessment of pain. To corroborate, pain may be classified based on different factors,⁷ such as: 1) *physiological* (e.g. somatic, visceral, neuropathic), 2) *temporal* (e.g. acute, chronic), 3) *systemic* (e.g. musculoskeletal, neurological, psychological, respiratory, cardiovascular, gastrointestinal, genitourinary, other visceral, mixed) and 4) *etiological* (e.g. genetic, trauma, operative, infective, cancer, toxic, degenerative, mechanical, dysfunctional, psychological, or unknown). Pain is also classified based on pain mechanisms,^{13,14} such as, *adaptive/physiological pain* (i.e. nociceptive, inflammatory) and *maladaptive/pathological pain* (i.e. neuropathic, dysfunctional). It should be noted that the term “chronic pain” is within the temporal classification, and the term “maladaptive pain” (neuropathic and dysfunctional) is within the mechanism-based classification. Maladaptive pain is a common entity of chronic pain,¹⁵⁻¹⁷ and commonly is persistent, so can also be considered as chronic pain.⁶⁸

Currently pain diagnosis is primarily based on signs and symptoms, sometimes in combination with clinical evidence of structural/tissue damage. However, this diagnosis provides limited information regarding the mechanisms underlying the pain experience of the individual patient. It has been suggested that pain diagnosis and management should be mechanism-based.¹⁴ Therefore, pain assessment tools should clearly provide information on pain mechanisms (Figure 4). Clinical observations (signs/symptoms) do not always correlate with mechanism-based appraisals, but it is essential to assess or quantify the important and diverse phenomena related to pain mechanisms such as hyperalgesia (increased pain response), allodynia (lowered pain threshold), wind up (increased pain response in dorsal horn), referred pain (pain felt in a part of the body other than its actual source), and tenderness (local tissue sensitivity).

QST results may be utilized to define the territory and pathways of pain mechanisms (sensory mapping) or perhaps to identify sensory phenotypes of pain mechanisms. The rationale for employing QST,^{18-22,66} to facilitate mechanism-based pain assessment includes: 1) QST responses differ for an affected part versus an unaffected part and for patients versus controls, 2) patients can be categorized (sub-grouped) according to QST responses and it may reflect underlying mechanisms, 3) QST responses may be useful to predict treatment outcomes, and 4) treatment may alter QST responses, which can reflect influences on underlying mechanisms. Future research should focus on clearly linking the reliable and valid QST responses with specific pain mechanisms and treatment outcomes.

Benefits of QSTs and future direction

Recent studies suggest that QST may be useful in differential diagnosis, including detection of hypersensitivity and other pathogenesis of pain.^{18,20,21,26,39,40} It has been suggested that mapping of the anatomical distribution of sensory changes (e.g. hypoesthesia) with QST is a means of identifying the source of the pathological findings in peripheral nerve, plexus, root, central (spinal or cerebral).²⁰ QST is considered an ideal clinical outcome measure for identifying relevant somatosensory profile/patterns associated with certain stages of altered nociceptive input and for documenting pain modulation.⁴¹ Clinical uses of QST in musculoskeletal pain management have already been suggested,^{22,39,42,43,67,69} as some QST modalities are found to be reliable and valid for clinical assessment of musculoskeletal pain disorders.^{39,42-45,49-53}

It has been suggested that pain management should be based on a relational classification system of pain.⁴⁶ Under this mechanism-based approach *adaptive* or physiological pain (e.g.

nociceptive, inflammatory) and *maladaptive* or pathological pain (e.g. neuropathic, dysfunctional) should be managed differently.^{8,13} QST can be used to categorise these subtypes of pain, and can provide a potential means to monitor change over time in response to treatment (outcome evaluation).²¹

Current approaches to assessment have limitations. Electrodiagnosis can diagnosis nerve compression or laceration, but small nerve fiber pathology is not well defined by electrodiagnosis.¹⁹ Electrodiagnostic tests are uncomfortable, time consuming and expensive and thus repeated evaluations over time are neither patient centered or fiscally responsible. Imaging is useful in some cases such as post-stroke pain, whereas it cannot differentiate between pain of central origin (due to brain tissue damage) and musculoskeletal pain (due to physical disability). Moreover, imaging is not able to detect physiological lesions that may be causing pain. Thus, while both have a role in clinical evaluation they are insufficient for diagnosis or follow-up in sensory disorders. However, the QST finding (sensory hypo-function) from only one side of the painful body (in post-stroke pain) supports the first diagnosis (central pain).

QST has been shown to be useful for a wide range of clinical conditions,^{18,19} including: 1) disorders with pain as a major manifestation (e.g. post-herpetic neuralgia, complex regional pain syndrome, HIV (human immunodeficiency virus) induced neuropathy, neoplastic disorder, pain in non-neuropathic disorders), 2) other etiologies of small fibers pathology (e.g. diabetic neuropathy, uremic neuropathy, drug and toxicity- induced neuropathy, entrapment neuropathies), 3) disorders of the central nervous system (e.g. cerebral lesions, multiple sclerosis, predominantly motor disorders, spinal cord and radiculopathies).¹⁸ QST may also be useful to differentiate neck pain categories where it has been shown to differentiate people with neck pain

that have neural involvement from those with only musculoskeletal signs/symptoms.⁴⁰ A recent consensus from the IASP expert panel,⁶⁷ reported that QST is capable of providing important and unique information from the somatosensory system, which would be valuable in assessment of patients with pain.

Although there is emerging evidence that suggests a role for QST in pain management, the evidence to direct the specific modalities, techniques, diagnostic or therapeutic prediction rules is lacking in many respects. There is a need to continue testing to develop reliable and clinically feasible QST protocols that require less time and inexpensive portable equipment. For example, the current perception threshold test^{40,44} has similar reliability to other less costly tests such as Semmes Weinstein Monofilaments (moderate cost)^{45,70} or ice-water immersion test (low cost)^{43,39} or the ten test (no cost)^{39,42,71}. Head to head comparisons of these tests as screening, diagnostic, or evaluative tools will be needed to determine which tests provide better reliability and validity. Future research should also focus on longitudinal prospective studies with a large cohort of patients are required to justify the prognostic and evaluative properties of different sensory modalities; and to compare different sensory modalities, assessment protocols, indicators, and decision rules. Since QST is not used consistently,⁷² there is a need for a knowledge translation strategy⁶⁹ to facilitate implementation of QST in clinical research and practice.

Conclusion

The evidence supports the ability of QST to assess nerve function in processing of sensory and pain perceptions. Tests of threshold detection are most used in practice, but stimulus intensity rating testing may be useful for evaluating patient change over time. Many test

protocols have been described with moderate to high reliability; but there are insufficient head-to-head comparisons to select the best QST.

QST may provide a semi-subjective method for examining sensation as a mean of recognizing potential changes in the nociceptive pathways or it may help clarify vague or conflicting findings in clinical examination. QST might be a useful tool in determining pathogenesis, classification, differential diagnosis, prognosis, clinical outcome measures, or efficacy of treatment. Due to the diverse etiopathogenetic basis of musculoskeletal pain disorders, a broad range of reliable and valid QST measures are necessary to analyze the various disease entities. The evidentiary basis is currently sparse and does not provide sufficient information about which sensory modalities, test procedures and decision rules are best to use QST as a diagnostic and evaluate tool. QST may play a role to monitor the disease prognosis and outcome evaluation in therapy intervention but only continued research within homogenous parameters of QST will define this role.

References

1. IASP. Global year against musculoskeletal pain: Epidemiology of Musculoskeletal Pain [IASP Web site]. October 2009. Available at: <http://www.iasp-pain.org/AM/AMTemplate.cfm?Section=Home&TEMPLATE=/CM/ContentDisplay.cfm&SECTION=Home&CONTENTID=9287>. Accessed November 05, 2013.
2. Crombie IK, Croft PR, Linton SJ, LeResche L, Von Korff M, eds. *Epidemiology of pain*. Seattle: IASP press, 1999.
3. Kelsey JL, Hochberg MC. Epidemiology of Chronic Musculoskeletal Disorders. *Ann Rev Public Health*. 1999;9: 379-401.
4. United States Department of Labor. Nonfatal occupational injuries and illnesses requiring days away from work [Bureau of Labor Statistics Web site]. March 31, 2009. Available at: http://www.bls.gov/news.release/archives/osh2_11202008.pdf. Accessed November 05, 2013.

5. National Center for Health Statistics. Health, United States 2006 with Chartbook on Trends in the Health of Americans. Hyattsville, MD: 2006. Available at: <http://www.cdc.gov/nchs/data/hsr/hsr06.pdf>. Accessed November 05, 2013.
6. IASP. Declaration of Montreal [IASP Web site]. September 3, 2010. Available at: <http://www.iasp-pain.org/PainSummit/DeclarationOfMontreal.pdf>. Accessed November 05, 2013.
7. Merskey H, Bogduk N, eds. *Classification of chronic pain*. Seattle: IASP press, 1994.
8. Woolf CJ. Pain: Moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med*. 2004;140(6):441-451.
9. Henry JL. The need for knowledge translation in chronic pain. *Pain Res Manag*. 2008;13(6):465.
10. Lim EC, Sterling M, et al. Central hyperexcitability as measured with nociceptive flexor reflex threshold in chronic musculoskeletal pain: A systematic review. *Pain*. 2011;152:1811-1820.
11. Mallen C, Peat G, et al. Prognostic factors for musculoskeletal pain in primary care: a systematic review. *Br J Gen Pract*. 2007;57: 655–661.
12. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature*. 1983;306:686-688.
13. Woolf CJ. What is this thing called pain? *J Clin Invest*. 2010;120:3742-44.
14. Woolf CJ, Bennett G, Doherty M, et al. (1999). Towards a mechanism-based classification of pain? *Pain*. 1998;77:227-29.
15. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: A maladaptive response of the nervous system to damage. *Annu Rev Neurosci*. 2009;32:1-32.
16. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: Risk factors and prevention. *Lancet*. 2006;367:1618-1625.
17. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery: A review of predictive factors. *Anesthesiology*. 2000;93:1123-1133.
18. Zaslansky R, Yarnitsky D. Clinical applications of quantitative sensory testing (QST). *J Neurol Sci*. 1998;153:215-238.
19. Yarnitsky D, Granot M. Quantitative sensory testing. In: Cervero F, Jensen T, eds. *Handbook of clinical neurology*. Amsterdam: Elsevier; 2006:397-409.
20. Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *J Pain*. 2009;10:556-572.

21. Pavlakovic G, Petzke F. The role of quantitative sensory testing in the evaluation of musculoskeletal pain conditions. *Curr Rheumatol Rep*. 2010;12:455-461.
22. Courtney CA, Kavchak AE, et al. Interpreting joint pain: quantitative sensory testing in musculoskeletal management. *J Orthop Sports Phys Ther*. 2010;40:818-825.
23. Yarnitsky D and Pud D. Quantitative sensory testing. In: Binnie CD, Cooper R, et al., eds. *Clinical Neurophysiology*, Volume 1. Amsterdam: Elsevier B.V;2004:305-332.
24. Chong PST, Cros DP. Technology literature review: Quantitative sensory testing. *Muscle Nerve*. 2004;29:734-747.
25. Backonja, M., & Lauria, G. Taking a peek into pain, from skin to brain with ENFD and QST. *Pain*. 2010;151:559-560.
26. Arendt-Nielsen L, Graven-Nielsen T. Translational aspects of musculoskeletal pain: from animals to patients. In: Graven-Nielsen T, Arendt-Nielsen L; Mense S, eds. *Fundamentals of musculoskeletal pain*. Seattle: IASP press, 2008:347-366.
27. Lauria G, Hsieh ST, Johansson O, et al. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fibre neuropathy. *J Periph Nerv Sist*; 2010;15:79–92.
28. Low PA, Tomalia VA, Park K. Autonomic Function Tests: Some Clinical Applications. *Journal of Clinical Neurology* 2013;9:1-8.
29. Peltier A., Smith AG, Russell JW, et al. Reliability of quantitative sudomotor axon reflex testing and quantitative sensory testing in neuropathy of impaired glucose regulation. *Muscle Nerve*. 2009;39:529-535.
30. Fechner G. Elements of psychophysics: *Elemente der psychophysik*, vol. 2. Leipzig, Germany: Breitkopf and Härtel, 1860.
31. von Frey M. Ueber den Gebrauch von Reizhaaren. In: *Untersuchungen über die Sinnesfunctionen der mensch-lichen Haut. Erste Abhandlung: Druckempfindung und Schmerz. Abhandlungen der mathematisch-physischen Classe der Königlich Sachsischen Gesellschaft der Wissenschaften*. 1896; 23: 208-217.
32. Head H, Holmes G. Sensory disturbances from cerebral lesions. *Brain*. 1911. 34:102-254.
33. Stevens SS. Neural Events and the Psychophysical Law. *Science*. 1970;170:1043-1050.
34. Hansson P, Backonja M, Bouhassira D. Usefulness and limitations of quantitative sensory testing: Clinical and research application in neuropathic pain states. *Pain*. 2007;129:256-259.
35. Hansson P, Lindblom U. Hyperalgesia assessed with quantitative sensory testing in patients with neurogenic pain. In: Willis WD, ed. *Hyperalgesia and allodynia*. New York: Raven Press; 1992:335-43.

36. Lindblom U, Verrillo RT. Sensory functions in chronic neuralgia. *J Neurol Neurosurg Psychiatry*. 1979;42:422-35.
37. Kelly KG, Cook T, Backonja MM. Pain ratings at the threshold are necessary for interpretation of quantitative sensory testing. *Muscle Nerve*. 2005;32:179-184.
38. Krantz DH. Threshold theories of signal detection. *Psychological Review*. 1969;76:308-324.
39. Uddin Z, MacDermid JC, Packham T. Clinical implementation of two Quantitative Sensory Tests: Cold Stress Test and The Ten Test. *Physiotherapy Practice and Research*. 2014; 35(1):33-40.
40. Uddin Z, MacDermid JC, Galea V, et al. The Current Perception Threshold Test Differentiates Categories of Mechanical Neck Disorder. *J Orthop Sports Phys Ther*: In Press.
41. Nijs J, Van Houdenhove B, Oostendorp RA. Recognition of central sensitization in patients with musculoskeletal pain: application of pain neurophysiology in manual therapy practice. *Man Ther*. 2009;15:135-141.
42. Uddin Z, MacDermid JC, Packham T. The Ten Test for Sensation. *J Physiother*. 2013; 59:132-132.
43. Uddin Z, MacDermid JC, Packham T. Ice-water (cold stress) immersion testing. *J Physiother*. 2013;59(4):277-277.
44. Uddin Z, MacDermid JC, Galea V, et al. Reliability Indices, Limits of Agreement and Construct Validity of Current Perception Threshold Test in Mechanical Neck Disorder. *Crit Rev Phys Rehabil Med*. 2013; 25(3-4): 25–37.
45. Uddin Z, MacDermid JC, Ham H. Test-Retest Reliability and Validity of Normative Cut-offs of the Two Devices Measuring Touch Threshold: Weinstein Enhanced Sensory Test and Pressure Specified Sensory Device. *Hand Therapy*. 2014: 2014:19(1):3-10.
46. Woolf CJ, Max MB. Mechanism-based pain diagnosis: Issues for analgesic drug development. *Anesthesiology*. 2001;95:241-249.
47. Woolf CJ, Salter MW. Neuronal plasticity: Increasing the gain in pain. *Science*. 2000;288:1765-1768.
48. Spicher C, Mathis F, Degrange B, et al.. Static mechanical allodynia (SMA) is a paradoxical painful hypo-aesthesia: Observations derived from neuropathic pain patients treated with somatosensory rehabilitation. *Somatosens Mot Res*. 2008;25:77-92.
49. Ohrbach R, Gale EN. Pressure pain thresholds, clinical assessment, and differential diagnosis: reliability and validity in patients with myogenic pain. *Pain*. 1989;39:157-69.
50. Walton DM, Macdermid JC, Nielson W, et al. Reliability, standard error, and minimum detectable change of clinical pressure pain threshold testing in people with and without acute neck pain. *J Orthop Sports Phys Ther*. 2011;41:644-50.

51. Park G, Kim CW, Park SB, et al. Reliability and usefulness of the pressure pain threshold measurement in patients with myofascial pain. *Ann Rehabil Med*. 2011;35:412-417.
52. Shakoor N, Agrawal A, Block JA. Reduced lower extremity vibratory perception in osteoarthritis of the knee. *Arthritis Rheum*. 2008;59:117-121.
53. Shakoor N, Lee KJ, Fogg LF, et al. Generalized vibratory deficits in osteoarthritis of the hip. *Arthritis Rheum*. 2008;59:1237-1240.
54. Lacomis D. Small-fiber neuropathy. *Muscle Nerve*. 2002;26:173-188.
55. Stewart JD, Low PA, Fealey RD. Distal small fiber neuropathy: Results of tests of sweating and autonomic cardiovascular reflexes. *Muscle Nerve*. 1992;15:661-665.
56. Giulliani, MJ, Stewart JD, Low PA. Distal small fiber neuropathy. In: Law PA, ed. *Clinical Autonomic Disorders*. Philadelphia: Lippincott-Raven, 1997:699–714.
57. Holland NR, Crawford TO, Hauer P, et al. Small-fiber sensory neuropathies: Clinical course and neuropathology of idiopathic cases. *Ann Neurol*. 1998;44:47-59.
58. Periquet M, Novak V, Collins M, et al. Painful sensory neuropathy prospective evaluation using skin biopsy. *Neurology*. 1999;53:1641-1641.
59. Tobin K, Giuliani MJ, Lacomis D. Comparison of different modalities for detection of small fiber neuropathy. *Clin Neurophysiol*. 1999;110:1909-1912.
60. Novak V, Freimer M, Kissel J, et al. Autonomic impairment in painful neuropathy. *Neurology*. 2001;56:861-868.
61. Bell C. Idea of a new anatomy of the brain; submitted for the observation of his friends. 1811. In: Cranefield PF. *The way in and the way out: François Magendie, Charles Bell and the roots of the spinal nerves*. New York: Futura; 1974.
62. Sherrington CS. *The Integrative Action of the Nervous System*. Cambridge, UK: Cambridge Univ. Press, 1906.
63. Nafe, JP. A quantitative theory of feeling. *J. Gen. Psychol*. 1929;2:199-211.
64. Lloyd DPC. Post-tetanic potentiation of response in monosynaptic reflex pathways of the spinal cord. *J Gen Physiol*. 1949;33(2):147–170.
65. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science*. 1965;150(3699):971–9.
66. Cruz-Almeida Y, Fillingim RB. Can Quantitative Sensory Testing Move Us Closer to Mechanism-Based Pain Management? *Pain Medicine*. 2014;15(1):61-72.
67. Backonja M, Attal N, Baron R, Bouhassira D, Drangholt M, Dyck P, et al. Value of quantitative sensory testing in neurological and pain disorders: NEUPSIG consensus. *Pain*. 2013;154(9):1807-19.

68. Uddin Z, MacDermid JC. Pain Hypersensitivity: A bio-psychological explanation of chronic musculoskeletal pain and underpinning theory. *Pain Studies and Treatment*. 2014;2(2):31-35.
69. Uddin Z, MacDermid JC. A knowledge translation perspective on the two quantitative sensory tests and their usability with clinicians. *Journal of Novel Physiotherapies*. 2014: In Press.
70. MacDermid JC, Kramer JF, Roth JH. Decision making in detecting abnormal semmes-weinstein monofilament thresholds in carpal tunnel syndrome. *J Hand Ther*. 1994;7(3), 158-162.
71. Durrant N. The Reliability and Validity of the Ten Test and Exploring a New Visual Version. MSc [dissertation]. Hamilton(ON): McMaster University; 2014.
72. MacDermid JC, Walton DM, Cote P, et al. Use of outcome measures in managing neck pain: an international multidisciplinary survey. *Open Orthop J* 2013;7:506-520.

Figures and Tables

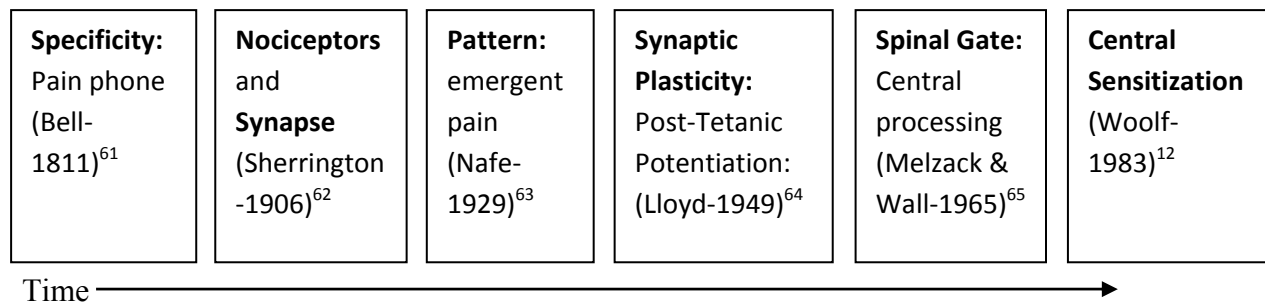


Figure 1. Evolution in theories of pain science and central sensitivity

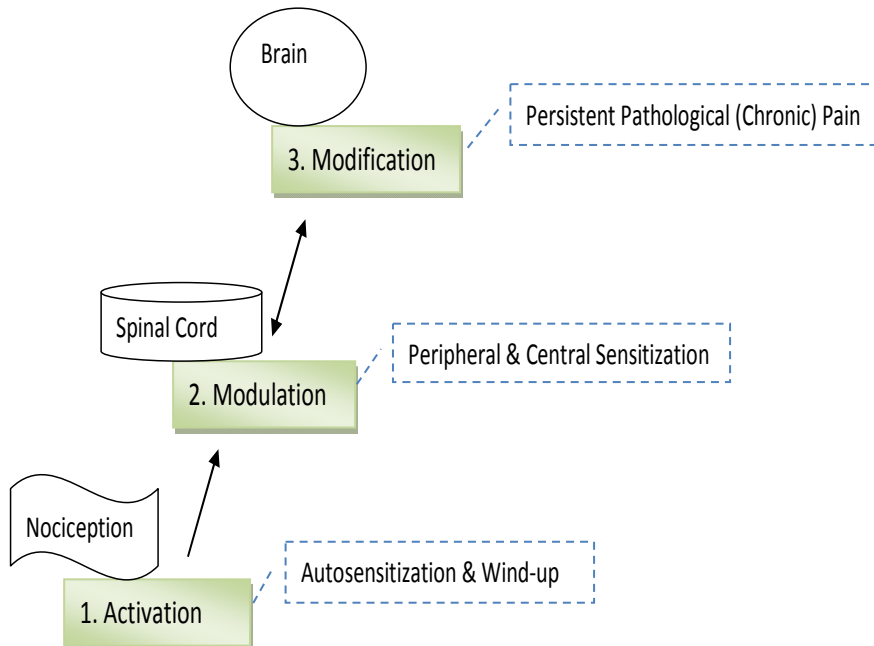


Figure 2. Stages of neural process in somatosensory system to produce pain hypersensitivity and chronicity (i.e. maladaptive pain). Adapted from Woolf & Salter, 2000.⁴⁷

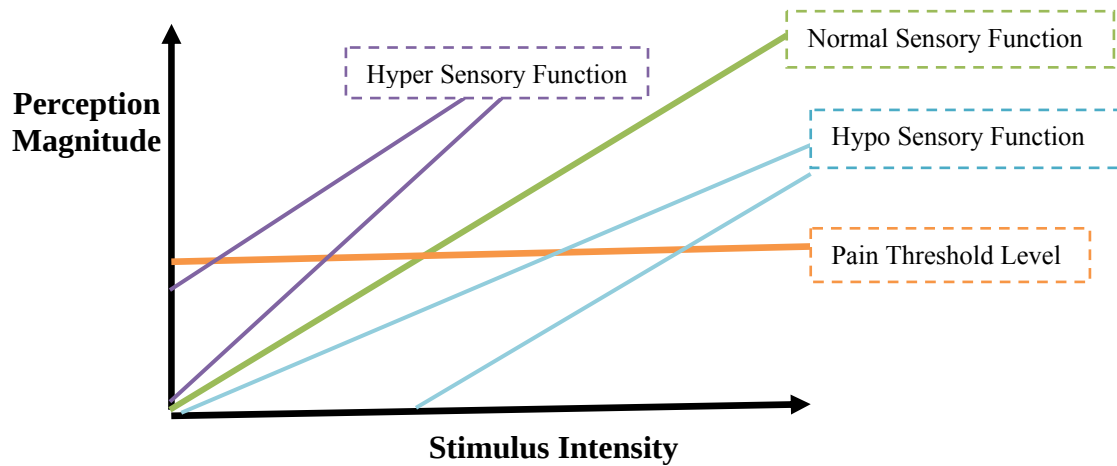


Figure 3. Stimulus-response ranges for normal, hypo, and hyper sensory function (Adapted from Arendt-Nielsen & Yarnitsky, 2009).²⁰ A normal or altered slope can represent deviation from normal sensation. In some cases (e.g. neuropathic pain) a combination of hypo and hyper sensory function can be seen.^{20,48} QST is a unique technique for clinicians to measure hyper sensory function.¹⁹ Reprint permitted from Uddin Z, et al. 2014.³⁹

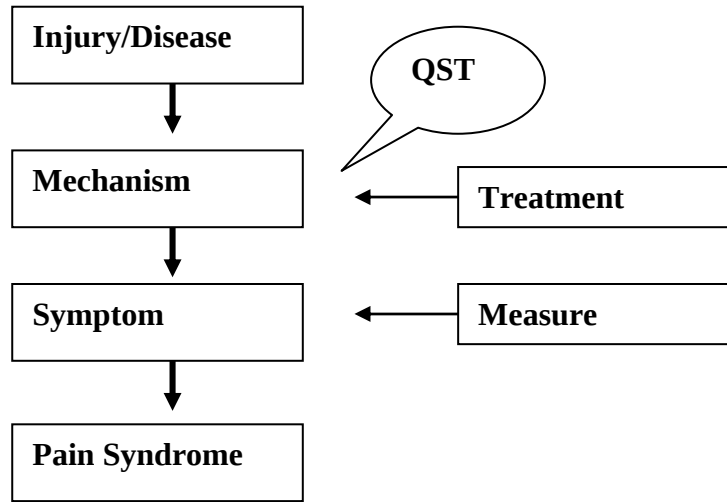


Figure 4. Diagram representing the relationship between etiologic or disease factors, pain mechanisms, clinical symptoms, and pain syndromes. Ideally, pain management is to treat the mechanisms (not just to suppress the symptom/syndrome). Despite the associated challenges, QST is capable of exploring aspects of pain mechanisms. Current clinical pain measurement techniques assess symptoms generated by the mechanisms, which are not equivalent to the mechanisms themselves (modified from Woolf & Max, 2001).⁴⁶

<i>Basal Pain Sensitivity</i>	Hypersensitivity	Hyperesthesia (Hyperalgesia, Allodynia)
	Normal sensitivity	
	Hyposensitivity	Hypoesthesia (Numbness, Paresthesia)

Figure 5. Basal pain sensitivity and abnormal pain response detection

Table 1. Comparisons of diagnostic sensitivities of nerve fibers assessment methods in small-fibers neuropathy (adapted from Lacomis D, 2002).⁵⁴ Reprint permitted from Uddin Z, et al. 2014.³⁹

References	Abnormal Cardioagal testing (%)	Reduced epidermal nerve fiber density (%)	Abnormal Pin or Cold sensation clinical examination (%)	Abnormal QSART (%)	Abnormal QST (cool or heat pain) (%)
Stewart et al. (1992), ⁵⁵	28	-	78	80	-
Giulliani et al. (1997), ⁵⁶	66	—	59	80	-
Holland et al. (1998), ⁵⁷	-	81	90	-	60
Periquet et al. (1999), ⁵⁸	-	87.5	~45	59	*72
Tobin et al. (1999), ⁵⁹	75	-	80	80	67
Novak et al. (2001), ⁶⁰	57	74	-	68	*85

Legend: QSART-quantitative sudomotor axon reflex test, QST- quantitative sensory testing,
*Cold or vibration

Table 2. An overview of common clinical bedside examination and QST

<i>Stimulus</i>	<i>Bedside Exam</i>	<i>QST</i>	<i>Target fiber (central pathway)</i>
Cold	Thermoroller, test tube devices	Thermal testing QSTs	Aδ (spinothalamic)
Heat			C (spinothalamic)
Light touch (static)	Q-tip/cotton	Calibrated monofilament	Aβ (Lemniscal)
Vibration	Tuning fork	Vibrometer	Aβ (Lemniscal)
Pinprick	Pin	Calibrated Pin	Aδ, C(spinothalamic)
Pressure (blunt)	Examiner's thumb	Algometer	Aδ, C (spinothalamic)

Table 3. An example of stimulus modalities and pain measures parameter in QST

<i>Stimulus Modalities</i>	<i>Pain Measurement Parameters</i>
Electrical	Pain Threshold
Contact Thermal (heat, cold)	Pain Threshold/Tolerance
Immersion Thermal (heat, cold)	Suprathreshold Scaling (e.g.VAS, NRS)
Mechanical (Pressure, Touch, Vibration)	Pain Threshold/Tolerance, Temporal Summation
Thermal, Ischemic	Conditioned Pain Modulation
Chemical (e.g. capsaicin, hypertonic saline, glutamate)	Cerebral Responses (e.g. EEG, fMRI, PET) Muscle Reflexes (e.g. R3 reflex)

Table 4. Examples of modality-related QST parameters and methods

<i>QST modality</i>	<i>QST parameter</i>	<i>Method</i>
Current	Current Perception Threshold	Method of limits
Vibration	Vibration threshold	Method of limits
Pointing touch	Touch threshold	Method of limits
Light touch	Touch threshold	Method of levels
Blunt Pressure	Pressure pain threshold and tolerance	Method of levels

Objectives of the Thesis Work

The overarching objective of my doctoral thesis research is to produce evidence that informs our understanding of how central or neuropathic pain perceptions contribute to gain in musculoskeletal pain and ongoing disability. I have assessed aspects of validity of QST in clinical musculoskeletal pain. In the long-term, I hope to use this knowledge to develop and test innovative approaches to manage abnormal pain responses in patients with chronic pain. As a first step toward my long-term goal, I have used cross-sectional and cohort studies to investigate sensory changes and identifies factors of disability due to pain in my doctoral research program. My aim is to develop clinical assessment tools and to identify the subset of psychological, behavioral, comorbid condition, disease severity, and neural sensitivity variables that predict adverse pain (abnormal pain reaction) outcomes that persist into a chronic state.

Overall thesis focus

My thesis is focused on sensory evaluation and its role as a predictor for chronic pain and disability in musculoskeletal disorders of the neck, shoulder and hand. The work contributes in knowledge for measurement properties of different sensory tests, and determines how sensory measures behave as risk indicators. This thesis evaluated measurement issues of QST (such as

reliability and validity) in clinical contexts and the purpose targeted discrimination, evaluation and perdition in different musculoskeletal pain conditions.

My PhD study evaluated threshold parameters of static QST. The study has examined both methods (limits and levels). For example, (I) study 1 and 2 (*in chapter 2 and 3*) are based on only methods of limits, (II) study 3 and 4 (*in chapter 5 and 5*) are based on both methods, (III) study 5 (*in chapter 6*) is based on only methods of levels. Overall this thesis has evaluated 5 QST modalities in both methods (Table 4 and 5).

Table 5. Title of the study manuscripts

<i>Thesis Chapter</i>	<i>Manuscript Title</i>	<i>Current Status in Journal</i>
Chapter 2	Reliability Indices, Limits of Agreement and Construct Validity of Current Perception Threshold Test in Mechanical Neck Disorder	Published: <i>Crit Rev Phys Rehabil Med.</i> 2013;25(3-4): 25–37.
Chapter 3	The Current Perception Threshold Test Differentiates Categories of Mechanical Neck Disorder	Published: <i>J Orthop Sports Phys Ther.</i> 2014;44(7):532-540.
Chapter 4	Test-Retest Reliability and Validity of Normative Cut-offs of the Two Devices Measuring Touch Threshold: Weinstein Enhanced Sensory Test and Pressure Specified Sensory Device	Published: <i>Hand Therapy.</i> 2014;19(1):3-10.
Chapter 5	Psychophysical and Patient Factors as Determinants of Pain, Function and Health Status in Shoulder Disorders	Under review: <i>Int J Shoulder Surg</i>
Chapter 6	The Effect of Pressure Pain Sensitivity and Patient Factors on Self-reported Pain-disability in Patient with Chronic Neck Pain.	Accepted: <i>The Open Orthopedics Journal.</i>

CHAPTER 2: Study 1

Published: Critical Reviews™ in Physical and Rehabilitation Medicine

Citation:

Uddin Z, MacDermid JC, Galea V, Gross AR, Pierrynowski MR. Reliability Indices, Limits of Agreement and Construct Validity of Current Perception Threshold Test in Mechanical Neck Disorder. *Crit Rev Phys Rehabil Med*. 2013;25(3-4): 25–37.

Reliability Indices, Limits of Agreement and Construct Validity of Current Perception Threshold Test in Mechanical Neck Disorder

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ABSTRACT

Objective. To evaluate the reliability and validity of Current Perception Threshold (CPT) tests in patients with Mechanical Neck Disorder (MND). **Methods.** The rapid-CPT protocol was performed at three frequencies (5, 250, 2000 Hz) using 3 dermatomal locations (C6-C8) on the hand of patients with MND (N=106). A subset of patients (N=34) was reassessed at a second visit to determine the test-retest reliability. For inter-trial reliability the fingertip of both hands were assessed. Internal consistencies of CPT between frequencies were calculated from CPT test scores in the most affected hand. Construct validity of CPT was evaluated by correlating the 3 composite scores derived from the CPT tests with the Neck Disability Index (NDI) and Cervical Spine Outcomes Questionnaire (CSOQ). **Results.** Inter-trial reliability was good to excellent (ICC =0.73-0.82, $p<0.001$). Test-retest reliability of CPT scores was fair to excellent (ICC =0.47-0.86, $p<0.001$). The mean retest difference and the 95% limits of agreement were: 0.3 ± 3 (in 2000Hz and 250Hz), and 0.1 ± 3.9 (in 5Hz). A small to medium-sized correlation was found between CPT and NDI or CSOQ ($r =0.24-0.37$). **Conclusions.** CPT was consistent across occasions and was associated with neck disability.

Keywords: *Quantitative Sensory Testing, Current Perception Threshold, Neck Pain, hypoesthesia, hyperesthesia*

Abbreviations: NP = Neck pain; MND = Mechanical Neck Disorder; QST = Quantitative Sensory Testing; CPT = Current Perception Threshold; NDI = Neck Disability Index; CSOQ = Cervical Spine Outcome Questionnaire; ICC = Intraclass Correlation Coefficient

I. INTRODUCTION

Neck pain (NP) is a common health problem among the adult population and can arise following injury, or as a result of a gradual onset mechanical disorder [1-3]. The yearly prevalence of NP is 30-50% among the general population [2, 3] and the estimated lifetime prevalence of NP is above 66% [4]. NP disables about 5% of the adult people [4, 5]. It is difficult to detect any specific etiology or systemic disease in most cases of NP and these cases are commonly labeled as non-specific neck pain [6]. NP related to neuromuscular pathology and articular dysfunction is considered as Mechanical Neck Disorder (MND) [6, 7]. It can arise due to any dysfunction, degeneration, or injury and is classified based on the nature of the signs and symptoms [8, 9].

Evidence supports that sensory disturbances are more associated with neck disability in MND than are degenerative and/or radiological findings [9-12]. A large community based British study [13] supported the key role of neurological factors in NP. Poor recovery in NP is associated with widespread sensory hypersensitivity [14, 15]. Research studies [16, 17] and a systemic review [18] have demonstrated evidence of central hyperexcitability in musculoskeletal pain. Generalized sensory hyposensitivity (hypoesthesia) and hypersensitivity (hyperesthesia) is a feature in a subset of chronic neck disorders [19]. There is sufficient evidence that abnormal sensory findings are prognostic of poorer clinical outcomes in chronic pain conditions and specifically in NP. This provides sufficient rationale for including sensory evaluation in the assessment of patients with NP.

Quantitative Sensory Testing (QST) is semi-subjective method of measuring the intensity of stimulus required for sensory perception. QST involves evaluating the person's interpretation of a series of calibrated sensory stimuli. QST can evaluate the minimum threshold detection, perception of pain or integration of sensory inputs. Hypersensitivity of pain can be detected by administering a sensory threshold test to determine the least amount of sensory input required for pain perception. QST is psychophysical testing that evaluates the functionality from sensory receptors to the brain and can be used to detect reorganization in the nociceptive pathways [20]. It is possible to evaluate the sensory processing of both large and small afferent fibres by selecting different sensory inputs in QST [20, 21].

Current Perception Threshold (CPT) test is a type of QST, which quantifies the sensory threshold from transcutaneous electrical nerve stimulation. The CPT test is neuroselective [22, 23], where three different impulse frequencies (5 Hz, 250 Hz, and 2000 Hz) are used to determine the patient's sensation threshold for three types of sensory nerve fibers (C-fiber, A δ -fiber, and A β - fiber) [27-29]. However, traditional diagnostic methods for the peripheral nervous system (e.g. electromyography, nerve conduction velocity, evoked potential) primarily focus on the large myelinated A β - fiber. Both large and small fibres targeting CPT might potentially be useful in differentiating subtypes of NP or monitoring improvements in sensory function with treatment. It has been suggested that a potential benefit of CPT is that it is able to assess a range of fibers including small (pain) fibers [22, 26]. Some studies support the potential role of a 5Hz CPT test targeting small nerve (c-fiber) pathology [27-29]. However, a potential disadvantage of CPT and other QST is that they require patient interpretation/cooperation, unlike nerve conduction tests which are more objective.

There is controversy about the use of CPT. The American Association of Neuromuscular and Electrodiagnostic Medicine has not supported the use of CPT [23]. Others suggest CPT is superior to nerve conduction test for the assessment of peripheral nerve integrity [22]. The US Food and Drug Administration has cleared CPT devices for the use of sensory threshold and nerve conduction measures [24, 25]. There is insufficient evidence to support the use of CPT for diagnosis of cervical radiculopathy. CPT has potential to differentiate neck pain with/without sensory impairment which can be useful for prognosis, or to identify subgroups. A prerequisite to using CPT as a QST for any of these purposes is an understanding of whether CPT provides reliable scores in patients with NP and is related to NP and disability. Therefore, the aims of this study were to estimate the following across 3 CPT frequencies and 3 digits (i.e. 3 test locations) in patients with MND: 1. The reliability coefficients across trials or occasions; 2. The mean test-retest difference and limit of agreement; 3. The correlation between CPT score and neck disability as measured (i.e. Neck Disability Index and Cervical Spine Outcomes Questionnaire).

II. MATERIALS AND METHODS

A. Study design and participants

The study was approved by the McMaster University Research Ethics Board. Informed consent was obtained from all participants prior to testing. All patients (n = 106) underwent a standardized physical examination to assess exclusion criteria and to establish that neck pain was related to mechanical dysfunction. An experienced orthopaedic manual physical therapist (with more than 10 years of experience in the evaluation of neck disorders) performed a musculoskeletal examination to verify the presence of MND and check exclusion criteria. Inclusion criteria were: more than 18 years of age, neck presents with neck pain, stiffness or

tenderness. Exclusion criteria were: headache not of cervical origin (e.g. migraine, tension-type headache), disorders with definite or possible long tract signs, neurological disease, stroke systematic failure (e.g. polymyalgia, fibromyalgia, fatigue syndrome), neck injuries with fracture or dislocation, any damage to nerves of the elbow or wrist, upper quadrant loss (amputation), spinal surgery in the previous year, diffuse connective tissue disease (e.g. rheumatoid arthritis), arthritis associated with spondylitis, rheumatic syndromes (e.g. infection, metabolic or endocrine disease), prolonged steroid use (> 3 months), diabetes or if patients had conditions that precluded participation on the test procedures.

The neurological scan included checking myotomal weakness (C1-T1), dermatomal sensory light touch scan (C1-T1), and deep tendon reflexes (C6-biceps, C6-brachioradialis, and C7/8-triceps). Joint play test and neural tension provocation tests were performed. Patients as described in Table 1 were recruited.

B. Outcome Measures

1. CPT test procedure. CPT was performed using the rapid protocol (R-CPT) of the Neurometer CPT/C (Neurotron, Incorporated; Baltimore, MD, USA). All CPT tests were performed in a quiet room, and the temperature was maintained between 22°C and 25°C. Patients were seated in a comfortable chair with a back support and armrests. Standardized instructions and the test procedures were clearly explained before testing. The R-CPT (rapid test of CPT) protocol required the patient to self-administer electrical stimuli, increasing in intensity through a series of 25 predetermined levels. The patient pressed and held a specific button to start the test and released the button as soon as a stimulus could be detected. Neither the examiner nor the patient was able to see scores until testing was completed. The CPT stimulus

was delivered via small surface gold-plated electrodes placed on the medial and lateral sides of the distal phalanx (Figure 1) at the pulp of the three fingers (thumb=D1, middle=D3, and little=D5) to target 3 different nerve roots (C6, C7, and C8). The testing was repeated at 3-different frequencies (2000Hz, 250Hz, and 5Hz). The R-CPT values (numerical score range 1 to 25) determine the minimal stimulus (between 0 to 10 mA) that the patient could detect. Both hands were tested. Data from hands were entered into a database creating variables for the most affected hand and either a second affected hand in people with bilateral symptoms or as unaffected hand where symptoms were unilateral.

All CPT scores were collected from the three fingers using three types of frequency (nine individual CPT test items/variables). A subset of patients (N = 34) was rescheduled for repeat testing 2-14 days after the initial test. The same CPT protocol was repeated at the second visit, and same evaluator performed the two tests. All other patients were assessed on one occasion.

2. Neck pain and disorder measure. The Neck Disability Index (NDI) is a self-reported neck-specific outcome measure, consisting of 10 item questions (e.g. pain intensity, personal care, lifting, reading, headache, concentration, work, driving, sleeping, and recreation) [30, 33]. Each item is scored out of 5 and a total score of 50 is computed; the lower the score the less the self-rated disability [30, 33].

3. Cervical Spine Outcome Questionnaire (CSOQ). The CSOQ was developed to include a broad range of deficits related to NP [31, 32]. CSOQ is a multidimensional self-reported outcome and composite of six subscales (e.g. two pain severity, a psychological distress, a functional disability, a physical symptom, and a health care utilization) [31]. Each subscale (domain) is scored separately and converted to the ranges of 0 to 100 (higher score

indicates greater dysfunction). We calculated an average score from the six measures to interpret CSOQ (out of 100), and an average from the two pain-related subscales/domains measure of CSOQ to interpret pain severity (out of 100).

C. Data Analysis

Descriptive analyses of variables were performed to check for outliers (which were checked for data errors) and to determine data properties. Normality testing (e.g. Kolmogorov-Smirnov, Shapiro-Wilk, and QQ-Plot) was done prior to performing analytical statistical tests. All statistical procedures were performed on SPSS 17.0 software package (SPSS Inc., Chicago, IL). Bland-Altman plots were made using MedCalc software version 12.3.0 (Broekstraat, Mariakerke, Belgium).

1. Reliability. Reliability coefficients were determined for within an occasion (between trials) and between occasions for each location/digit and frequency individually. Reliability was determined using intraclass correlation coefficient (ICC, model 2,1) [34] and Bland and Altman techniques [35-37]. ICC's were calculated as described by Shrout and Fleiss [34] and point estimates were interpreted according to Fleiss [38] as: $ICC > 0.75$ = excellent; ICC between 0.40 and 0.75 = fair to good; $ICC < 0.40$ = poor. The Bland-Altman method [35-37] involves plotting the difference between tests against their mean value; and calculation of the mean difference across all subjects. The limits of agreement are determined by calculating two standard deviations around the mean difference.

2. Construct validity. Construct validity was evaluated by assessing whether CPT scores were associated with neck disability. We expected a significant, but low to moderate relationship given that uniform sensory loss is not a predominant symptom in all patients with neck pain.

Pearson's r was used to determine the relationship between the 3 CPT scores (i.e. 2000Hz, 250Hz, and 5Hz) from the most affected hand of all patients with the pain subcomponents and total scores of the NDI, and COSQ. Correlation coefficients (r) interpretation was according to Cohen's rating of correlation effect sizes [39]: small ≥ 0.10 , medium ≥ 0.30 , and large ≥ 0.50 .

III. RESULTS

The inter-trial reliability ICC showed good to excellent reliability (between 0.73 and 0.82, $p < 0.001$) [Table 2]. For test-retest reliability the ICC showed fair to excellent reliability (0.47 to 0.86, $p < 0.001$) at all three frequencies [Table 3]. The Bland-Altman plot demonstrated a minimal mean difference between test occasions (no bias) and a similar limits of agreement across the 3 frequencies (-0.3 ± 3 in 2000Hz and 250Hz; and 0.1 ± 3.9 in 5Hz test) [Figure 2_{a,b,c}].

A small to medium sized significant correlation ($r = 0.24$ to 0.37 , $p < 0.05$) was found between CPT and self-reported measures (NDI and CSOQ) [Table 4].

IV. DISCUSSION

This study indicates that CPT testing can provide moderate to highly reliable test scores in patients with MND, and these scores are weakly to moderately correlated with self-reported pain measures. This suggests a potential role for the use of CPT in patients with NP, but also caution in considering these tests as a definitive indicator of impairment. Lower sensory thresholds to perceive stimuli as painful have been shown to be prognostic in certain subtypes of NP [40-42] and CPT is an option for testing for this feature. The fact that it was significantly associated with pain and poorer overall function supports this application. There is relatively

little evidence about sensory detection thresholds across dermatomes [43] and different sensory modalities that can be utilized in sensory evaluation. CPT is one option for assessing sensory detection threshold to electrical stimuli which has potential advantages of neuroselectivity and direct stimulation of fiber subtypes. However, this study does not suggest it is superior to other QST methods since this was not explored.

Our sampling may also have affected study results. Given this was a preliminary study on the use of CPT in NP, we elected to include a broad range of patients with MND to depict non-specific NP group. This MND group has less sensitivity than some other subtypes of NP (e.g. whiplash, cervical radiculopathy), and where sensory abnormalities are more common [40-42]. This may explain why our correlations between CPT and self-report measures were not stronger since the proportion of sensory abnormalities in our sample may have been low.

Measurement issues pertaining to disability may also affect the observed associations. We selected the NDI because it is a commonly used patient reported outcome measuring tool in NP [37]. The NDI is comprised mostly of functional items [30, 37] that are not directly related to sensory symptoms, nor fine dexterity. The NDI has only one question on pain. While we elected to examine how this item related to CPT scores, the item was not validated for that purpose. The CSOQ is multidimensional [31, 32] and does have domains/items related to arm/hand symptoms and pain. However, less is known about the measurement properties of the CSOQ. Any problems in measurement of pain and function would dissipate correlations between these measures and CPT. We did not find differences between the NDI and CSOQ correlations which suggest that both self-report measures reflected pain to a similar extent. Since CPT itself was moderately reliable, this would also tend to dissipate the correlations between CPT and function and may have underestimated the true relationship between sensory function and pain. Since we expected

CPT to assess one of many biologic components that contribute to neck disability, the mild to moderate relationship observed is consistent with a variably important role for sensory disturbances in functional disability. Each CPT test frequency demonstrated at least some positive relationship with NDI and CSOQ scores. The relationship was strongest between thumb sensory thresholds and disability measures. This may reflect that sensory disturbances were more prominent in the C6 dermatome; or the importance of the thumb in hand function.

The moderate to high reliability we found supports judicious use of CPT, but is less preferable than having consistently high reliability. This level of reliability is consistent with other studies evaluating sensory detection [44-47]. Thus, while we did not directly compare CPT to sensory test devices or protocols our findings suggest similar performance to measures that are currently used. Perception may be challenging to assess in some patients. Previous studies suggest that data from sensory trials tend to be more unstable than motor tests [45], so a moderate amount of random error may be inherent to sensory evaluation. Sensory perception testing requires that patients attend to the stimulus and attention can vary substantially even within in a single session. Proper stabilization of the body part being tested and avoidance of other sensory inputs from either the examiner or the environment should be used to mitigate these sources of error. We used the rapid CPT protocol which is the quickest and least burdensome form of CPT testing but also least precise. The rapid version test involves increasing the stimulus until the patient perceives it. We selected this approach because it provided a quick test that would be clinically feasible for screening multiple dermatomes. More rigorous environmental controls or use of standardized procedures in future studies might improve reliability coefficients and may be warranted if these measures are being used to evaluate patient change over time.

Normal sensory thresholds for dermatomes with different test devices and procedures have not been clearly established for CPT in NP; although normal touch thresholds have been reported to be higher in the cervical dermatomes than values for fingertips [43]. The prevalence of abnormal sensory thresholds across dermatomes in patients with or without NP [43] should be defined in larger cohorts who are subdivided into age and gender groups and followed over time to increase confidence when these scores should be considered abnormal. Longitudinal studies are needed to determine the prognostic and evaluative properties of different sensory testing modalities to determine the optimal methods for research and practice. Since we only evaluated one modality we did not determine how CPT compares to other modalities and cannot say that is preferable, or inferior, to other sensory screening methods.

The optimal CPT protocols for identifying the location, nature and severity of the sensory impairments in patients with NP is challenging given that sensory changes can be diffuse and highly variable between patients. This is reflected in our results. Sensory alterations can affect different sides, dermatomes, or areas within a dermatome. Testing the fingertip area may not reflect all sensory dysfunctions within the dermatome, even though we selected 3 sites that are meant to target 3 specific nerve roots (C6, C7, and C8). Test protocols and decision rules facilitate more consistent application and interpretation of sensory tests but more complicated decision rules for QST tend to increase inter-rater disagreements on whether sensibility is “normal” [48]. For all these reasons, establishing clear rules on what constitutes normal or abnormal sensory thresholds requires further study. It is virtually impossible to address this range of remaining questions about sensory threshold detection in NP within a single study, because of the large response burden that would be required. Given the large gaps in our understanding of

the sensory evaluation in NP, multiple primary studies are needed followed by “systematic reviews” to synthesize findings across studies.

This study suggests that CPT is moderately reliable and related to neck disability in a group of people with varying types of MND (i.e. non-specific NP). Our results are preliminary and should be considered in light of the limitations. The main limitations of CPT for screening patients with MND are (a) the optimal screening protocol (sites, frequencies, and subtests) have not been defined and require multiple additional studies, (b) active cooperation with patients is required, and like most other QST there are limitations when relying on consistent subject attention and participation. Finally, the test options we used for CPT were not necessarily optimal for screening and we were unable to compare different CPT protocols.

V. CONCLUSION

CPT is reliable and valid for assessment of sensory detection threshold in patients with MND. Longitudinal prospective studies are needed to determine the prognostic and evaluative properties of CPT, and to compare different sensory testing modalities.

REFERENCES

1. Bot S, Van der Waal J, Terwee C, et al. Incidence and prevalence of complaints of the neck and upper extremity in general practice. *Ann Rheum Dis*. 2005;64(1):118-123.
2. Bovim G, Schrader H, Sand T. Neck pain in the general population. *Spine*. 1994;19(12):1307-1309.
3. Hogg-Johnson S, van der Velde G, Carroll LJ, et al. The burden and determinants of neck pain in the general population. *European Spine Journal*. 2008;17:39-51.
4. Côté P, Cassidy JD, Carroll L. The saskatchewan health and back pain survey: The prevalence of neck pain and related disability in saskatchewan adults. *Spine*. 1998;23(15):1689-1698.

5. Côté P, Cassidy JD, Carroll LJ, et al. The annual incidence and course of neck pain in the general population: A population-based cohort study. *Pain*. 2004;112(3):267-273.
6. Borghouts JA, Koes BW, Bouter LM. The clinical course and prognostic factors of non-specific neck pain: A systematic review. *Pain*. 1998;77(1):1-13.
7. Gross AR, Haines T, Goldsmith CH, et al. Knowledge to action: A challenge for neck pain treatment. *J Orthop Sports Phys Ther*. 2009;39(5):351-363.
8. Reading I, Walker-Bone K, Palmer KT, et al. Anatomic distribution of sensory symptoms in the hand and their relation to neck pain, psychosocial variables, and occupational activities. *Am J Epidemiol*. 2003;157(6):524-530.
9. Abdulkarim J, Dhingsa R, L Finlay D. Magnetic resonance imaging of the cervical spine: Frequency of degenerative changes in the intervertebral disc with relation to age. *Clin Radiol*. 2003;58(12):980-984.
10. Van der Donk J, Schouten JS, Passchier J, et al. The associations of neck pain with radiological abnormalities of the cervical spine and personality traits in a general population. *J Rheumatol*. 1991;18(12):1884-1889.
11. Pettersson K, Hildingsson C, Toolanen G, et al. MRI and neurology in acute whiplash trauma: No correlation in prospective examination of 39 cases. *Acta Orthopaedica*. 1994;65(5):525-528.
12. Karlsborg M, Smed A, Jespersen H, et al. A prospective study of 39 patients with whiplash injury. *Acta Neurol Scand*. 1997;95(2):65-72.
13. Coggon D, Cyrus Cooper D. Prevalence and occupational associations of neck pain in the british population. *Scand J Work Environ Health*. 2001;27(1):49-56.
14. Sterling M, Jull G, Vicenzino B, Kenardy J, et al. Physical and psychological factors predict outcome following whiplash injury. *Pain*. 2005;114(1-2):141-148.
15. Sterling M, Jull G, Kenardy J. Physical and psychological factors maintain long-term predictive capacity post-whiplash injury. *Pain*. 2006;122(1-2):102-108.
16. Sterling M. Differential development of sensory hypersensitivity and a measure of spinal cord hyperexcitability following whiplash injury. *Pain*. 2010;150(3):501-506.
17. Desmeules J, Cedraschi C, Rapiti E, et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis & Rheumatism*. 2003;48(5):1420-1429.

18. Lim EC , Sterling M, Stone A, et al. Central hyperexcitability as measured with nociceptive flexor reflex threshold in chronic musculoskeletal pain: A systematic review. *Pain*. 2011;152(8):1811-1820.
19. Chien A, Eliav E, Sterling M. Whiplash (grade II) and cervical radiculopathy share a similar sensory presentation: An investigation using quantitative sensory testing. *Clin J Pain*. 2008;24(7):595.
20. Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *The Journal of Pain*. 2009;10(6):556-572.
21. Chong PST, Cros DP. Technology literature review: Quantitative sensory testing. *Muscle Nerve*. 2004;29(5):734-747.
22. Weseley S, Sadler B, Katims J. Current perception: Preferred test for evaluation of peripheral nerve integrity. *ASAIO Journal*. 1988;34(3):188-193.
23. Baquis G, Brown W, Capell J, et al. AAEM Equipment and Computer Committee. Technology review: The neurometer® current perception threshold (CPT). *Muscle Nerve*. 1999;22:523-531.
24. U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health. Neurometer CPT. Available at, http://www.accessdata.fda.gov/cdrh_docs/pdf/K964622.pdf
25. Cano C, Ronald Dei Cas M, Ballantine L, Carino T. Decision Memorandum. 2003. Available@ <http://creedongill.com/nofaulttrial/CMS-on-CPT.pdf>
26. Botez SA, Herrmann DN. Pitfalls of diagnostic criteria for small fiber neuropathy. *Nature Clinical Practice Neurology*. 2008;4(11):586-587.
27. Yamashita T, Kanaya K, Sekine M, et al. A quantitative analysis of sensory function in lumbar radiculopathy using current perception threshold testing. *Spine*. 2002;27(14):1567-1570.
28. Liao MF, Lee M, Hsieh MJ, et al. Evaluation of the pathophysiology of classical trigeminal neuralgia by blink reflex study and current perception threshold testing. *The journal of headache and pain*. 2010;11(3):241-246.
29. Park R, Wallace MS, Schulteis G. Relative sensitivity to alfentanil and reliability of current perception threshold vs von frey tactile stimulation and thermal sensory testing. *Journal of the Peripheral Nervous System*. 2001;6(4):232-240.
30. Vernon H, Mior S. The Neck Disability Index: a study of reliability and validity. *J Manipulative Physiol Ther* 1991;14:409-415.

31. BenDebba M, Heller J, Ducker TB, et al. Cervical spine outcomes questionnaire: its development and psychometric properties. *Spine* 2002;27:2116-2123.
32. Skolasky RL, Riley LH, Albert TJ. Psychometric properties of the Cervical Spine Outcomes Questionnaire and its relationship to standard assessment tools used in spine research. *Spine J.* 2007;7:174-179.
33. MacDermid JC, Walton DM, Avery S, et al. Measurement properties of the neck disability index: A systematic review. *J Orthop Sports Phys Ther.* 2009;39(5):400-417.
34. Shrout PE, Fleiss JL. Intraclass correlations: Uses in assessing rater reliability. *Psychol Bull.* 1979;86(2):420-408.
35. Bland JM, Altman DG: Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986, 1:307-311.
36. Bland JM, Altman DG. Statistical methods for assessing agreement between measurements. *Biochem Clin.* 1987;11:399-404.
37. Mantha S, Roizen MF, Fleisher LA, Thisted R, Foss J. Comparing methods of clinical measurement: Reporting standards for bland and altman analysis. *Anesthesia & Analgesia.* 2000;90(3):593-602.
38. Fleiss JL: *The Design and Analysis of Clinical Experiments.* New York, Wiley; 1986.
39. Cohen J. *Statistical power analysis for the behavioral sciences.* Lawrence Erlbaum; 1988.
40. Chien A, Eliav E, Sterling M. Hypoaesthesia occurs with sensory hypersensitivity in chronic whiplash—further evidence of a neuropathic condition. *Man Ther.* 2009;14(2):138-146.
41. Chien A, Eliav E, Sterling M. Hypoesthesia occurs in acute whiplash irrespective of pain and disability levels and the presence of sensory hypersensitivity. *Clin J Pain.* 2008;24(9):759-766.
42. Chien A, Sterling M. Sensory hypoaesthesia is a feature of chronic whiplash but not chronic idiopathic neck pain. *Man Ther.* 2010;15(1):48-53.
43. Voerman VF, van Egmond J, Crul BJP. Normal values for sensory thresholds in the cervical dermatomes: A critical note on the use of semmes-weinstein Monofilaments. *American journal of physical medicine & rehabilitation.* 1999;78(1):24-29.
44. Grunert BK, Wertsch JJ, Matloub HS, et al. Reliability of sensory threshold measurement using a digital vibrogram. *J Occup Med.* 1990, 32: 100-102.
45. MacDermid J, Kramer J, McFarlane R, et al. Inter-rater agreement and accuracy of clinical tests used in diagnosis of carpal tunnel syndrome. *Work.* 1997;8(1):37-44.

46. Hubbard MC, MacDermid JC, Kramer JF, et al. Quantitative vibration threshold testing in carpal tunnel syndrome: analysis strategies for optimizing reliability. *J Hand Ther.* 2004, 17: 24-30.
47. Novak CB, Mackinnon SE, Williams JI, et al. Establishment of reliability in the evaluation of hand sensibility. *Plast Reconstr Surg.* 1993, 92: 311-322.
48. MacDermid JC, Kramer JF, Roth JH. Decision making in detecting abnormal semmes-weinstein monofilament thresholds in carpal tunnel syndrome. *J Hand Ther.* 1994;7(3):158-162.

TABLES

Table 1. Participants Demographics (N=106)

Variable	Characteristic
Age (in year)	Mean = 45.43 (SD=11.88), min-max=19-74
Gender	Female = 86, Male = 20
Duration of Pain (in months)	Mean = 24.67 (SD=21.43)
2-3 months	5.26%
3 –12 months	10.53%
Over 12 months	84.21%
NDI score	Mean = 32.77 (SD = 18.42)
CSOQ score	Mean = 38.72 (SD = 14.92)
Dominant Side	Right = 81.4%, Left = 18.6%
Affected	Unilateral = 49.1%, Bilateral = 50.9%
First affected side	Right = 55.7%, Left = 44.3%
Second affected side	Right = 20.8%, Left = 32%, Neither = 47.2%
Unaffected side	Right =24.5%, Left =22.7%, Neither= 52.8%

Legend: NDI= Neck Disability Index (in %) out of 50; CSOQ = Cervical Spine Outcome Questionnaire (out of 100); SD = standard deviation; N = number of participants

Table 2. Inter-trial reliability of CPT test frequencies in three digits, at $p < 0.001$, $N = 106$

<i>Frequency</i>	<i>Side Tested</i>	<i>ICC</i>	<i>95% CI</i>
CPT 2000Hz	The most affected	0.78	0.69-0.85
	Second affected	0.81	0.70-0.86
	Unaffected	0.79	0.66-0.88
CPT 250 Hz	The most affected	0.73	0.62-0.82
	Second affected	0.82	0.71-0.90
	Unaffected	0.80	0.66-0.88
CPT 5 Hz	The most affected	0.80	0.71-0.87
	Second affected	0.78	0.63-0.87
	Unaffected	0.81	0.69-0.89

Legend: ICC = Intraclass Correlation Coefficient (Bold > 0.75 = excellent); CI = Confidence Interval (lower-upper); N = number of participants. Both hands were tested ($N = 106$, there was 7 missing values). Data from hands were organized according to the most affected hand ($N = 99$) and either a second affected hand ($N = 53$) in people with bilateral symptoms or as unaffected hand ($N = 46$) where symptoms were unilateral.

Table 3. Test-Retest Reliability of CPT test score in the most affected side ($N = 34$), $p < 0.001$

<i>Test Frequency</i>	<i>ICC (95% CI)</i>		
	<i>D1</i>	<i>D3</i>	<i>D5</i>
2000Hz	0.73 (0.45-0.87)	0.47 (0.07-0.73)	0.78 (0.56-0.89)
250Hz	0.55 (0.08-0.78)	0.66 (0.33-0.83)	0.81 (0.61-0.90)
5Hz	0.73 (0.45-0.87)	0.74 (0.49-0.87)	0.86 (0.71-0.93)

Legend: D1 = digit 1 (thumb); D3 = digit 3 (middle); D5 = digit 5 (little); ICC = Intraclass Correlation Coefficient (bold values exceed 0.75 indicate excellent level); CI = Confidence Interval (lower-upper); N = number of participants.

Table 4. Correlation of CPT (in affected hand) with NDI and CSOQ, N=106

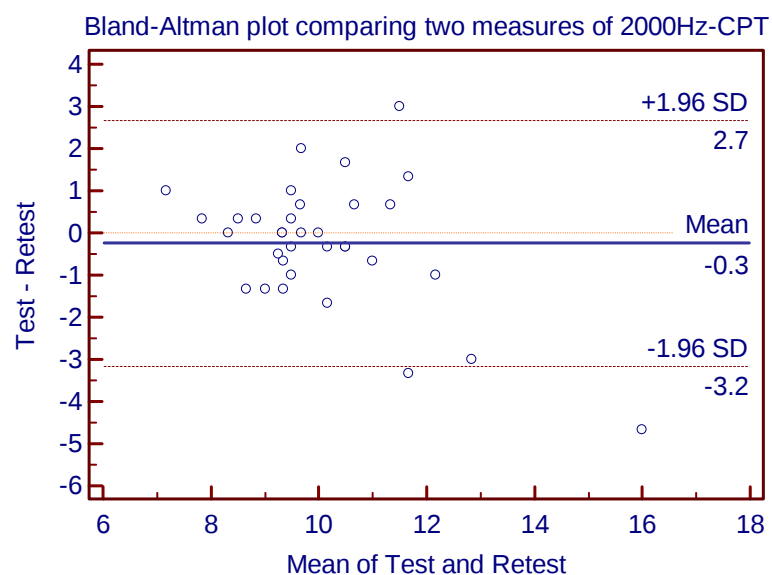
CPT	Test area	NDI	Pain intensity of NDI	CSOQ	Pain severity of CSOQ
2000Hz	D1	0.28**	0.35**	0.29**	0.26*
	D3	-	0.28**	-	0.24*
	D5	-	-	-	-
250Hz	D1	0.29**	0.37**	0.35**	0.28*
	D3	-	0.26*	-	-
	D5	-	-	-	-
5Hz	D1	-	0.25*	0.26*	-
	D3	-	-	-	-
	D5	-	-	-	-

**Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed). Non-significant correlations are removed [blank (-) spaces]. D1 = digit 1 (thumb); D3 = digit 3 (middle); D5 = digit 5 (little); NDI= Neck Disability Index; COSQ = Cervical Spine Outcomes Questionnaire. The correlations >0.30 are bolded.

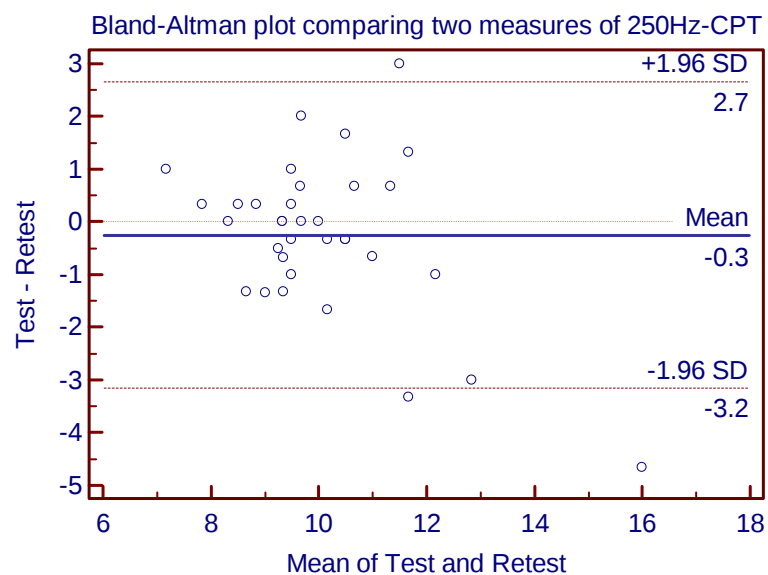
FIGURES



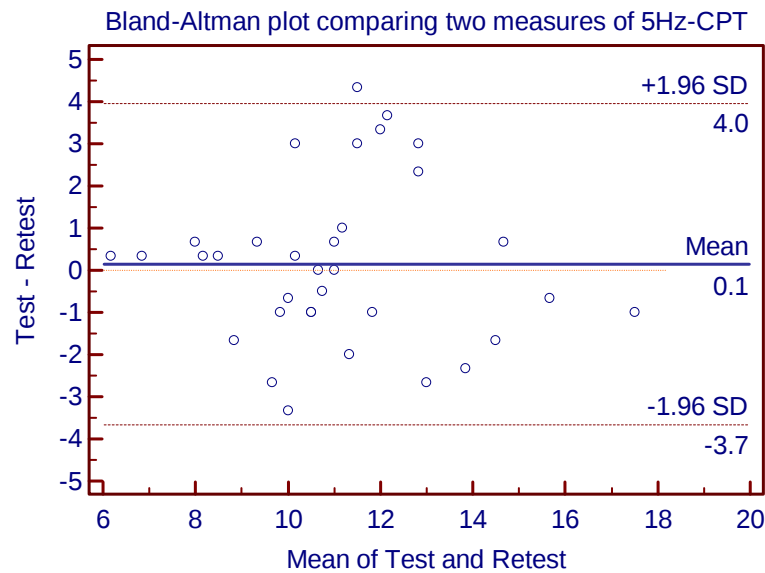
Figure 1. Set-up of the current perception threshold (CPT) test procedure. The Rapid-CPT values (1 to 25) obtained from the minimal strength of alternating current (between 0 to 10 mA) stimulus that the patient could detect.



(2a) The difference plot shows limit of agreement between two tests of CPT at 2000Hz.



(2b) The difference plot shows limit of agreement between two tests of CPT at 250Hz.



(2c) The difference plot shows limit of agreement between two tests of CPT at 5Hz.

Figure 2_{a,b,c}. Bland-Altman plot compared limit of agreement between two measurements (test-retest) of CPT in the most affected hand (N = 34): 2000Hz (a), 250Hz (b), 5Hz (c). The differences between test and retest are drawn against the mean of test and retest in the 34 paired measurements. The line defining the mean difference between test and retest measures (middle solid line) is minimally offset when compared with no error line (middle dotted line at zero level). The large dashed lines define the limits of agreement which are ± 1.96 standard deviations around the mean difference. Every small circle (N=34) represents one participant.

CHAPTER 3: Study 2

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The Current Perception Threshold Test Differentiates Categories of Mechanical Neck Disorder

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Conflict of Interests: We, the authors of the manuscript, do not have a direct/indirect financial relation with the commercial/non-commercial identities mentioned in the paper that might lead to a conflict of interests.

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Abstract

Study Design: Cross-sectional discriminative analysis.

Objective: To determine whether current perception threshold (CPT) can differentiate between categories of patients with mechanical neck disorders (MNDs).

Background: Neck pain is the third most common musculoskeletal disorder, affecting a third of all adults each year. It can present as neck pain without musculoskeletal signs; neck pain with musculoskeletal signs but no neurological signs; neck pain with neurological signs. CPT testing can assess altered sensory perception that may reflect neurological changes.

Methods: Patients with MNDs (n=106) were classified into 3 groups based on a standardized musculoskeletal examination process performed by an experienced physiotherapist blinded to CPT scores. The 3 groups were defined as: MND-I, neck pain without musculoskeletal signs (n=60); MND-II, neck pain with musculoskeletal signs (n=29); MND-III, neck pain with neurological signs (n=17). A rapid protocol of CPT testing was performed at 3 frequencies (5, 250, 2000 Hz), using 3 dermatomal locations on the hand. A 1-way ANOVA with post hoc comparison and effect sizes were calculated to compare the mean CPT score between the groups. A binary logistic regression model was used to predict probability of higher CPT in MND-III and used to create a receiver operating characteristic (ROC) curve.

Results: Mean CPT differed significantly across the 3 MND groups (MND-I, 9.7; MND-II, 10.6; and MND-III, 11.8; $P < .001$, $\eta^2 = .6$). Post hoc comparisons indicated differences between MND-I and MND-II ($P = .05$) and between MND-II and MND-III ($P = .01$), that were large effect sizes (MND I versus II, $d = 1$ and MND II versus III, $d = 2.2$). CPT testing was able to distinguish between MND II and III when a threshold value of greater than 11 was used to indicate MND-III. The predicted probability of abnormal CPT in MND-III had an estimated 73% sensitivity and 81% specificity; the odds ratio was 11.5 ($P = .001$) for the differentiation capacity of CPT between MND-II and III with a cut-off of 11. The area under the ROC curve (AUC) was .84 (95% CI = .72 to .96, $P < .001$).

Conclusions: CPT testing has moderate discriminatory accuracy, specificity, and sensitivity for classification of MND categories into neck pain with or without neurological signs.

Key words: Cervical spine, Hypersensitivity, Neck Pain Categories, Neurological sign

Introduction

Neck pain is a common musculoskeletal disorder,^{1-3,10,16,21,48} with a yearly prevalence estimated at roughly 30- 50% in the general population.^{5,11,15,20-22} Almost everyone experiences neck pain at some point in their lifetime.²¹ Neck pain has a large financial impact across a number of industrial countries.¹⁶ Neck pain is characterized by episodes of exacerbation and recovery,^{10,11} although the factors that control the frequency and intensity of these episodes are not well understood. Most individuals are labeled as having non-specific neck pain as it is often difficult to detect any systemic disease or specific etiology responsible for the pain.² This group of patients, assumed to have neuromuscular or articular dysfunction, are perceived to have mechanical neck disorders (MNDs).² MNDs can arise due to any dysfunction, degeneration, and injury to the neck; and is sometimes classified based on whether there are neurological signs or symptoms. Patients with neck disorders may have coexistent signs of neural involvement, including pain radiating down the arms and weakness or numbness in the upper extremity.^{1,36,51}

There is no definitive diagnostic procedure for MND.^{21,43} MND assessment is further challenged by a lack of standard classification. Multiple features could be considered in the description of MND including anatomical location of symptoms, etiology, clinical characteristics, severity of symptoms, duration of symptoms, history, physical findings, and functional movement patterns. In 1987, the Quebec Task Force (QTF) on Spinal Disorders classification⁴⁰ defined 4-subgroups of MND based on the anatomic distribution of pain and neurological symptoms. This classification differs from that described in 1995 by the QTF for Whiplash Associated Disorders⁵⁴ and the clinical classification from the Neck Pain Task

Force.^{21,43} The validity of these classifications has been questioned,¹⁷ but they remain commonly used. There is evidence that the QTF classification levels have moderate discriminative and predictive validity.³² Because sensory dysfunction suggests neurological involvement, the extent to which different sensory tests can facilitate separation of discrete categories of MND is an aspect of their discriminative validity. Sensory evaluation might support classification, particularly to help differentiate MND-II and MND-III (**TABLE 1**) in a complex clinical situation.

Neurological signs and symptoms may be a more salient feature of neck disorders than degenerative changes or radiological findings.^{21,46,47,59} The most common neurological finding is sensibility disturbance as motor changes are uncommon.^{1,8,14,24,46,47,59} Evidence suggests that poor recovery in musculoskeletal pain, and especially neck disorders,⁵⁵⁻⁵⁷ is associated with widespread sensory hypersensitivity (central hyper-excitability).^{12,18,19,30,55,61,62} Generalized sensory hypoesthesia (hyposensitivity) and hyperesthesia (hypersensitivity) are a common feature in chronic neck disorder.⁷ Therefore, sensory evaluation can be used for diagnosis, prognosis, and outcome evaluation in neck pain. The relationships between mechanism, symptoms, diagnosis, and functional limitations are not yet clearly established in neck disorders.^{13,23,28,31,34,46,53} Recent evidence suggest that sensory findings are prognostic.^{56,57} It is apparent that there is a need for studies that evaluate the measurement properties of different sensory tests.

Quantitative sensory testing (QST) consists of applying a controlled sensory stimulus while evaluating how a person interprets that stimulus. The interpretation can focus on 5

elements: 1) the minimum stimulus perceived, 2) localization, 3) threshold at which the stimulus is perceived or perceived as painful, 4) tolerance, and 5) differentiation of different sensory inputs. For example, pain hypersensitivity can be detected by threshold tests that assess the least amount of sensory input required for detection, or experienced as pain. By selecting different sensory inputs in QST, it is possible to evaluate the sensory processing of both large and small afferent nerve fibres. Moreover, QST can be used to measure both hypoesthesia and hyperesthesia in each case as an abnormality of sensory function. Mapping of the anatomical distribution of sensory changes (eg, hypoesthesia) has been suggested as a means of identifying the source of the pathological dysfunction.⁶⁹ Clinical uses of QST in orthopaedic physical therapy practice are already suggested.⁶⁸

The current perception threshold (CPT) test is a neuroselective QST technique, where 3 different impulse frequencies (5 Hz, 250 Hz, and 2000 Hz) are used to determine the patient's ability to detect a controlled electrical stimulus and where frequencies are thought to preferentially assess 3 types of sensory nerve fibers (C-fiber, A δ -fiber, A β -fiber). The CPT test has been used successfully as a reliable and valid assessment in different clinical studies for sensory evaluation.^{25,29,37,38,39,41,44,49,50,52,63} The CPT test has been reported consistent across occasions (ICC for intertrial reliability = .73-.82 and test-retest reliability = .47-.86, $P < 0.001$) in patient with neck disorder, and the test threshold was associated with neck disability.⁶⁷ However, there is no study evaluating its ability to discriminate subgroups of neck pain. Therefore, the aim of this study was to evaluate the extent to which CPT can differentiate MND categories. Specific objectives were to estimate the following in subgroups of patients with MND II versus MND III:

(1) the difference in absolute scores (and associated effect sizes); and (2) the CPT scores that best differentiated these subgroups.

METHODS

Participants

Individuals seeking care for neck pain were recruited from local physiotherapy clinics. The standardized examination procedure diagram for patients' recruitment is in **APPENDIX 1**. This study was approved by the McMaster University Research Ethics Board, and informed consent was obtained from all participants prior to testing. All patients (n = 106) underwent a standardized physical examination to establish that neck pain was related to mechanical dysfunction and to determine whether neurological features were present. The musculoskeletal examination process was performed by an experienced orthopaedic manual physical therapist with more than 10 years of experience in evaluation of neck disorders.

Inclusion in the study was based on the presence of neck pain, stiffness, or tenderness. Exclusion criteria were: less than 18 years of age, neck disorders with definite or possible long tract signs, headache not of cervical origin (eg, migraine, tension-type headache), neck injuries with fracture or dislocation, spinal surgery in the previous year, diffuse connective tissue disease (eg, rheumatoid arthritis), arthritis associated with spondylitis, rheumatic syndromes (eg, infection, metabolic, or endocrine disease), systematic failure (eg, polymyalgia, fibromyalgia, fatigue syndrome), any damage to nerves of the elbow or wrist, upper quadrant loss (amputation), neurological disease, stroke, diabetes, prolonged steroid use (greater than 3 months), or if patients had conditions that precluded performing the test procedures.

Study design

A standardized neurological scan was performed (**APPENDIX**) and included examination of deep tendon reflexes (C5-biceps, C6-brachioradialis, and C7/8-triceps), myotomal weakness (C1 to T1), and dermatomal sensory light touch function (C1 to T1). Neural tension provocation test (Elvey's test for upper limb) and joint play tests for cervical spine (Spurling test, axial loading test), and Hoffmann reflex test were performed. The examination was performed prior to CPT testing. The CPT evaluation was performed by an examiner blinded to the neurological examination results. Patients were assigned to 1 of 3 groups (MND-I, MND-II, and MND-III) based as indicated in **TABLE 1**. Participant's characteristics and demographics are described in **TABLE 2**.

CPT and outcome measures

CPT testing was performed using the Rapid protocol of the Neurometer CPT/C (Neurotron, Incorporated; Baltimore, MD, USA). All CPT tests were performed in a quiet room with the temperature between 22°C and 25°C. Patients were seated in a comfortable chair with armrests and a back support. Standardized instructions were provided and procedures were explained, including 2 practice trials, at the beginning of the test.

The Rapid protocol of the CPT (R-CPT) required the participant to self-administer electrical stimuli, increasing in intensity through a series of 25 predetermined levels. The participant pressed and held a button to start the test and released the button as soon as a stimulus could be detected. Neither examiner nor participants were able to see scores until testing was

completed. The non-noxious stimulus was delivered via small surface electrodes placed on the medial and lateral sides of the distal phalanx (**FIGURE 1**) of 3 fingers (thumb=D1, middle finger=D3, and little finger=D5) of the most affected hand to target 3 different nerve roots (C6, C7, and C8, respectively). The R-CPT values (numerical score ranging between 1 and 25) are obtained from the minimal intensity of alternating current (between 0 and 10 mA) that the patient could detect. The testing was repeated at 3 current frequencies (2000 Hz, 250 Hz, and 5 Hz) in a random order. Hence, in total 9 CPT tests were performed, 3 fingers and 3 frequencies per finger, on the hand of the most affected side.

Data Analysis

Descriptive analyses of variables were performed to verify the quality of data and normality testing (eg, Kolmogorov-Smirnov, Shapiro-Wilk, QQ-Plot) was completed prior to performing analytical statistical tests. All statistics were performed on SPSS 17.0 software package (SPSS Inc., Chicago, IL). The threshold for significance was set at 0.05. A 1-way ANOVA with post hoc (Tukey's HSD) comparisons was done to compare the mean CPT score (for individual frequency and combination of 3 types of frequency) between the 3 groups of MND. The effect size was estimated to describe the differences between groups. As a preliminary step, we looked at the significance of each of the 3 CPT frequencies as predictor, and then formed a composite CPT score.

A multiple regression analysis evaluated the influence of suspected covariates (eg, age, gender, and pain duration) on the CPT test in the most affected hand. In the discriminative analysis, the dependent variable was MND categories (MND-II and MND-III) and the results of

the 9 CPT tests were used as the predictor variables for membership in 1 of the categories. We used a binary logistic regression model (**FIGURE 2**) to predict the probability of MND-III; where CPT was the dependent variable and MND categories were the binary covariate (0,1). Goodness of Fit Testing (**FIGURE 2**) was performed to check the quality of the model. After forming a composite CPT score, a new variable (predicted probability) was created when the logistic regression was performed. The predicted probability was used as the test variable and CPT score greater than 11 as the state variable (where the value of state variable = 1). Finally, a Receiver Operating Characteristic (ROC) curve was created from predicted probability (test variable) using the binary covariate (state variable).

RESULTS

Mean CPT differed significantly across the 3 MND groups (MND-I, 9.7; MND-II, 10.6; and MND-III, 11.8; $P < .001$, $\eta^2 = .6$) [**TABLE 3**]. The univariate discriminator was best at 2000 Hz for MND-I versus II ($P = .001$) and at 250 Hz for MND-II versus III ($P = .03$). The composite score discriminator was significant between the 3 groups: MND-I versus MND-II ($P = .05$) and MND-II versus MND-III ($P = .01$). Post hoc comparisons were significant between MND-I and MND-II ($P = .05$) and between MND-II and MND-III ($P = .01$) [**TABLE 4**]. Large effect sizes were observed in CPT threshold between MND groups (MND-I versus MND-II, Cohen's $d = 1$ and MND-II versus MND-III, $d = 2.2$). CPT was discriminative and differentiated between the subgroups (**FIGURE 3**). The 3 covariates (age, gender, and duration of pain) were not significant predictors of CPT scores. The CPT score from the middle finger at 250 Hz was the strongest predictor of neurological signs in our discriminative model ($OR = 3$, $\beta = 1.1$, $P =$

.03). The binary logistic regression model, where CPT > 11 was used as the cut-off point, predicted the probability of neurological sign with an estimated 73% sensitivity and 81% specificity. The odds ratio was 11.5 ($P = .001$) for the differentiation capacity of CPT between MND-II and MND-III at this cut-point (**TABLE 5**). The area under the ROC curve (AUC) was .84 (95% CI = .72 to .96, $P < .001$, **FIGURE 4**).

DISCUSSION

We found that CPT testing can distinguish between subgroups of patients with neck pain classified by an experienced orthopaedic physiotherapist as having some neurological involvement (MND-III) versus those who did not (MND-II). Moderate specificity and sensitivity for classification of MND categories (II versus III) was demonstrated when a cut-off score of 11 was used on the CPT rapid test.

CPT was able to differentiate sensory hypoesthesia in this sample of patients with chronic neck disorders. CPT is a sensory threshold test that uses different current frequencies. It is less objective than electrodiagnostic methods like nerve conduction and EMG. However, it does provide an assessment of both large (touch/vibration) and small (pain) sensory nerve fibers. CPT tests use electrical stimuli that target nerve fibers directly whereas other quantitative threshold tests target receptors for sensory modalities like vibration or temperature. The discriminative ability of CPT suggests that it has value in diagnosis or prognosis. However, because the study did not compare different sensory test modalities, it cannot suggest which of the available sensory test tools is optimal.

Given that we found moderate discriminative ability for CPT, one might question whether this could be improved. We used the Rapid-CPT protocol which is performed by increasing the stimulus until the patient perceives the stimulus; versus the full protocol that involves a repeated forced choice protocol. While the rapid test is more feasible for screening, it may have more random error that would interfere with accurate discrimination and increase the minimal detectable change. Thus, clinically, therapists might wish to switch to the forced choice protocol for evaluation if screening is positive and sensory status is being used to indicate treatment response over time. Previous studies suggest that data from sensory testing tend to be more unstable than tests of motor function,³³ so a moderate amount of random error may be inherent to sensory evaluation. Sensory perception testing requires that patients attend to the stimulus and so proper technique including stabilization of the body part being tested and avoidance of other sensory inputs from either the examiner or the environment are required to mitigate sources of error. Patients in this study were tested in a quiet environment; however, more rigorous controls could be investigated as a means of improving focus during tests eg, the use of ear plugs and blindfolds to decrease environmental distractors.

A recent study ranked the parameters of pain sensitivity according to discriminative ability in individuals with chronic low back pain and found a single electrical stimulus based test best at targeting C-fibers pain threshold and neuropathic pain (AUC=0.87).⁴² Our study is consistent with those findings as CPT includes a C-fiber targeting electrical stimulus (ie, CPT of 5 Hz). CPT can detect small fiber neuropathies,⁴ but differs from nerve conduction velocity tests. Nerve conduction velocity is independent of patient's conscious efforts and decisions; whereas CPT is dependent on patient comprehension and choices. However, the CPT method has been

used to evaluate peripheral sensory dysfunction,^{25,37,38,49,52} and successfully applied in many clinical studies.^{6,26,27,39,41,44,50}

Despite emerging literature about the usefulness of CPT, there are limitations. For example, hyperesthetic, normative, and hypoesthetic values of Rapid-CPT are not yet well-established, and the test threshold values can vary according to the location of the test. In spite of this, previous studies suggest a diagnostic or sensory evaluative role for CPT test to detect neural sensitivity (hyper and/or hypo) in different pathological conditions.^{27,29,39,41,44,45,50,63} To exemplify this, CPT evaluation has been used to assess lumbar radiculopathy,⁶³ trigeminal neuralgia,²⁹ complex regional pain syndrome,⁵⁰ small fiber neuropathies (eg, diabetic foot),⁴¹ orthognathic (jaw/maxillofacial) surgeries,⁴⁴ vulvodynia,³⁹ and skin irritation conditions.²⁷ In this study, we added to the body of knowledge on CPT by establishing that CPT is discriminative in MND. It may provide a semi-objective method of examining sensation as a mean of recognizing potential changes in the nociceptive pathways or help explain clinical examination findings. The CPT test is one method to classify MND in a similar way as a more complex clinical decision made by a clinician. Our results are also consistent with a recent study that indicated distinct somatosensory profiles (QST sensory profile evaluation) in patients with nonspecific neck-arm pain versus cervical radiculopathy despite having common pain characteristics.⁵⁸

The optimal CPT protocols for patients with MND were not determined by this study and defining clear criteria can be difficult, because the nature of the sensory symptoms reported in cervical pathology could be diffuse. We found that the 250 Hz test (which has the capacity to assess thin myelinated A δ -fiber/pain fiber) for the middle finger assessment (which targets the

C7 nerve root and dermatome) was the strongest predictor of MND-III. The 2 most common levels affected in the cervical spine are C5-C6 and C6-C7 affecting the C6 and C7 dermatomes.⁶⁴ The C7 dermatome tends to centre on the middle finger and extends along the back of the arm. However, dermatomes are not discrete and their distribution varies across individuals.⁶⁵ In a rat model it has been demonstrated that C7 contributes 6% to the ulnar nerve, 16% to the radial nerve, and 19% to the median nerve.⁶⁶ Because the 3 peripheral nerve branches in the hand have a derivation at the C7 root, they all may contribute to the overall sensory function in the hand. Normal dermatomal values have not been clearly established for CPT in neck pain; although normal touch thresholds have been reported to be higher in dermatomes than values established for fingertips.⁶⁰ Ideally, there would be clear rules for a clinician to establish whether a sensory examination is normal in neck pain, but there are multiple factors that can potentially affect the results. More complicated decision rules for QST tend to increase interrater disagreements on whether sensibility is “normal”.³⁵ For all these reasons, establishing clear rules on normal or abnormal values requires further study.

Age was not a significant covariate in this study which contradicts the results of a previous study on CPT testing in the hand.⁹ The role of different covariates that affect normal sensory thresholds and how it varies across different instruments and procedures would need to be evaluated to ascertain the optimal test methods. It is virtually impossible to evaluate these multiple issues within a single study, because of the response burden that would be required. Therefore multiple studies, followed by systematic reviews will be needed to determine how sensory assessments should be best implemented in clinical practice. In 2009, the Neck Pain Task Force⁴³ did not recommend the use of QST for neck pain assessment, but they included

neurological signs in Grade-III (category-3) in their new classification. This suggests a need for stronger evidence on sensory evaluation in neck patients is needed.

Our results are preliminary and should be considered in light of the limitations. First, as we focused on a single sensory examination approach we cannot say how CPT compares to other sensory modalities. We could not explore all CPT test options and those we selected were not necessarily optimal for screening. Second, our sample size of MND-III was small for ROC analysis and thus the AUC may be imprecise. Third, the testing site (finger tips), may not be appropriate for neck pain evaluation, because it may not capture all sensory deficits in the dermatome. Finally, the referent diagnostic examination cannot be considered a gold standard for subtypes of neck pain. We used a standardized examination and experienced manual therapists to optimize the reliability and validity, but these are subject to rater differences.

CPT is able to differentiate (screen) for neural involvement in neck pain, but is not being proposed as a replacement for a thorough clinical examination such as the one we used to assign subtypes of neck pain in this study. These examinations commonly use light touch as one component of the examination process. CPT does have a cost that is greater than other sensory screening tools currently used by physical therapists including Semmes Weinstein Monofilaments (moderate cost),^{34,74} or ice-water immersion test (low cost)^{71,72} or the ten test (no cost).^{72,73} Head to head comparisons of these tests as screening, diagnostic, or evaluative tools will be needed to determine which tools are best for different practice and research applications.

CONCLUSION

CPT demonstrates moderate discriminative validity in differentiating 3 subgroups of MND. It may play a role in establishing different prognostic or diagnostic subgroups and specifically in assessing prognosis or mechanistic studies that target neurological focused therapy interventions. Longitudinal prospective studies with a large cohort of patients are required to justify the prognostic and evaluative properties of different sensory modalities; and to compare different sensory modalities, assessment protocols, indicators, and decision rules.

KEY POINTS

Findings: CPT testing can differentiate MND categories with moderate discriminatory power.

Implication: CPT might be useful for screening to classify patients with neck pain into clinically relevant subgroups.

Caution: This study is subject to imprecision based on a relatively small sample and the lack of certainty about optimal methods for testing sensory dysfunction.

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REFERENCES

1. Abdulkarim J, Dhingra R, L Finlay D. Magnetic resonance imaging of the cervical spine: Frequency of degenerative changes in the intervertebral disc with relation to age. *Clin Radiol*. 2003;58(12):980-984.

2. Borghouts JA, Koes BW, Bouter LM. The clinical course and prognostic factors of non-specific neck pain: A systematic review. *Pain*. 1998;77(1):1-13.
3. Bot S, Van der Waal J, Terwee C, et al. Incidence and prevalence of complaints of the neck and upper extremity in general practice. *Ann Rheum Dis*. 2005;64(1):118-123.
4. Botez SA, Herrmann DN. Pitfalls of diagnostic criteria for small fiber neuropathy. *Nature Clinical Practice Neurology*. 2008;4(11):586-587.
5. Bovim G, Schrader H, Sand T. Neck pain in the general population. *Spine*. 1994;19(12):1307-1309.
6. Carley D, Lior L, Elizabeth M, Linda B, Kimberly K. Measuring urinary sensation with current perception threshold: A comparison between method of limits and method of levels. *Obstet Gynecol Int*. 2012: 868915.
7. Chien A, Eliav E, Sterling M. Whiplash (grade II) and cervical radiculopathy share a similar sensory presentation: An investigation using quantitative sensory testing. *Clin J Pain*. 2008;24(7):595-603.
8. Coggon D, Cyrus Cooper D. Prevalence and occupational associations of neck pain in the british population. *Scand J Work Environ Health*. 2001;27(1):49-56.
9. Costantini M, Tunks K, Wyatt C, Zettel H, MacDermid JC. Age and upper limb tension testing affects current perception thresholds. *Journal of Hand Therapy*. 2006;19(3):307-317.
10. Côté P, Cassidy JD, Carroll L. The saskatchewan health and back pain survey: The prevalence of neck pain and related disability in saskatchewan adults. *Spine*. 1998;23(15):1689-1698.
11. Côté P, Cassidy JD, Carroll LJ, Kristman V. The annual incidence and course of neck pain in the general population: A population-based cohort study. *Pain*. 2004;112(3):267-273.
12. Desmeules J, Cedraschi C, Rapiti E, et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis & Rheumatism*. 2003;48(5):1420-1429.
13. Di Fabio R, Boissonnault W. Physical therapy and health-related outcomes for patients with common orthopaedic diagnoses. *J Orthop Sports Phys Ther*. 1998;27(3):219-230.
14. Fagerlund M, Björnebrink J, Pettersson K, Hildingsson C. MRI in acute phase of whiplash injury. *Eur Radiol*. 1995;5(3):297-301.
15. Fejer R, Kyvik KO, Hartvigsen J. The prevalence of neck pain in the world population: A systematic critical review of the literature. *European spine journal*. 2006;15(6):834-848.

16. Ferrari R, Russell AS. Neck pain. *Best Practice & Research Clinical Rheumatology*. 2003;17(1):57-70.
17. Freeman MD, Croft AC, Rossignol AM. "Whiplash associated disorders: Redefining whiplash and its management" by the quebec task force: A critical evaluation. *Spine*. 1998;23(9):1043.
18. Greening J, Lynn B. Vibration sense in the upper limb in patients with repetitive strain injury and a group of at-risk office workers. *Int Arch Occup Environ Health*. 1998;71(1):29-34.
19. Greening J, Lynn B, Leary R. Sensory and autonomic function in the hands of patients with non-specific arm pain (NSAP) and asymptomatic office workers. *Pain*. 2003;104(1):275-281.
20. Guez M, Hildingsson C, Nilsson M, Toolanen G. The prevalence of neck pain. *Acta Orthopaedica*. 2002;73(4):455-459.
21. Haldeman S, Carroll L, Cassidy JD, Schubert J, Nygren Å. The bone and joint decade 2000–2010 task force on neck pain and its associated disorders. *European Spine Journal*. 2008;17:5-7.
22. Hogg-Johnson S, van der Velde G, Carroll LJ, et al. The burden and determinants of neck pain in the general population. *European Spine Journal*. 2008;17:39-51.
23. Hunter J. Physical symptoms and signs and chronic pain. *Clin J Pain*. 2001;17(4):S26.
24. Karlsborg M, Smed A, Jespersen H, et al. A prospective study of 39 patients with whiplash injury. *Acta Neurol Scand*. 1997;95(2):65-72.
25. Katims JJ, Rouvelas P, Sadler BT, Weseley SA. Current perception threshold: Reproducibility and comparison with nerve conduction in evaluation of carpal tunnel syndrome. *ASAIO Journal*. 1989;35(3):280-284.
26. Kim SJ, Lim SU, Won YH, et al. The perception threshold measurement can be a useful tool for evaluation of sensitive skin. *Int J Cosmetic Sci*. 2008;30(5):333-337.
27. Lee E, An S, Lee TR, Kim HK. Development of a novel method for quantitative evaluation of sensory skin irritation inhibitors. *Skin Research and Technology*. 2009;15(4):464-469.
28. Lee H, Nicholson LL, Adams RD. Neck muscle endurance, self-report, and range of motion data from subjects with treated and untreated neck pain. *J Manipulative Physiol Ther*. 2005;28(1):25-32.
29. Liao MF, Lee M, Hsieh MJ, et al. Evaluation of the pathophysiology of classical trigeminal neuralgia by blink reflex study and current perception threshold testing. *The journal of headache and pain*. 2010;11(3):241-246.

30. Lim EC, Sterling M, Stone A, Vicenzino B. Central hyperexcitability as measured with nociceptive flexor reflex threshold in chronic musculoskeletal pain: A systematic review. *Pain*. 2011;152(8):1811-1820.
31. Ljungquist T, Jensen IB, Nygren A, Harms-Ringdahl K. Physical performance tests for people with long-term spinal pain: Aspects of construct validity. *J Rehabil Med*. 2003;35(2):69-75.
32. Loisel P, Vachon B, Lemaire J, et al. Discriminative and predictive validity assessment of the quebec task force classification. *Spine*. 2002;27(8):851.
33. MacDermid J, Kramer J, McFarlane R, Roth J. Inter-rater agreement and accuracy of clinical tests used in diagnosis of carpal tunnel syndrome. *Work*. 1997;8(1):37-44.
34. MacDermid JC, Gross AR, Galea V, McLaughlin LM, Parkinson WL, Woodhouse L. Developing biologically-based assessment tools for physical therapy management of neck pain. *J Orthop Sports Phys Ther*. 2009;39(5):388-399.
35. MacDermid JC, Kramer JF, Roth JH. Decision making in detecting abnormal semmes-weinstein monofilament thresholds in carpal tunnel syndrome. *J Hand Ther*. 1994;7(3):158-162.
36. Walton DM, Macdermid JC, Nielson W, Teasell RW, Nailer T, Maheu P. A descriptive study of pressure pain threshold at 2 standardized sites in people with acute or subacute neck pain. *J Orthop Sports Phys Ther*. 2011;41(9):651-657.
37. Masson E, Boulton A. The neurometer: Validation and comparison with conventional tests for diabetic neuropathy. *Diabetic Med*. 1991;8(S2):S63-S66.
38. Masson E, Veves A, Fernando D, Boulton AJM. Current perception thresholds: A new, quick, and reproducible method for the assessment of peripheral neuropathy in diabetes mellitus. *Diabetologia*. 1989;32(10):724-728.
39. Murina F, Bianco V, Radici G, Felice R, Signaroldi M. Electrodiagnostic functional sensory evaluation of patients with generalized vulvodynia: A pilot study. *Journal of lower genital tract disease*. 2010;14(3):221-224.
40. Nachemson A, Spitzer W, LeBlanc F. Scientific approach to the assessment and management of activity-related spinal disorders. A monograph for clinicians. report of the quebec task force on spinal disorders. *Spine*. 1987;12(Suppl 7):S1-S59.
41. Nather A, Keng Lin W, Aziz Z, Ong CHJ, Feng B, Lin CB. Assessment of sensory neuropathy in patients with diabetic foot problems. *Diabetic Foot & Ankle*. 2011; 2: 10.3402/dfa.v2i0.6367.

42. Neziri AY, Curatolo M, Limacher A, et al. Ranking of parameters of pain hypersensitivity according to their discriminative ability in chronic low back pain. *Pain*. 2012 ;153(10):2083-2091.
43. Nordin M, Carragee EJ, Hogg-Johnson S, et al. Assessment of neck pain and its associated disorders:: Results of the bone and joint decade 2000-2010 task force on neck pain and its associated disorders. *J Manipulative Physiol Ther*. 2009;32(2):S117-S140.
44. Park JW, Choung PH, Kho HS, Kim YK, Chung JW. A comparison of neurosensory alteration and recovery pattern among different types of orthognathic surgeries using the current perception threshold. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*. 2011;111(1):24-33.
45. Park R, Wallace MS, Schulteis G. Relative sensitivity to alfentanil and reliability of current perception threshold vs von frey tactile stimulation and thermal sensory testing. *Journal of the Peripheral Nervous System*. 2001;6(4):232-240.
46. Peterson C, Bolton J, Humphreys BK. A cross-sectional study correlating degeneration of the cervical spine with disability and pain in united kingdom patients. *Spine*. 2003;28(2):129-133.
47. Pettersson K, Hildingsson C, Toolanen G, Fagerlund M, Björnebrink J. MRI and neurology in acute whiplash trauma: No correlation in prospective examination of 39 cases. *Acta Orthopaedica*. 1994;65(5):525-528.
48. Picavet H, Schouten J. Musculoskeletal pain in the netherlands: Prevalences, consequences and risk groups, the DMC3-study. *Pain*. 2003;102(1-2):167-178.
49. Pitei D, Watkins P, Stevens M, Edmonds M. The value of the neurometer in assessing diabetic neuropathy by measurement of the current perception threshold. *Diabetic Med*. 1994;11(9):872-876.
50. Raj PP, Chado HN, Angst M, et al. Painless electrodiagnostic current perception threshold and pain tolerance threshold values in CRPS subjects and healthy controls: A multicenter study. *Pain Practice*. 2001;1(1):53-60.
51. Reading I, Walker-Bone K, Palmer KT, Cooper C, Coggon D. Anatomic distribution of sensory symptoms in the hand and their relation to neck pain, psychosocial variables, and occupational activities. *Am J Epidemiol*. 2003;157(6):524-530.
52. Rendell MS, Dovgan DJ, Bergman TF, O'Donnell GP, Drobny EP, Katims JJ. Mapping diabetic sensory neuropathy by current perception threshold testing. *Diabetes Care*. 1989;12(9):636-640.

53. Schaefele MK, Boden SD. Physical function measurements in neck pain. *Phys Med Rehabil Clin N Am*. 2003;14(3):569-588.
54. Spitzer WO, Skovron M L, Salmi LR, et al. Scientific monograph of the Quebec Task Force on Whiplash-Associated Disorders: redefining “whiplash” and its management. *Spine*. 1995;20:S1-73.
55. Sterling M. Differential development of sensory hypersensitivity and a measure of spinal cord hyperexcitability following whiplash injury. *Pain*. 2010;150(3):501-506.
56. Sterling M, Jull G, Kenardy J. Physical and psychological factors maintain long-term predictive capacity post-whiplash injury. *Pain*. 2006;122(1-2):102-108.
57. Sterling M, Jull G, Vicenzino B, Kenardy J, Darnell R. Physical and psychological factors predict outcome following whiplash injury. *Pain*. 2005;114(1-2):141-148.
58. Tampin B, Slater H, Hall T, Lee G, Briffa NK. Quantitative sensory testing somatosensory profiles in patients with cervical radiculopathy are distinct from those in patients with nonspecific neck-arm pain. *Pain*. 2012;153(12):2403-14.
59. van der Donk J, Schouten JS, Passchier J, van Romunde LK, Valkenburg HA. The associations of neck pain with radiological abnormalities of the cervical spine and personality traits in a general population. *J Rheumatol*. 1991;18(12):1884-1889.
60. Voerman VF, van Egmond J, Crul BJP. Normal values for sensory thresholds in the cervical dermatomes: A critical note on the use of semmes-weinstein Monofilaments1. *American journal of physical medicine & rehabilitation*. 1999;78(1):24-29.
61. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. *Pain*. 2011;152(3):S2-S15.
62. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature*. 1983 ;306(5944):686-688.
63. Yamashita T, Kanaya K, Sekine M, Takebayashi T, Kawaguchi S, Katahira G. A quantitative analysis of sensory function in lumbar radiculopathy using current perception threshold testing. *Spine*. 2002;27(14):1567-1570.
64. Hakimi K, Spanier D. Electrodiagnosis of cervical radiculopathy. *Phys Med Rehabil Clin N Am*. 2013;24(1):1-12.

65. Slipman CW, Plastaras CT, Palmitier RA, Huston CW, Sterenfeld EB. Symptom provocation of fluoroscopically guided cervical nerve root stimulation: Are dynatomal maps identical to dermatomal maps? *Spine*. 1998;23(20):2235-2242.
66. Li R, Machol JA, Liu X, et al. C7 nerve root sensory distribution in peripheral nerves: A BOLD fMRI investigation at 9.4 T. *Muscle Nerve*. 2014 49(1):40-6.
67. Uddin Z, MacDermid JC, Galea V, Gross AR, Pierrynowski MR. Reliability Indices, Limits of Agreement and Construct Validity of Current Perception Threshold Test in Mechanical Neck Disorder. *Crit Rev Phys Rehabil Med*. 2013;25(3-4):25–37.
68. Courtney CA, Kavchak AE, Lowry CD, O'Hearn MA. Interpreting joint pain: quantitative sensory testing in musculoskeletal management. *J Orthop Sports Phys Ther* 2010;40(12):818-825.
69. Arendt-Nielsen L, Yarnitsky D (2009). Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *The Journal of Pain*. 2009;10(6):556-572.
70. Fletcher JP, Bandy WD. Intrarater reliability of CROM measurement of cervical spine active range of motion in persons with and without neck pain. *J Orthop Sports Phys Ther* 2008;38(10):640-645.
71. Uddin Z, MacDermid JC, Packham T. Ice-water (cold stress) immersion testing. *Journal of Physiotherapy*. 2013;59(4):277-277.
72. Uddin Z, MacDermid JC, Packham T. Clinical implementation of two Quantitative Sensory Tests: Cold Stress Test and The Ten Test. *Physiotherapy Practice and Research*. 2014;35(1):33-40.
73. Uddin Z, MacDermid JC, Packham T. The Ten Test for Sensation. *Journal of Physiotherapy*. 2013; 59(2):132-132.
74. Uddin Z, MacDermid JC, Ham H. Test-Retest Reliability and Validity of Normative Cut-offs of the Two Devices Measuring Touch Threshold: Weinstein Enhanced Sensory Test and Pressure Specified Sensory Device. *Hand Therapy*. 2014;19(1):3-10.

TABLE 1. Classification of MND in this study was based on the Quebec Classification of Whiplash Associated Disorders (1995)⁵⁴ and clinical assessment.

<i>Category</i>	<i>Signs and symptoms (1995 classification)⁵⁴</i>	<i>How assessed (APPENDIX)</i>
I	Neck complaint of pain, stiffness, or tenderness only; No physical sign(s)	History and structured cervical scan examination
II	Neck complaint AND Musculoskeletal sign(s) (reduced ROM and point tenderness)	Either of the following: 1. Reduced ROM – measured by CROM ⁷⁰ 2. Point tenderness- measured by manual examination
III	Neck complaint AND Neurological sign(s) (altered deep tendon reflex, muscle weakness and sensory deficits)	Any of the following based on cervical screen: 1. Altered deep tendon reflex 2. Myotomal weakness 3. Dermatomal sensory deficits or positive neural tension test
IV	Neck complaint AND Fracture or dislocation	Imaging (not eligible for this study)

Abbreviations: CROM, Cervical Range of Motion device ; ROM, Range of Motion

TABLE 2. Participants (n=106) demographics.

Variable	MND-I (n=60)	MND-II (n=29)	MND-III (n=17)
Age (years)	45.6 ± 9.4	41.4 ± 14.8	50.8 ± 11.3
Gender	F= 46, M= 14	F= 28, M= 1	F= 12, M= 5
Pain duration (in month)	14.3 ± 11.2	16.5 ± 13.3	24.2 ± 15.5
NDI (in %)	35 ± 17.3	26.4 ± 12.3	40.9 ± 20.7
CSOQ (0 to 100)	42.9 ± 15.3	36.2 ± 13.4	45.6 ± 23.1

Abbreviations: CSOQ, Cervical Spine Outcome Questionnaire; F, female; M, male; MND, Mechanical Neck Disorder; MND-I, Quebec Task Force classification of MND-type 1; MND-II, Quebec Task Force classification of MND-type 2; MND-III, Quebec Task Force classification of MND-type 3; NDI, Neck Disability Index (in %). Data are means and standard deviations

TABLE 3. CPT scores

Test Frequency	Test site (Finger)	CPT scores		
		MND-I	MND-II	MND-III
2000 Hz	Thumb	8.3 ± 2.1	10.3 ± 3.7	12.1 ± 3.1
	Middle	8.4 ± 1.9	10.3 ± 3.1	11.5 ± 3.4
	Little	8.8 ± 2.2	10.5 ± 4.6	10.7 ± 3.3
<i>Mean of 3 sites</i>		<i>8.4 ± 1.5</i>	<i>10.4 ± 3.1</i>	<i>11.4 ± 2.9</i>
250 Hz	Thumb	9.7 ± 1.7	10.3 ± 2.5	12.2 ± 2.6
	Middle	9.6 ± 1.7	10.3 ± 2.2	11.6 ± 2.5
	Little	10 ± 1.9	10.8 ± 2.7	11.65 ± 3
<i>Mean of 3 sites</i>		<i>9.8 ± 1.3</i>	<i>10.5 ± 1.8</i>	<i>11.8 ± 2.3</i>
5 Hz	Thumb	10.7 ± 2.9	10.5 ± 3.1	12.7 ± 3.1
	Middle	10.5 ± 3	10.8 ± 2.7	11.1 ± 3.5
	Little	11.4 ± 2.8	11.5 ± 2.9	12.7 ± 3.6
<i>Mean of 3 sites</i>		<i>10.8 ± 2.4</i>	<i>10.9 ± 2.3</i>	<i>12.2 ± 2.9</i>
<i>Total (composite) score</i>		<i>9.7 ± 1.1</i>	<i>10.6 ± 0.4</i>	<i>11.8 ± 0.7</i>

Data are means and standard deviations

TABLE 4. Post Hoc comparison between 3 Frequencies of CPT.

Frequency (Hz)	P value (MND-I vs MND-II)	P value (MND-II vs MND-III)
2000	.001**	.364
250	.158	.030*
5	.974	.260
<i>Mean of 3 tests (combined)</i>	.051*	.012**

Results show that individually a single frequency does not have sufficient capacity to differentiate between the 3 MND groups. However, combining the 3 frequencies show significant capacity to differentiate all 3 subgroups.

TABLE 5. The discriminative model.

		Neurological sign or probability of MND-III			
		Yes	No		
CPT test outcome	Positive	11	6	Sensitivity = 73.3% (95%CI: 44.9 to 92.1)	Odds Ratio 11.5 (<i>P</i> = 0.001)
	Negative	4	25	Specificity = 80.7% (95%CI: 62.5 to 92.5)	

The model (probability cut-point = 0.5 = no discrimination) and classification demonstrate a sensitivity of 73% and specificity of 81%. The binary classification for MND-II versus MND-III groups was based on a threshold value greater than 11 for MND-III (cut-off = 11). Key: Neurological sign or probability of MND-III (Yes = 1, No = 0), Sensitivity (true positive rate); Specificity (true negative rate); 95%CI, Confidence Interval; *P*, Probability value.

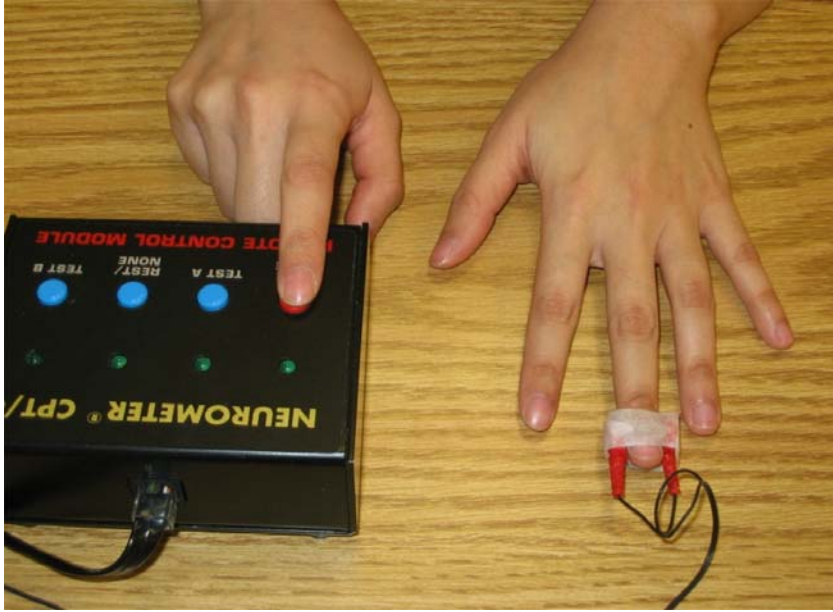


FIGURE 1. Current perception threshold (CPT) test procedure. The Rapid-CPT values (1 to 25) is obtained from the minimal strength of alternating current (between 0 to 10 mA) stimulus that the patient could detect.

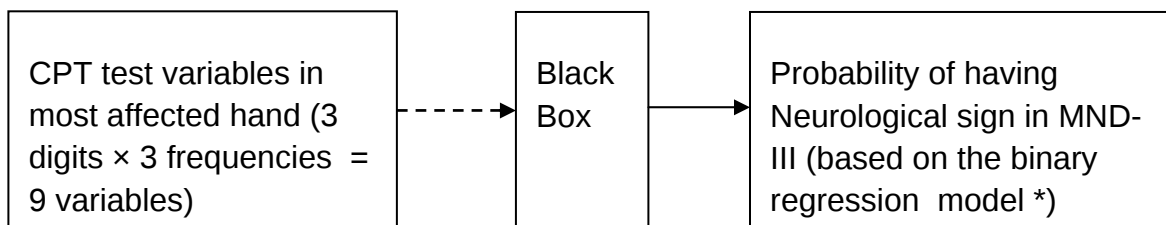


FIGURE 2. A good fit logistic regression prediction model, $\chi^2 = 6.2$ ($P = 0.05$) was used where,* no neurological involvement (MND-II) is 0; and suspected neurological sign (MND-III) is 1. In this model, CPT test for the middle finger at 250 Hz was found as the strongest predictor of reporting neurological sign or MND-III (OR = 3, $\beta = 1.1$, $P = 0.03$).

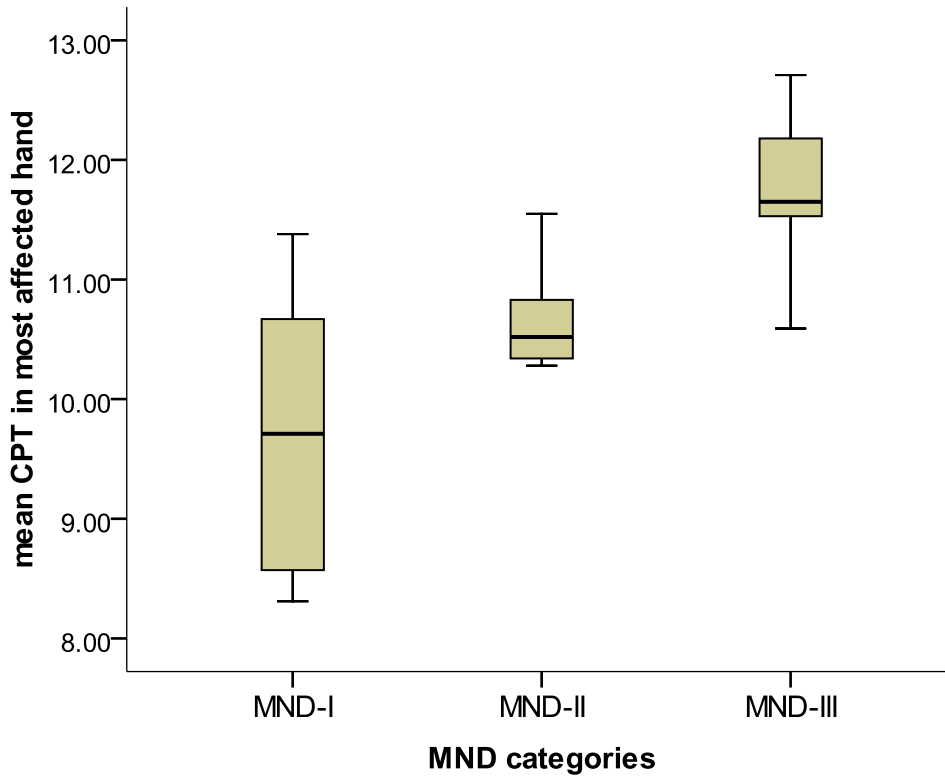


FIGURE 3. This Box-whisker plot is showing current perception threshold (CPT) level/value by groups (MND-I, neck pain without musculoskeletal signs; MND-II, neck pain with musculoskeletal signs; MND-III, neck pain with neurological signs). Thick black line inside the box indicates median; the box height indicates 25-75% inter-quartile range; the whiskers indicates 95% confidence interval. The Effect Size and *P* value for the differences: (1) between MND-I and MND-II ($d = 1$, $P = .05$); (2) between MND-II and MND-III ($d = 2.2$, $P = .01$). Mean $\pm$ SD CPT score: MND-I, 9.7 ± 1.1 ; MND-II, 10.6 ± 0.4 ; MND-III, 11.8 ± 0.7 . Here, CPT > 11 is a better cut-off point to differentiate MND-II from MND-III.

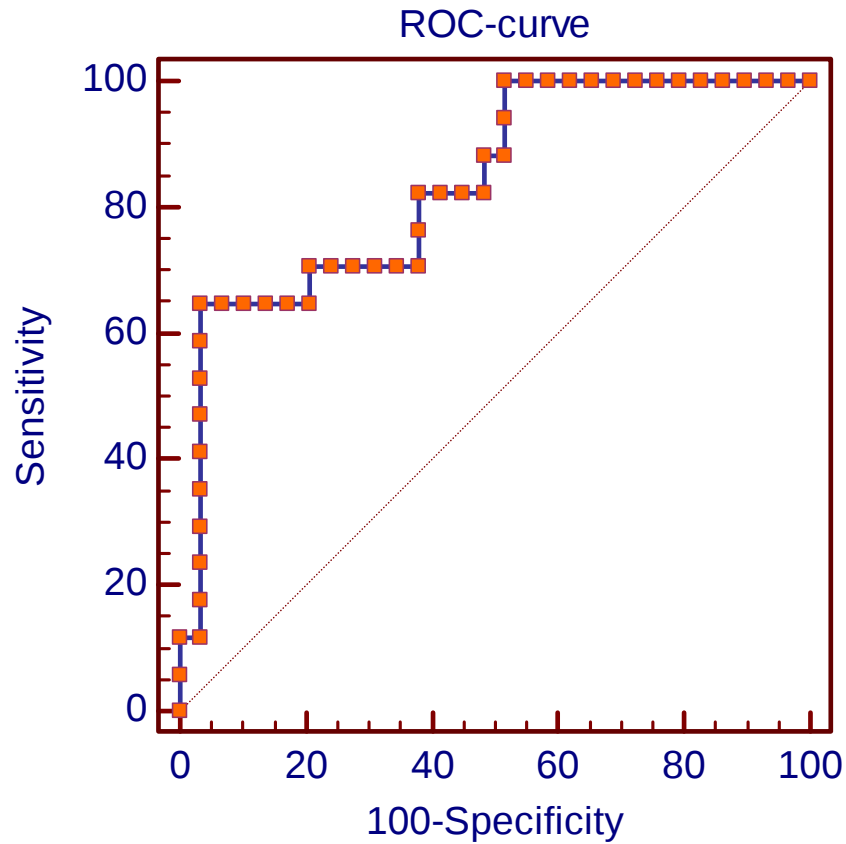


FIGURE 4. The Receiver Operating Characteristic (ROC) curve represents the true positive rate (sensitivity) versus false positive rate (100 – specificity). The area under the ROC curve (AUC) = .84 (95% CI, .70 to .93), $P < .001$. The curve was created based on the predicted probability of binary classification of MND-II (neurological involvement absent and MND-III (neurological involvement present).

APPENDIX: Cervical screening form

THE PATIENT'S PRIMARY COMPLAINT MUST BE ONE OF (check all that apply):

- ☐ neck pain ☐ neck stiffness ☐ neck tenderness

THE PATIENT'S NECK PAIN IS ASSOCIATED WITH (check all that apply)

- ☐ Cervicogenic headache
- ☐ Pain referral to the proximal extremity (proximal deltoid to elbow)
- ☐ Pain referral to the distal extremity (beyond elbow)

NEUROLOGICAL SCAN (check all that apply)

- ☐ Absent neurological signs
- ☐ Diminished deep tendon reflexes
 - ☐ C6 biceps ☐ C6 brachioradialis ☐ C7-8 triceps
- ☐ Myotomal weakness (most common examples are provided)
 - ☐ C1/C2 neck flexion ☐ C6 elbow flexion or wrist extension
 - ☐ C3 neck side bend or retraction ☐ C7 elbow extension or wrist flexion
 - ☐ C4 shoulder elevation ☐ C8 thumb extension or ulnar deviation
 - ☐ C5 shoulder abduction ☐ T1 hand adductors or abductors
- ☐ Dermatomal (C1-T1) sensory disturbance
 - ☐ C1/C2 ☐ C6
 - ☐ C3 ☐ C7
 - ☐ C4 ☐ C8
 - ☐ C5 ☐ T1

SPECIAL TESTS

- ☐ Positive neural tension provocation test
- ☐ Positive joint play test

CHAPTER 4: Study 3

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Full Title:

Test-Retest Reliability and Validity of Normative Cut-offs of the Two Devices Measuring Touch Threshold: Weinstein Enhanced Sensory Test and Pressure Specified Sensory Device

Short Title:

Reliability-Validity of WEST and PSSD

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Abstract

Introduction. Touch threshold screening instruments must accurately distinguish normal versus abnormal sensation to screen nerve pathology. This study was conducted to find out whether two touch threshold measuring devices [i.e. Weinstein Enhanced Sensory Test (WEST) and Pressure Specified Sensory Device (PSSD)] provide consistent results and indicators of “normal” sensation, and secondarily what rules best define normality.

Methods. The study design was a cross-sectional reliability and validity assessment with 23 healthy participants. Instruments were applied in random order on the pulp of the middle and little fingers of both hands; with 5 applications on each digit. Cutoffs of 3, 4 and 5 correct responses were used to classify the response as being normal. Weighted kappa and percent agreement were used to indicate test-retest reliability of the WEST, and validity was determined by calculating the percentage of normal controls that achieved a normal score. The Bland-Altman method was used to characterize the re-test reliability of PSSD, and validity was determined by whether the mean of the score is different from the normative scores.

Results. The agreement between test and retest of WEST (detection level=3/5) was almost perfect ($k=1$). The average percentage of normal detection of the WEST on 2 test/re-test was 93% and 97% (detection level=4/5) and 82% and 85% (detection level=5/5). All mean PSSD tests values found within the predetermined normal range. The Bland-Altman plot demonstrated a minimal mean difference between test occasions and similar limits of agreement across the 4 test locations.

Discussion. The study found that more than 90% of the tests with healthy young participants were reliable and valid in relation to their ability to detect a normal WEST filament or PSSD within a normal force range. Our study was limited by small sample with healthy participants.

Key words: Touch, Threshold, Sensory, Reliability, Validity

Abbreviations: QST = quantitative sensory testing; WEST = Weinstein Enhanced Sensory Test; PSSD= Pressure Specified Sensory Device; 2PD = two-point discrimination; 1-PS = one-point static

Introduction

Sensory evaluation is essential for diagnosis and outcome measurement in patients with nerve injury or compression and neuropathic pain.¹⁻⁵ In peripheral neuropathy and nerve compression, the function of both small and large myelinated fibres are affected.⁶ Therefore, to diagnose and monitor peripheral nerve function, the Peripheral Neuropathy Association,⁷ the European Federation of Neurological Societies,³ as well as the American Diabetes Association and American Academy of Neurology⁸ recommended quantitative sensory testing (QST) for touch threshold measure. Touch threshold is the smallest force at which the detection of touch perception occurs. A threshold value above or below normal curve indicate abnormal functioning (e.g. hypoesthesia and hyperesthesia). Touch threshold tests are useful for measuring tactile sensation and mechanical pain.^{3,6,9} Measurement of touch sensation is a critical dimension of function since it measures how humans interact within virtual and real environments.¹⁰ Motor function largely depends upon a constant inflow of sensory impulses¹¹ and touch sensation inflow is essential to optimize motor functions.

The Weinstein Enhanced Sensory Test (WEST) and Pressure Specified Sensory Device (PSSD) are two common QST devices used to measure touch threshold. The WEST device is a modernized version of the von Frey hair filaments.¹²⁻¹⁴ Frey's filaments were developed on the principle of Euler's buckling law¹⁵ and introduced in 1890.^{14,16,17} In the 1960s, a series of calibrated nylon monofilaments was developed based on the Frey's hairs filaments (i.e. Semmes-Weinstein Monofilaments).^{13,14} Later, the WEST was developed to maintain manufacturing consistency and clinical portability.¹⁴ It introduced hemispherical tips of the enhanced filaments to reduce slippage and standardize the size of applicator head.¹⁸ The filaments were calibrated to indicate the applied force threshold in milligrams and normal digit tip values were established.¹⁴ The traditional screening kit includes 5 filaments with the smallest diameter one indicating normal sensation. As such the score is ordinal with 1 normal option and 4 levels of abnormal choice. A systematic review of sensory tests used following nerve injury and repair suggested that monofilament testing (WEST or Semmes-Weinstein Monofilaments) is a standardized test for touch threshold measure.¹⁹ This review indicated that there is incomplete information on the reliability of the WEST.¹⁹

In comparison to the WEST, the PSSD was developed to test touch threshold on a continuous scale. It measures touch threshold through 0.9 mm² prongs attached to a force transducer.²⁰⁻²² which can be used to measure two-point discrimination (2PD) by applying 2 points^{23,24} or one-point static (1-PS) touch threshold by using a single prong of this device.²⁵ The PSSD-2PD test has been criticised on both conceptual and methodological basis since the distance or force can be varied making it difficult to have a consistent metric.^{2,19} The PSSD introduced computerized equipment to standardized pressure threshold testing across a

continuous scale which contrasts with the ordinal metric used by WEST or Weinstein monofilaments.^{20,26,27} Normative data of PSSD have been established,²⁰ although few studies have focused on the 1-PS test.

A single probe (e.g. 1-PS of PSSD) or monofilament (e.g. WEST) application is capable of engaging fast and slow-adapting receptors ($A\beta$ and $A\delta$ sensory fibers) involved in pressure/touch perception.²⁸ However, there is insufficient studies that have performed a head to head comparison of different test devices and protocols.²⁹ Further, the protocols for testing and assignments of a normal score are variable across studies.³⁰ This can make it difficult to compare different instruments. Given that the WEST device measurement is an ordinal scale; unlike the PSSD is which is a continuous scale this has implications for how “normal” is determined.³⁰ The computerized PSSD may be more able to measure small gradient of change than a 5-point scale. However, it may be less discriminative. Further, the PSSD mechanical precision may be counterbalanced by differences between tools in relation to tester-related measurement error since it can be challenging to control the force variations when the device is applied by the human-hand.²⁹⁻³¹ However, since there are limited data defining reliability,² it has not been established whether the PSSD does have greater measurement error. In brief, these two devices each have potential strengths and weaknesses which can affect their measurement properties. The present study was conducted to find out whether the two touch threshold measuring devices (WEST and 1-PS of PSSD) consistently produce similar results (reproducible) and whether the test values are within the control range (normative value) when used in people without sensory dysfunction.

Methods

Subjects.

The study was approved by the McMaster University Research Ethics Board, and informed consent was obtained from all participants (N = 23) prior to testing. The participants were recruited through flyers inside the university campus. Inclusion criteria for the study were: age between 18 and 44 years,). Exclusion criteria were: hand pathology, inability to follow study procedures, or co-existing medical conditions that affect the hand including neurological disorders, connective tissue disease, arthritis, or diabetes. Participant's characteristics and demographics are described in Table 1.

Procedures.

All tests were performed in a quiet room with the temperature between 22°C and 25°C. Standardized instructions and procedures were clearly explained at the beginning of the test. Subjects were seated in a comfortable chair with armrests and a back support across from the examiner, and the arm of the subject was placed on a table. The finger to be tested was immobilized by fixing it in a moldable “clay”. The tests were done on the pulp of (glabrous skin) of middle and little fingers of both hands (in 4 test locations). Tests were applied with different time intervals and participants were instructed to state verbally (WEST) or fire a trigger (PSSD) whenever they detected a touch. The order of tests and fingers to be tested was randomized for each subject. Participants were blind folded in order to prevent anticipation of touch sensation.²³ Touch thresholds were measured using WEST and PSSD on two occasions within 2-14 days by the same examiner.

Sensory Tests.

WEST. The test was done using the Monofilament Nerve Test (WEST-hand™, Connecticut Bioinstruments, Riverdale, NY, USA). The test was performed principally according to the protocol used by Schulz and colleagues.¹⁴ WEST device is comprised of a hand held portable device with five different diametric filaments [Figure 1]. Each of the five distinct filaments on this device has calibrated force value into which subjects can be categorized. The plastic handheld rod is used to apply the filament force to a particular anatomic skin site. Using the lightest filament first, the pressure was applied five times on different parts of the middle and the little finger of each hand. Each time the subject felt sensation, they were asked to give a verbal response (e.g. Yes). If the subject could not detect three stimuli out of five, the next lightest filament was applied to the skin. The touch detection threshold was determined as the lightest filament at least three out of five applications were detected. This test was performed at middle and little fingers of both hands. A monofilament rod marking score of 2.83 (force value = 0.0677 g) is considered “normal” for the hand.² The measure is often reported by actual force values,² in which the normal values (for 80% of the population) have been defined for men and women 55 years of age or younger = 0.035 g.^{2,14} This value is within the limit of 2.83 (logarithmic marking) filament, and we used it as the reference point of normal (normative cut-offs).

PSSD. The test was done using NK-PSSD device (NK Biotechnical Corporation, Minneapolis, MN, USA). The test was performed principally according to the protocol by Dellon, et al^{20,22} and Kaneko, et al.³² The device has two prongs, each of which has a hemispherical tip with an area of 0.9 mm². However, we used one-point static (1-PS) test using a single prong in

this study to be more comparable in construct to the WEST [Figure 2]. The ends of the prong that interfaced with the instrument were mounted on force transducers. In each test, the instrument was calibrated to zero for gravity and then slowly lowered the device into contact with the subject's finger. The prong was pressed against the skin surface to be tested with slowly increasing force until the subject responded by pressing a hand-held button as soon as the sensation is perceived. At this point, the computer displays the minimum perceptible pressure at which the individual stimulus was perceived. Five such trials were performed for each finger, and a trimmed mean value was calculated; the highest and lowest values were removed, and the average values of the remaining three trials were used as the threshold of touch perception as recommended by the developer. The test was performed at middle and little fingers of both dominant and nondominant hands. The unit of PSSD measurement is grams per millimeter squared. The normative value has been reported as 0.5 g/mm² (in asymptomatic index finger) and 0.4 g/mm² (in asymptomatic little finger) for the 1-PS test for people less than 45 years of age.²⁰ The normative value of the index finger was used in this study to interpret the value of the middle finger as the both fingers are innervated by the median nerve.

Data Analysis.

Data quality checking was performed before statistical analysis. Descriptive statistics (e.g. skewness, kurtosis) and test of normality (Kolmogorov-Smirnov, Shapiro-Wilk, Histogram, and QQ-Plot) were conducted on continuous variables. All statistics were performed on SPSS 17.0 software package (SPSS Inc., Chicago, IL). Bland-Altman plots were made using MedCalc software version 12.3.0 (Broekstraat, Mariakerke, Belgium). Weighted kappa and percent agreement were used to measure test-retest reliability of WEST. The magnitude of weighted

kappa agreement was interpreted as follow: ≤ 0 = poor, 0.01–0.20=slight, 0.21–0.40=fair, 0.41–0.60=moderate, 0.61–0.80=substantial, and 0.81–1=almost perfect.^{33,34} The mean PSSD scores on each occasion and the mean difference between test and retest with 95% limits of the agreement were calculated. The Bland-Altman method was used to plot the difference between PSSD tests against their mean value to determining of the overall mean difference across all subjects.³⁵⁻³⁷ The limits of agreement were determined by calculating two standard deviations around the mean difference. The validity of WEST was assessed by the percentage of normal controls achieving the predefined normal score (value of 2.83). This was determined using 3 different decision rules (e.g. whether 3, 4 or 5 correct responses were required for a normal test designation). The validity of PSSD test was determined by whether the mean of the score is different from the normative scores. (0.5 g/mm² for middle and 0.4 g/mm² for the little finger).

Results

The weighted kappa between test and retest of the WEST (at detection level=3 stimuli out of 5) found almost perfect agreement ($k=1$, 100% agreement) for all test locations (Table 2_a). The average percentage of normal detection of the WEST was calculated as: test and retest = 93.48% and 96.74% (at detection level=4 stimuli out of 5); 81.52% and 84.78% (at detection level= all 5 stimuli) [Table 2_{b,c}].

The mean PSSD values for 2 test occasions and differences with standard deviations for 4 test locations indicated no significant difference between the mean of test or retest values, or with normative values (Table 3). The Bland-Altman plot demonstrated a minimal mean difference between test occasions and similar limits of agreement across the 4 test locations: 0.06

± 0.36 (dominant middle finger), 0.02 ± 0.17 (dominant little finger), 0.04 ± 0.23 (non-dominant middle finger) and 0.00 ± 0.34 (non-dominant little finger) [Figure 3_{a,b,c,d}].

Discussion

This study found that more than 90% of people without hand pathology were able to detect the stimulus sample with either the test PSSD or WEST as the test device using 3 or 4 correct responses out of 5 as a criterion. Data suggests that requiring 5/5 repetitions to be detected to assign normality is overly rigorous and would decrease test specificity since up to 20% of people failed to detect at least 1 application (80% specificity). Either 3/5 (100% detected as normal) or 4/5 (more than 90% detected as normal) correct responses provided high specificity. Our results are consistent with a systematic review¹⁹ that suggested the WEST meets criteria for a standardized test. Our results are also consistent with previous studies that reported that the PSSD is reliable²⁰ and valid.²⁷ This study has added evidence that the both (WEST and PSSD) devices are reliable and valid are capable of accurately and consistently identifying normal sensibility. The control of force variation of the PSSD test due to the examiner application of the device has been questioned as a source of error.² This did not impact or results in our study although it may be more of an issue in a patient sample or when evaluating change over time.

We found no bias in measurement between 2 different test intervals on the PSSD using a Bland and Altman approach since there was minimal inter-occasion mean differences. This suggests that learning or test accommodation were not an issue. However, the limits of agreement were wide suggesting substantial variations in scores between occasions are possible.

This did not appear to have a substantial effect on discrimination between normal and abnormal as the variation fell within the normal range. It may be an issue in looking at change over time.

The measurement properties of these two devices are different, and thus problematic to compare. The WEST uses an ordinal (logarithmic) scale where only 1 filament scored as a yes/no decision determines whether a person is identified as normal. This study recruited healthy participants and 100% of them were identified as normal (based on a minimum of 3 stimuli out of 5). The PSSD measures are measured on a continuous (interval) scale and as such a range of values are considered normal. In this study we identified whether scores were normal/abnormal and did not directly compare score values. A previous study compared monofilament-based test with PSSD and found poor inter-instrumental correlation.²⁶ In that study, the difference in ordinal versus interval measurement may have affected observed correlations.

Monofilament testing has shown discriminative validity in discrimination of patients from unaffected individuals in other studies. A systematic review on clinical diagnosis for carpal tunnel syndrome indicated 72% sensitivity and 62% specificity for monofilament test indicating moderate sensitivity and specificity.³⁸ This review noted that specificity was higher when participants were asymptomatic, rather than patients with different pathologies. Thus, the high specificity in detection of normality in this study may be partially related to our exclusion criteria. Previous studies suggest that the PSSD test has high sensitivity, but a low specificity in comparison to electrodiagnostic testing.²⁷ Moreover, a recent study suggested that PSSD has advantages over electrodiagnostic testing in Brachial plexus injury.³⁹ A cross-sectional study found that PSSD is better than monofilament testing to identify cutaneous sensibility in the foot.⁴⁰ Our findings suggest that the PSSD is as specific as the WEST in a young healthy sample.

Therefore, test selection may depend on test availability. The WEST is a hand-held device, readily commercially available, less expensive and more practical for screening purposes in terms of cost and ease of use.

More complicated decision rules for QST tend to increase inter-rater disagreements on whether sensibility is “normal”.⁴¹ For all these reasons, establishing clear rules on what constitutes normal or abnormal sensory thresholds requires further study. Previous studies suggest that data from sensory trials tend to be more unstable than motor tests,⁴² so a moderate amount of random error may be inherent to sensory evaluation. Our high reliability was on the decision made i.e. discrimination, not on absolute agreement on scores. Sensory perception testing requires that patients attend to the stimulus and so proper stabilization of the body part being tested and avoidance of other sensory inputs from either the examiner or the environment are critical to obtaining consistent attention to the sensory perception task. These factors explain why an expectation of 5/5 correct responses may be overly rigid, as our error margin for failed detection was up to 20% in this study using that criterion.

This study supports the reliability and specificity of these 2 tests. However, the study must be considered preliminary due to substantial limitations. The primary limitation was that we had a small sample size of healthy young participants without comorbid health problems. This happened due to using a convenience sample recruited from a university setting. Future studies should address larger samples and compare discrimination properties in a range of hand disorders with proper reference standards.

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Conflict of interest

None declared.

References

1. MacDermid JC, Doherty T. Clinical and electrodiagnostic testing of carpal tunnel syndrome: a narrative review. *J Orthop Sports Phys Ther.* 2004;34:565-588.
2. MacDermid JC. Measurement of Health Outcomes Following Tendon and Nerve Repair. *J Hand Ther.* 2005;18: 297-312.
3. Cruccu G, Anand P, Attal N, et al. EFNS guidelines on neuropathic pain assessment. *Eur J Neurol.* 2004;11:153-162.
4. Dellon AL. Evaluation of sensibility and re-education of sensation in the hand. Baltimore MD: Williams & Wilkins,1981.
5. Mackinnon SE, Dellon AL. Surgery of the peripheral nerve. New York: Thieme Medical Publishers,1988.
6. Heinbecker P, Bishop GH, O'leary J. Pain and touch fibers in peripheral nerves. *Arch Neuropsych.* 1933;29:771-789.
7. Arezzo JC, Bolton CF, Boulton A. Quantitative sensory testing: a consensus report from the Peripheral Neuropathy Association. *Neurology.*1993;43:1050-1052.
8. American Diabetes Association and American Academy of Neurology. Consensus Statement: Report and recommendations of the San Antonio Conference on diabetic neuropathy. *Diabetes Care.* 1988 Jul-Aug;11:592-597.
9. Zaslansky R, Yarnitsky D. Clinical applications of quantitative sensory testing (QST). *J Neurol Sci* 1998;153:215-238.

10. Robles-De-La-Torre G. The importance of the sense of touch in virtual and real environments. *Multimedia IEEE*. 2006;13:24-30.
11. Adams RD, Victor M, Ropper AH, eds. *Principles of Neurology*. New York: Mc Graw-Hill Companies, 2000, 722-728.
12. Bell-Krotoski J, Tomancik E. The repeatability of testing with Semmes-Weinstein monofilaments. *J Hand Surg*. 1987;12:155-161.
13. Weinstein S. Fifty years of somatosensory research: from the Semmes-Weinstein monofilaments to the Weinstein Enhanced Sensory Test. *J Hand Ther*. 1993;6:11-22.
14. Schulz LA, Bohannon RW, Morgan WJ. Normal digit tip values for the Weinstein Enhanced Sensory Test. *J Hand Ther*. 1998;11:200-205.
15. Euler L. *Methodus Inveniendi Lineas Curvas Maximi Minimive Proprietate Gaudentes. Additamentum I: De Curvis Elasticis* (Zurich, 1744). In: *Opera Omnia I*, Vol. 24. Zurich: Birkhauser 1952: 231-297.
16. Fruhstorfer H, Gross W, Selbmann O. von Frey hairs: new materials for a new design. *Eur J Pain*. 2001;5:341-342.
17. von Frey M. Ueber den Gebrauch von Reizhaaren. In: *Untersuchungen über die Sinnesfunctionen der menschlichen Haut. Erste Abhandlung: Druckempfindung und Schmerz. Abhandlungen der mathematisch-physischen Classe der KoE niglich Sachsichen Gesellschaft der Wissenschaften* 1896; 23: 208-217.
18. Al Qattan M. A modified technique of using the WEST device for testing finger and thumb pulp sensitivity. *Plast Reconstr Surg*. 1998;101:547-548.
19. Jerosch-Herold C. Assessment of sensibility after nerve injury and repair: a systematic review of evidence for validity, reliability and responsiveness of tests. *J Hand Surg Eur*. 2005;30:252-264.
20. Dellon, Lee., and Keller, Kelly. Computer-Assisted quantitative sensorimotor testing in patients with carpal and cubital tunnel syndromes. *Ann Plast Surg*. 1997;38: 493-502.
21. Dellon ES, Mourey R, Dellon AL. Human pressure perception values for constant and moving one-and two-point discrimination. *Plast Reconstr Surg* 1992;90:112-117.
22. Dellon ES, Keller KM, Moratz V, et al. Validation of cutaneous pressure threshold measurements for the evaluation of hand function. *Ann Plast Surg*. 1997;38:485-92.
23. Weber vEH. *Über den tastsinn*. *Archiv für Anatomie, Physiologie und Wissenschaftliche Medicin*: 1835;152-160.

24. Lundborg G, Rosen B. The two-point discrimination test—time for a re-appraisal? *J Hand Surg Eur.* 2004;29:418-422.
25. Sinha UK, Rhee J, Alcaraz N, et al. Pressure-specifying sensory device: Quantitative sensory measurement in the oral cavity and oropharynx of normal adults. *Ear, Nose Throat J.* 2003;82:687-690.
26. Dellon ES, Crone S, Mouery R, et al. Comparison of the Semmes-Weinstein monofilaments with the pressure-specifying sensory device. *Restorative Neurol Neurosci* 1993;5:323-326.
27. Tassler P, Dellon A. Correlation of measurements of pressure perception using the pressure-specified sensory device with electrodiagnostic testing. *J Occup Environ Med.* 1995;37:862-866
28. Bell-Krotoski J. Light touch-deep pressure testing using Semmes-Weinstein monofilaments. In: Hunter J, Schneider L, Mackin E, Callahan A, eds. *Rehabilitation of the hand*. St Louis: CV Mosby, 1989:585-593.
29. Bell-Krotoski J, Weinstein S, Weinstein C. Testing sensibility, including touch-pressure, two-point discrimination, point localization, and vibration. *J Hand Ther.* 1993;6:114-123.
30. Patel MR., and Bassini L. A comparison of five tests for determining hand sensibility. *J Reconstr Microsurg.* 1999;15:523-526.
31. Bell-Krotoski JA, Buford WL. The force/time relationship of clinically used sensory testing instruments. *Journal of Hand Therapy* 1997;10:297-309.
32. Kaneko A, Asai N, Kanda T. The influence of age on pressure perception of static and moving two-point discrimination in normal subjects. *Journal of Hand Therapy* 2005;18:421-425.
33. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159-174.
34. Sim J, Wright CC. The kappa statistic in reliability studies: use, interpretation, and sample size requirements. *Phys Ther* 2005;85:257-268.
35. Bland JM, Altman DG: Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* .1986;1:307-311.
36. Bland JM, Altman DG. Statistical methods for assessing agreement between measurements. *Biochem Clin.* 1987;11:399-404.
37. Mantha S, Roizen MF, Fleisher LA, et al. Comparing methods of clinical measurement: Reporting standards for bland and altman analysis. *Anesthesia & Analgesia.* 2000;90:593-602.
38. MacDermid JC, Wessel J. Clinical diagnosis of carpal tunnel syndrome: a systematic review. *J Hand Ther.* 2004; 17:309-319

39. Nath RK, Bowen ME, Eichhorn MG. Pressure-specified sensory device versus electrodiagnostic testing in brachial plexus upper trunk injury. *J Reconstr Microsurg* 2010;26:235-242.
40. Wood WA, Wood MA, Werter SA, et al. Testing for Loss of Protective Sensation in Patients with Foot Ulceration A Cross-sectional Study. *J Am Podiatr Med Assoc* 2005;95:469-474.
41. MacDermid JC, Kramer JF, Roth JH. Decision making in detecting abnormal semmes-weinstein monofilament thresholds in carpal tunnel syndrome. *J Hand Ther.* 1994;7:158-162.
42. MacDermid J, Kramer J, McFarlane R, et al. Inter-rater agreement and accuracy of clinical tests used in diagnosis of carpal tunnel syndrome. *Work.* 1997;8:37-44.

Table 1. Participants Demographics (N = 23)

<i>Variable</i>	<i>Characteristic</i>
Age (in years)	Mean = 22.96 (SD = 5.03)
Gender	Female = 15 (65.2%), Male = 8 (34.8%)
Dominant Side	Right = 20 (87%), Left = 3 (13%)

Legend: SD = standard deviation; n = number of participants;

Table 2. a) Weighted Kappa value and percentage of agreement between the test and retest results of Weinstein Enhanced Sensory Test (WEST) based on the minimum (3 stimuli out of 5) detection level. b) Percentage of WEST meets the expected value of 2.83 (0.0677 g = normal) based on the detection level of 4 stimuli out of 5. c) Percentage of WEST meets the expected value of 2.83 (0.0677 g = normal) for all 5 stimuli.

Test Location in Hand	a)* Weight ed Kappa	a)* Percentage of Agreement	b)** Percentage of Normal detection		c)*** Percentage of Normal detection	
			Test	Retest	Test	Retest
Dominant Middle Finger	1	100%	86.96% (20)	91.30% (21)	73.91% (17)	91.30% (21)
Dominant Little Finger	1	100%	91.30% (21)	100% (23)	78.26% (18)	73.91% (17)
Non Dominant Middle Finger	1	100%	100% (23)	95.65% (22)	91.30% (21)	86.96% (20)
Non Dominant Little Finger	1	100%	95.65% (22)	100% (23)	82.61% (19)	86.96% (20)
<i>Average</i>	<i>1</i>	<i>100%</i>	<i>93.48%</i>	<i>96.74%</i>	<i>81.52%</i>	<i>84.78%</i>

Percentage of normal test scoring compared to predefined normal score value of 2.83 for *3 stimuli out of 5 (Normal =3/5 normal tests), **4 stimuli out of 5 (Normal =4/5 normal tests), ***all 5 stimuli (Normal =5/5 normal tests). Value in parentheses indicate the participant's number.

Table 3. Mean PSSD (Pressure Specified Sensory Device) scores in each occasion (i.e. test and retest) and the mean difference between test and retest with 95% limits of agreement.

Test Location in Hand	Mean Test value in g/mm ² (SD)	Mean Retest value in g/mm ² (SD)	Mean test-retest difference (95% limits of agreement)
Dominant Middle Finger	0.46 (0.17)	0.39 (0.14)	0.06 (± 0.36)
Dominant Little Finger	0.37 (0.11)	0.35 (0.08)	0.02 (± 0.17)
Non Dominant Middle Finger	0.42 (0.18)	0.38 (0.11)	0.04 (± 0.23)
Non Dominant Little Finger	0.38 (0.11)	0.38 (0.14)	0.00 (± 0.34)

N.B. There is no significant difference between the mean of PDDS test value and established normative value (0.5 g/mm² for middle and 0.4 g/mm² for little finger). All test-retest values appear within the normal limit. SD = standard deviation

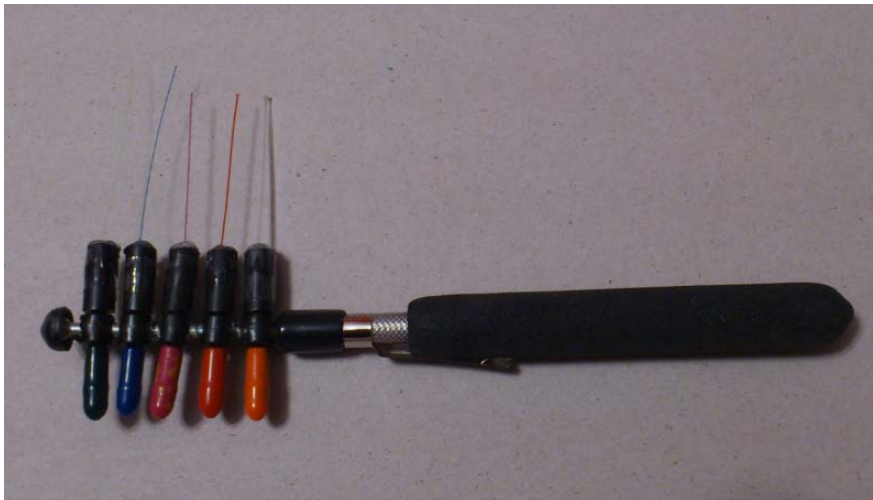
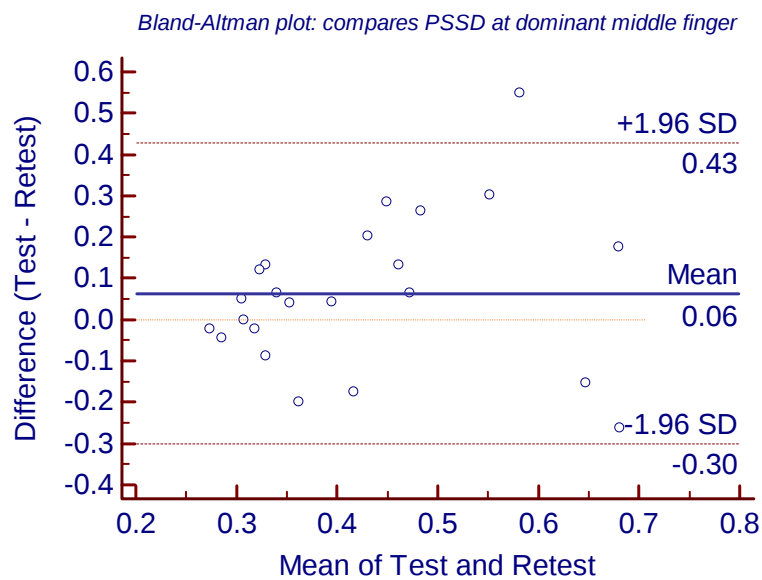


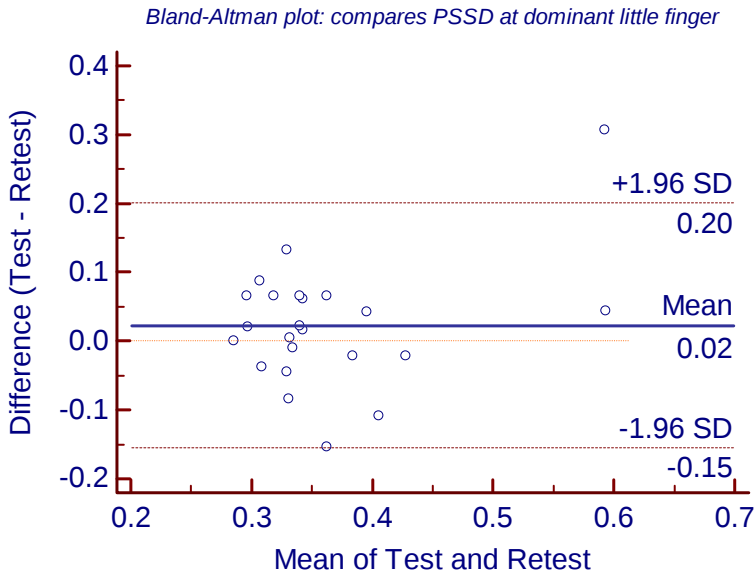
Figure 1: WEST device with five different diametric filaments. The lightest filament (left) was applied five times on different parts of the middle and the little finger of each hand.



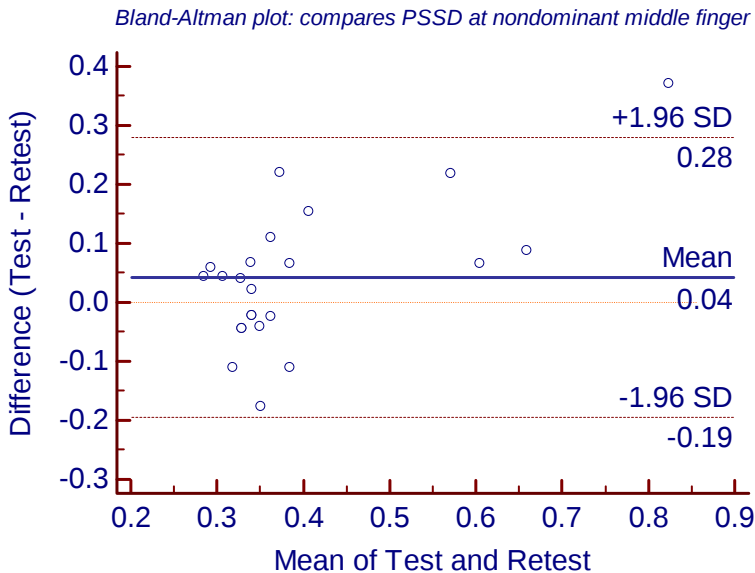
Figure 2 –PSSD device and application setup using a single prong on the middle finger (same procedure was applied at little finger).



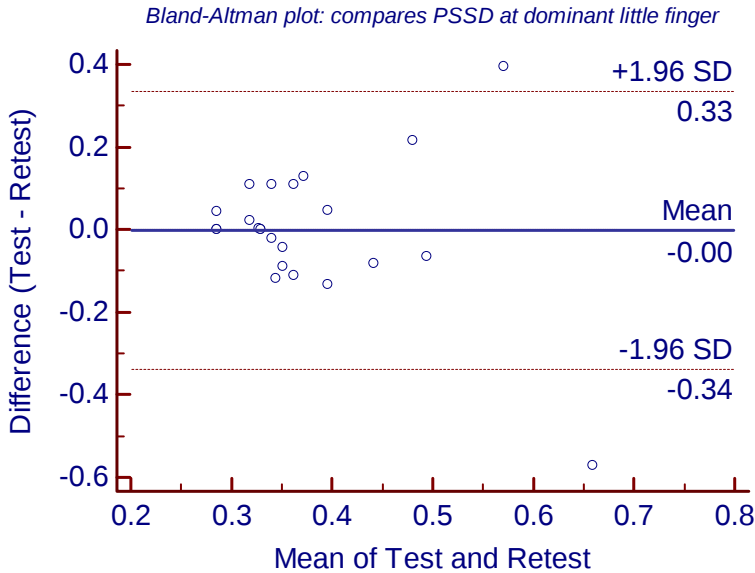
(a) The difference plot shows limit of agreement between two tests of PSSD tests in dominant middle finger



(b) The difference plot shows limit of agreement between two tests of PSSD tests in dominant little finger



(c) The difference plot shows limit of agreement between two tests of PSSD tests in nondominant middle finger



(d) The difference plot shows limit of agreement between two tests of PSSD tests in nondominant little finger

Figure 3. Bland-Altman plot compared limit of agreement between two measurements (test-retest) of PSSD in middle and little finger of both hands (N = 23). The difference between test and retest is drawn against the mean of test and retest in the 23 paired measurements. The line of limit of agreement (middle solid line) compared with perfect line (middle dotted line at zero level) and the mean differences are illustrated in plot.

CHAPTER 5: Study 4

Under review: Int J Shoulder Surg

Psychophysical and Patient Factors as Determinants of Pain, Function and Health Status in Shoulder Disorders

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Conflict of Interests: We, the authors of the manuscript, do not have a direct/indirect financial relation with the commercial/non-commercial identities mentioned in the paper that might lead to a conflict of interests.

Author Contributions: Zakir Uddin conceptualized the research questions, study designs, data collection, data analyses and writing the drafts of manuscripts. Dr. Joy MacDermid provided

required expertise, assisted with refining objectives and designs for each of the studies, assisted with establishing data collection and editing the manuscripts. Dr. Victoria Galea and Ms. Anita R Gross provided their content expertise, edited the manuscripts. Dr. Jaydeep Moro assisted with data collection.

Abstract

Objective: To estimate the extent to which psychophysical quantitative sensory test (QST) and patient factors (gender, age and comorbidity) predict pain, function and health status in people with shoulder disorders. To determine if there are gender differences for QST measures in current perception threshold (CPT), vibration threshold (VT) and pressure pain (PP) threshold and tolerance.

Design: A cross-sectional study design.

Setting: MacHAND Clinical Research Lab at McMaster University.

Subjects: 34 surgical and 10 nonsurgical participants were recruited.

Method: Participants were asked to complete self-reported outcome measures about pain (numeric pain rating, pain catastrophizing, shoulder pain and disability index) and health status (Short Form -12). Participants completed QST at 4 standardized locations and then a shoulder performance-based outcome measure (FIT-HaNSA). Pearson's r was computed to determine the relationships between QST variables and patient factors with either pain, function or health status. Eight regression models were built to analysis QST's and patient factors separately as predictors of either pain, function or health status. An independent sample t-test was done to evaluate the gender effect on QST.

Results: Greater PP threshold and PP tolerance was significantly correlated with higher shoulder functional performance ($r = .31-.44$) and lower self-reported shoulder disability ($r = -.32$ to $-.36$).

VT and CPT were not significantly related to pain, function or health status, with the exception of VT on the little finger where lower threshold was correlated to a lower pain intensity ($r = .50$) and better functional performance ($r = -.34$). Higher comorbidity was consistently correlated ($r = .31-.46$) with poorer pain, function and health status. Older age was correlated to more pain intensity and less function ($r = .31-.57$). In multivariate models, patient factors contributed significantly to pain, function or health status models ($r^2 = .19-.36$); whereas QST did not. QST was significantly different between males and females [in PP threshold (3.9-6.2, $p < .001$) and PP tolerance (7.6-12.6, $p < .001$) and CPT (1.6-2.3, $p = .02$)].

Conclusions: Psychophysical dimensions and patient factors (gender, age and comorbidity) affect self-reported and performance-based outcome measures in people with shoulder disorders. Given the multivariate nature of disability, large samples are required to identify the most important predictors and interactions.

Key Words: shoulder pain, abnormal sensory function, potential risk factors, sensory evaluation

Abbreviations: International Association for the Study of Pain (IASP); Quantitative Sensory Testing (QST); Current Perception Threshold (CPT); Vibration Threshold (VT); Pressure Pain (PP); Shoulder Pain and Disability Index (SPADI); Numeric Rating Scale (NRS); pain catastrophizing scale (PCS); Pearson r correlation (r); Intraclass Correlation Coefficient (ICC); Functional Impairment Test-Head and Neck, Shoulder, Arm (FIT-HaNSA); Quick Disability Subscale of Disabilities of the Arm, Shoulder and Hand (QuickDASH).

Introduction

Shoulder disorders are the third most common musculoskeletal disorder [1,2] and cause substantial disability [3,4]. Accordingly, the disorder is a medical and socio-economic challenge to society [5,7]. Systematic reviews have estimated a 1 to 3% incidence of shoulder pain and 5-47% yearly prevalence in the general population [6,7]. Reported incidence and prevalence figures of shoulder pain vary according to patient factors (e.g. age, gender, and comorbidity). Older age is associated with greater shoulder pain as arthritis [8,9] and rotator cuff degeneration [9] increase over the lifespan. Prevalence and incidence of shoulder pain has been reported to be higher in females [8], whereas gender is not a factor for radiological changes in the shoulder joint after controlling for age [9]. Comorbidity has been associated with poorer pain, function, and health status in patients with chronic rotator cuff tears [10].

Chronic shoulder pain development is common, as it has been estimated to affect 11% of the working population [11,12]. The International Association for the Study of Pain (IASP) has defined chronic pain as a pain syndrome lasting more than 3 months [13]. The IASP recognizes chronic pain as a serious global chronic health problem with substantial economic impact [14]. Chronic musculoskeletal pain has multiple aetiologies including chronic diseases like arthritis; acute injuries like fractures [15]; or can persist following major surgery [16]. Neuropathic pain (i.e. a lesion or disease of the somatosensory nervous system) [17] is a subset of the chronic pain population [18,19]. Neuropathic pain often presents with hypo or hyper-sensory function (i.e. hypoesthesia or hyperesthesia) [20]. These two abnormal sensory functions are also common in chronic pain [21].

It is now recognized that chronic (persistent) pain can become a disease [9]. There is a need for appropriate assessments that will identify risk factors and promote early intervention to reduce the burden [14,22]. Sensory abnormalities and persistent pain have been a reported risk factor for higher pain by 2.68 for hypoesthesia and 6.27 for hyperesthesia in a large population based study [23]. Psychophysical quantitative sensory testing (QST) is a choice for semi-objective (combination of subjective and objective) measurement of both hypo and hyper sensory function targeting small and large nerve fibers [20]. This has potential to contribute to the assessment of shoulder conditions, if it can be shown to help with diagnosis, treatment selection or prognosis.

Approaches to evaluating sensibility include methods that identify the ability to detect sensory stimuli or to perceive pain. Detection of sensory stimuli can include detection threshold or ability to discriminate different stimuli. Measurement of pain detection includes pain threshold or tolerance testing. A potential drawback to QST is the burden of testing, which can include time and equipment costs.

In musculoskeletal disorders, pain and function are primary health outcomes. Function can be measured by self-report or performance-based tests that are assumed to indicate patient's ability to be functional in daily life. Previous research has established, across numerous musculoskeletal conditions, that self-reported and performance-based measures are moderately related in musculoskeletal disorders.

The main objective of this study was to estimate the extent to which QST and patient factors (age, gender, and comorbidity) predict pain, function and health status in people with shoulder disorder. The second objective of this study was to determine if there are gender differences for QST (psychophysical) measures in current perception threshold (CPT) vibration threshold (VT) and pressure pain (PP) threshold and tolerance for this patient population.

Materials and Methods

Study design and participants

In a cross-sectional study design 34 surgical and 10 nonsurgical participants were recruited. The surgical group of participants undergoing surgery for rotator cuff tear, shoulder impingement, or total shoulder joint arthroplasty) were recruited from McMaster University affiliated orthopedic surgery clinics. The nonsurgical group of participants (with shoulder pain for more than 3 months and who may or may not have been seeking clinical care of shoulder pain) were recruited through flyers. The study protocol was approved by the Hamilton Integrated Research Ethics Board (a jointly constituted board of St. Joseph's Healthcare Hamilton, Hamilton Health Sciences and McMaster University's Faculty of Health Sciences). Informed consent was obtained from all participants prior to testing. All participants were asked to complete self-reported outcome measures and then underwent performance and quantitative sensory tests in the MacHAND clinical research lab at McMaster University.

Participants *inclusion criteria* were: age between 18-85 years, fluency in English (reading and speaking), ability to complete all assessments, complaints of pain limited to shoulder area,

documented or suspected shoulder pathology and confirmed by referring surgeon from physical examination or imaging evidence (only for surgical group), scheduled for shoulder impingement release or rotator cuff reconstruction or shoulder arthroplasty or combination of these shoulder surgeries (only for surgical group), at least 3 months duration of pain. *Exclusion criteria* were: any neurological disorders or pre-existing neuropathic pain as indicated by specific neuropathic pain treatment/diagnostic procedures, current pain complaints from prior shoulder surgery, history of recent shoulder fracture, tumor, cancer or infection, history of chronic pain disorder (previously diagnosed), currently under psychiatric management (from history of medication), high risk of surgery due to any comorbid condition, and patients who are unable to complete the test procedures.

Study Measures

All measures were summarized in Table 1, and described as follows:

1.0 Pain Measures

1.1 Shoulder Pain and Disability Index (SPADI) – Pain Subscale

Shoulder specific pain was measured using the pain subscale of the SPADI [24-26]. The SPADI contains five shoulder specific pain items (pain subscale). In the pain subscale, each item is rated on a 0-10 numeric scale (no pain to worst pain imaginable) and the total score is transformed in % (0-100). A systematic review [26] demonstrated that the SPADI is a reliable and valid ($ICC \geq .89$, $\alpha > .90$) measuring tool for shoulder disorder.

1.2 Numeric Rating Scale (NRS) of Pain

The 11-point NRS of pain was used to capture the participant's level of pain. The scale is anchored from (0-10) with the phrase "no pain" to "worst imaginable pain." Patients rated their current level of pain before testing. The NRS of pain has been shown to be reliable and valid [27-29]. NRS of pain is a sensitive scale and good for parametric data analysis [27].

1.3 Pain Catastrophizing Scale (PCS)

It is assumed that pain catastrophizing reflects a negative coping strategy that may affect cognition around pain. Pain catastrophizing was measured with a pain catastrophizing scale [30], which is a 13-item self-report scale. This scale measures three different categories of pain catastrophizing (e.g. rumination, magnification and helplessness) [31].

2.0 Function Measures

2.1 Functional Impairment Test-Head and Neck, Shoulder, Arm (FIT-HaNSA)

Functional performance was measured using the FIT-HaNSA that has been validated as a functional performance tests for shoulder disorders [32]. The FIT-HaNSA is a 15-minute function test for each arm with three components/levels tasks that require repeated movement of the upper limb. The testing time of each repeated task performance is up to 5 minutes. The actual duration of the patient's performance is measured by a stopwatch. The average time of the three tasks' performance is the score for the test. It was performed using the JTech JobSim System (JTECH Medical, Salt Lake City, UT, USA).

2.2 Shoulder Pain and Disability Index (SPADI) – Disability Subscale

Shoulder specific disability was measured using the disability subscale of the SPADI [24-26]. The SPADI contains 8 disability items (disability subscale). In the disability subscale, each

item is rated on a 0-10 numeric scale (no difficulty to so difficult requiring help) and the total score is transformed in % (0-100).

2.3 Disabilities of the Arm, Shoulder and Hand (QuickDASH)

The Quick-DASH [34] contains 11-items from the original DASH and in early studies, has shown equivalent psychometric properties [29,35-39]. The QuickDASH was scored using the disability/symptom section (11-items, scored 1-5). The assigned values for all completed responses (at least 10 of the 11-items) are summed and averaged to produce a score out of five. This value is then transformed to a 0-100 scale by subtracting one and multiplying by 25. A higher score is the indicator of greater disability.

3.0. Health Status Measures

3.1 Short Form 12 (SF-12)

The recognized and valid SF-12 [40] version 2 was used to measure overall health. The SF-12 consists of both physical and mental domains of 12-items. The scoring system is norm-based, and summary scores (summing across all 12-items) are obtained for each of the domains: physical component summary (PCS) score and mental component summary (MCS) score; a higher levels of health is indicated by a higher score

4.0 Quantitative Sensory Testing (QST)

4.1 Pressure Pain (PP) Sensitivity

PP threshold and PP tolerance [41-43] were measured using the computerized JTech algometer (JTECH Medical, Salt Lake City, UT, USA). The applied algometric pressures at an

“uncomfortable” (pain threshold) and at “intolerable” (pain tolerance) levels were determined by patient response using a standard protocol [44,45]. The shoulder (mid deltoid muscle) and shin (anterior aspect of tibia) of the affected side were tested (Figure 1).

4.2 Vibration Threshold (VT)

VT was measured in the hand using a 50 Hz vibrometer [46]. In this test, the subject's digit is placed lightly on the device's vibrating pin. A sample stimulus is provided as practice before testing. During the test, a ramped protocol of intermittent vibration stimuli is applied to the digit. The subject indicates when the stimulus was perceived with a handheld trigger. The vibrometer's software determines a threshold score after multiple cycles. The test was performed on the middle (D3) and little (D5) fingers (Figure 2).

4.3 Current Perception Threshold (CPT)

CPT testing [47-54,64] was performed using the Rapid Current Perception Threshold (R-CPT) protocol of the Neurometer CPT/C (Neurotron, Incorporated, Baltimore, MD, USA). The R-CPT test protocol requires the subject to self-administer electrical stimuli, increasing in intensity through a series of 25 predetermined levels. The subject presses and holds a button to start the test and releases the button as soon as a stimulus is detected. The test is double-blinded, and the non-noxious current is delivered via small surface electrodes placed on the medial and lateral sides of the distal phalanx. The Neurometer software determines the threshold score after multiple cycles. The test was performed at the 5Hz frequency on the tip of the middle (D3) and little (D5) fingers, as well as at the shoulder (mid deltoid) [Figure 3].

4.4 Patient Factor (Comorbidity Status)

The Katz comorbidity scale was used to detect the number and severity of 12 co-morbid conditions [55,56]. Participants are asked to indicate if they currently have the condition and whether or not they receive treatment for it, and whether activities are limited by the condition. A patient can receive a maximum of three points for each condition: one point for if they have been diagnosed with the comorbid health, one point if it requires treatment, and one point if causes activity limitation [55]. The total score is calculated by summing across 12-items [10].

Data Analysis

All data were entered into SPSS 17.0 software (SPSS Inc., Chicago, IL). Data quality checking was performed before statistical analysis. Descriptive statistics (e.g. skewness, kurtosis) and test of normality (Kolmogorov-Smirnov, Shapiro-Wilk, Histogram, and QQ-Plot) were conducted on all variables. Assumptions' of multiple regressions (e.g. multicollinearity and singularity, outliers, normality, linearity, homoscedasticity) were checked and met except for insufficient sample size.

Mean and standard deviation were calculated for all measuring variables (e.g. outcome, predictor and patients factor) for both the surgical and nonsurgical groups, as well as the total sample. Pearson correlation coefficients were computed to describe the relationships between QST variables and patient factors with either pain, function or health status. Eight regression models were built to analyze QST's and patient factors separately as predictors of either pain, function or health status. An independent sample t-test (equal variance assumed) was done to evaluate the gender effect on QST. Significant level was determined by $p < .05$ for all interpretation of data.

Results

All participants had shoulder pain but were able to complete the study protocol without difficulty, including 34 patients recruited from a surgical waitlist and 10 patients recruited from the community. The age of the two patient subgroups was similar. Patients from the community had less pain, better shoulder performance and function, better health status and were predominantly female; whereas surgical patients were predominantly male as described in Table 2.

The bivariate relationships between different QSTs variables or patient factors with either pain, function or health status are shown in Table 3. These correlations indicate that greater PP threshold and tolerance had significant relationships with better shoulder functional performance ($r = .31-.44$) and less self-reported shoulder disability ($r = -.32$ to $-.36$). VT or CPT were not significantly related to pain, function or health status; there was one exception VT on the small digit (D5) was correlated to NRS of pain ($r = .50$) and functional performance/ FIT-HANSA ($r = .34$). Amongst the patient factors a higher comorbidity score was consistently correlated ($r = .31-.46$) with poorer pain, function and health status. Older age was correlated to more pain (except pain catastrophizing) and less function ($r = .31-.57$).

The data listed in Table 4 indicated that when multiple individual pain and sensory variables were entered as potential predictors of health outcomes, individually, none were strong predictors. The only significant prediction in these sensory models was current perception threshold as a predictor of physical health status. The total variability explained by all sensory variables ranged from 21% to 34%. Contrary to expectations, the R^2 for the pain measures did

not exceed that obtained for function or health status measures. The regression models in Table 5 indicated that when age, gender and comorbidity (patient factors) were considered in a multivariate model of the same health outcomes, comorbidity was the most common predictor. Comorbidity was significantly related to pain catastrophizing, Quick-DASH scores, and both physical and mental health status. In these multivariate models, older age was also associated with higher shoulder disability on the SPADI and better mental health status. Despite significant predictors, the overall R^2 for these models ranged from 15% to 36%.

The impact of gender on QST scores was indicated in Table 6. Significant mean differences (male –female) were in PP threshold (3.9-6.2, $p < .001$) and PP tolerance (7.6-12.6, $p < .001$) tests (in all locations) and CPT in the middle finger and shoulder (1.6-2.3, $p = .02$).

Discussion

The study provided preliminary evidence suggesting that pain threshold and tolerance affect functional performance. This was indicated by moderate bivariate correlations. Age and comorbidity had higher correlations suggesting they may play a larger or more consistent role. The impact of isolated pain and sensory variables was less evident in multivariate modeling where despite explaining 34% of the functional performance score, significant individual predictors were not identified. Conversely, when examining age, gender and comorbidity in multivariate models, although higher R^2 values were not achieved, the significance of comorbidity as a determinant of pain catastrophizing, self-reported function and health status was identified. Although males demonstrated higher pain threshold and tolerance, gender was

not associated with differences in pain, function or health status when considering multivariate modeling. These findings indicate the complex multivariate nature of musculoskeletal outcomes.

Our findings suggest the need for continued investigation of the potential role for QST in evaluation of shoulder disorders. However, given that gender influences the QST scores obtained, multivariate models should be powered sufficiently to allow for separate modeling of males and females to identify the true impact of QST on functional outcomes or at minimum sufficient power to allow for gender interactions to be tested. Gender differences in QST may have masked associations between QST and the functional outcomes. The current stimulus of QST (i.e. CPT) was not correlated to pain, function or health status at any of the three sites tested by bivariate correlations. We used 5Hz CPT, which is neuroselective to assess small fibers (C fiber) that carry pain information [47,48,54]. In multivariate modeling of all QST with potential predictor, it was the only one to demonstrate a significant relationship with physical health status. Our previous studies supported consistency, moderate construct and discriminative validity, good specificity, and moderate sensitivity of CPT in neck disorders [64,68]. Since previous studies have suggested that CPT has moderate reliability, this strategy may provide for a more stable and comprehensive indicator. We had hoped our regression modeling of different sensory modalities would provide a clear choice about the preferred test modality. Although no clear superior choice was identified and CPT was more consistently related to outcomes. We had expected that it would predict shoulder pain-function. VT was not related to the most of the variables of pain, function or health status. Although VT on the little finger was positively correlated to pain intensity and negatively correlated to functional performance, these findings

should not be considered conclusive evidence of clinical importance since there were also a number of nonsignificant correlations. Previous research has demonstrated chronic diffuse upper limb pain is associated with an elevation of VT [65].

Older age was related to more shoulder pain without any indication of a pain catastrophizing effect. This concurs with previous studies integrating greater shoulder pathology with age [8,9]. Older age was also associated with poorer self-reported shoulder function and performance. This concurs with the increasing prevalence and severity of shoulder pathology with age. Comorbid conditions were negatively related to pain, function and health status in this study. This is in agreement with a previous study that reported that comorbidities negatively impact on preoperative pain, function, and health status in patients with chronic rotator cuff tears [10]. This study adds that comorbidity also increases pain catastrophizing. This is consistent with our emerging understanding of pain catastrophizing, which can be affected by genetic, physical and psychological characteristics as well as previous negative experiences with recovery [66,67].

The relatively small sample precluded us testing interactions between QST and other variable in order to perform a gender specific analysis. This may have contributed to the lack of prediction. However, a recent systemic review and meta-analysis demonstrated that QST poorly explains pain and disability (function) [60]. This suggests adoption of QST in evaluation of shoulder disorders would be premature before substantive empirical evidence supports the usefulness of this evaluation. The static QST measures used in the study provide a limited perspective on a complex pain processing system [20]. It has been suggested that dynamic QST is better as it assesses the spatial and temporal summation as well as descending modulation of

pain [20]. In addition, suprathreshold pain processing can be assessed by magnitude rating for a suprathreshold stimulus [20]. We used threshold and tolerance parameter for QST measures in this study because these are commonly used in clinical practice. However, stimulus intensity/magnitude rating parameters of QST may be more relevant to clinical features (e.g. pain, function).

Our findings reaffirm the importance of patient factors in explaining pain, self-reported and performance-based function. Previous studies have reported that age is associated with greater shoulder pain and degeneration [8,9] and age is a significant covariate for QST [61].

Gender is acknowledged as an important consideration in shoulder conditions because of differences in prevalence of different shoulder conditions by gender. For example, prevalence and incidence of shoulder pain have been reported higher in female than male [9]. Gender has been reported to be independent of radiological/degenerative changes [8]. Furthermore, gender differences in pain threshold and tolerance are well accepted [62,63,65]. This study also demonstrates that QST measures are more sensitive (lower threshold) in female. Specifically, PP threshold and tolerance were significantly lower in female. Previous study on QST has indicated pain thresholds are lower in female than male [62,63,65] and detection thresholds were independent of gender [62]. All PP threshold and tolerance test scores were lower in female than male, although some detection threshold based tests (e.g. VT, CPT) were gender independent in our study. The greater sensitivity of females to pain threshold and pain tolerance may reflect differences in how sensory inputs are received at the tissue level or how they are processed from the periphery to the brain. However, this study indicates that gender differences in pain

threshold and tolerance may not necessarily lead to gender differences in shoulder related health outcomes including pain, function or health status. This differential suggests that gender needs to be carefully considered when examining shoulder disorders, and that all hypotheses should be tested separately between male and female subject to assure that conclusions made apply across genders. Again, these requirements suggest the need for larger sample sizes; and prespecified gender analyses.

Regression model with insufficient sample size is the main limitation of this study. QST measure tells us somatosensory information based on the stimulus-response parameter, and it is limited by semi-objective psychophysical evaluation. We used static type of QST measures in this study as it is commonly used to obtain relative stable response, whereas it provides a limited perspective on a complex pain processing system.

Conclusion

This cross sectional descriptive study suggests psychophysical tests (specifically pressure pain threshold and tolerance) may play a role in self-reported and performance-based outcome measures (e.g. pain, function and health status) for shoulder disorders. However, our findings suggest that PP threshold and tolerance tests are gender dependent, and that age and comorbidity also affect these outcomes. Thus the findings must be considered inconclusive until studies use a larger sample size that enables testing of interactions between age and comorbidity with psychophysical measures; and that conduct gender-specific analyses to determine if the relationships hold true across genders. This would be necessary before the potential role for QST to provide useful information in managing shoulder disorders can be determined. This is

particularly important since gender has been shown to relate to pain threshold and tolerance, but not to pain intensity, catastrophizing or functional outcomes in this study. Future study should focus on defining these more complex relationships and may consider using alternative sensory evaluations including dynamic QST and pain magnitude rating (for a suprathreshold stimulus) to elucidate the relationship between suprathreshold pain processing, descending control or central integration of pain and clinical features of shoulder pain.

References

1. Parsons S, Breen A, Foster N, et al. Prevalence and comparative troublesomeness by age of musculoskeletal pain in different body locations. *Fam Pract.* 2007;24(4):308-316.
2. Laslett LL, Burnet SP, Jones JA, Redmond CL, McNeil JD. Musculoskeletal morbidity: The growing burden of shoulder pain and disability and poor quality of life in diabetic outpatients. *Clin Exp Rheumatol.* 2007;25:422-9.
3. Badcock L, Lewis M, Hay E, McCarney R, Croft P. Chronic shoulder pain in the community: A syndrome of disability or distress? *Ann Rheum Dis.* 2002;61(2):128-131.
4. Pope DP, Croft PR, Pritchard CM, Silman AJ. Prevalence of shoulder pain in the community: The influence of case definition. *Ann Rheum Dis.* 1997;56(5):308-312.
5. van der Heijden GJMG. Shoulder disorders: A state-of-the-art review. *Best Practice & Research Clinical Rheumatology.* 1999;13(2):287-309.
6. Luime J, Koes B, Hendriksen I, et al. Prevalence and incidence of shoulder pain in the general population; a systematic review. *Scand J Rheumatol.* 2004;33(2):73-81.
7. Kuijpers T, van der Windt DAWM, van der Heijden GJMG, Bouter LM. Systematic review of prognostic cohort studies on shoulder disorders. *Pain.* 2004;109(3):420-431.
8. Bonsell S, Pearsall IV A, Heitman R, Helms C, Major N, Speer K. The relationship of age, gender, and degenerative changes observed on radiographs of the shoulder in asymptomatic individuals. *J Bone Joint Surg Br.* 2000;82(8):1135-1139.
9. Cassou B, Derriennic F, Monfort C, Norton J, Touranchet A. Chronic neck and shoulder pain, age, and working conditions: Longitudinal results from a large random sample in France. *Occup Environ Med.* 2002;59(8):537-544.

10. Tashjian RZ, Henn RF, Kang L, Green A. The effect of comorbidity on self-assessed function in patients with a chronic rotator cuff tear. *The Journal of Bone & Joint Surgery*. 2004;86(2):355-362.
11. McBeth J, Jones K. Epidemiology of chronic musculoskeletal pain. *Best Practice & Research Clinical Rheumatology*. 2007;21(3):403-425.
12. Herin F, Vézina M, Thaon I, Soulat JM, Paris C. Predictors of chronic shoulder pain after 5 years in a working population. *Pain*. 2012;153(11):2253-2259.
13. Merskey H, Bogduk N. Task Force on Taxonomy of the International Association for the Study of Pain. Classification of chronic pain: descriptions of chronic pain syndromes and definition of pain terms. Seattle: IASP, 1994.
14. Declaration of Montréal by the International Association for the Study of Pain (IASP): PainSummit-2010; available at, <http://www.iasp-pain.org/Content/NavigationMenu/Advocacy/DeclarationofMontr233al/default.htm>
15. MacDermid JC, Donner A, Richards RS et al. Patient versus injury factors as predictors of pain and disability six months after a distal radius fracture. *J Clin Epidemiol*. 2002;55:849-54.
16. Macrae WA. Chronic post-surgical pain: 10 years on. *Br J Anaesth*. 2008;101:77–86.
17. IASP Taxonomy (available at), <http://www.iasp-pain.org/Content/NavigationMenu/GeneralResourceLinks/PainDefinitions/default.htm>
18. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery: A review of predictive factors. *Anesthesiology*. 2000;93(4):1123-1133.
19. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: A maladaptive response of the nervous system to damage. *Annu Rev Neurosci*. 2009;32:1-32.
20. Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *J Pain*. 2009;10(6):556-572.
21. Maier C, Baron R, Tölle T, et al. Quantitative sensory testing in the german research network on neuropathic pain (DFNS): Somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain*. 2010;150(3):439-450.
22. Scholz J, Woolf CJ. Can we conquer pain? *Nat Neurosci*. 2002;5:1062-1067.
23. Johansen A, Romundstad L, Nielsen CS, Schirmer H, Stubhaug A. Persistent postsurgical pain in a general population: Prevalence and predictors in the tromsø study. *Pain*. 2012. 153(7):1390-6.
24. Roach KE, Budiman-Mak E, Songsiridej N, Lertratanakul Y. Development of a shoulder pain and disability index. *Arthritis Care Res*. 1991;4(4):143-149.

25. MacDermid JC, Solomon P, Prkachin K. The Shoulder Pain and Disability Index demonstrates factor, construct and longitudinal validity. *BMC Musculoskelet Disord* 2006 February 10;7(1):12.
26. Roy JS, MacDermid JC, Woodhouse LJ. Measuring shoulder function: a systematic review of four questionnaires. *Arthritis Rheum*. 2009; 15;61(5):623-632.
27. Williamson A, Hoggart B. Pain: A review of three commonly used pain rating scales. *J Clin Nurs*. 2005;14(7):798-804.
28. Krebs EE, Carey TS. Accuracy of the pain numeric rating scale as a screening test in primary care. *J Gen Inter Med* 2007;22(10):1453-1458.
29. Mintken PE, Glynn P, Cleland JA. Psychometric properties of the shortened disabilities of the arm, shoulder, and hand questionnaire (QuickDASH) and numeric pain rating scale in patients with shoulder pain. *J Shoulder Elbow Surg*. 2009;18(6):920-926.
30. Sullivan HJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: development and validation. *Psychol Assess*. 1995;7:524-32.
31. Osman A, Barrios FX, Gutierrez PM, Kopper BA, Merrifield T, Grittmann L. The pain catastrophizing scale: Further psychometric evaluation with adult samples. *J Behav Med*. 2000;23(4):351-365.
32. MacDermid JC, Ghobrial M, Quirion KB et al. Validation of a new test that assesses functional performance of the upper extremity and neck (FIT-HaNSA) in patients with shoulder pathology. *BMC Musculoskelet Disord*. 2007;8:42.
33. Osman A, Barrios FX, Kopper BA, Hauptmann W, Jones J, O'Neill E. Factor structure, reliability, and validity of the pain catastrophizing scale. *J Behav Med*. 1997;20(6):589-605.
34. Beaton DE, Wright JG, Katz JN: Development of the QuickDASH: comparison of three item-reduction approaches. *J Bone Joint Surg Am*. 2005;87:1038-1046.
35. Fayad F, Lefevre-Colau MM, Gautheron V, Mace Y, Fermanian J, Mayoux-Benhamou A, Roren A, Rannou F, Roby-Brami A, Revel M, Poiraudau S: Reliability, validity and responsiveness of the French version of the questionnaire Quick Disability of the Arm, Shoulder and Hand in shoulder disorders. *Man Ther*. 2009;14:206-212.
36. Wu A, Edgar DW, Wood FM: The QuickDASH is an appropriate tool for measuring the quality of recovery after upper limb burn injury. *Burns*. 2007;33:843-849.

37. Matheson LN, Melhorn JM, Mayer TG, Theodore BR, Gatchel RJ: Reliability of a visual analog version of the QuickDASH. *J Bone Joint Surg Am.* 2006;88:1782-1787.
38. Imaeda T, Toh S, Wada T, Uchiyama S, Okinaga S, Kusunose K, Sawaizumi T: Validation of the Japanese Society for Surgery of the Hand Version of the Quick Disability of the Arm, Shoulder, and Hand (QuickDASH-JSSH) questionnaire. *J Orthop Sci.* 2006;11:248-253.
39. Gummesson C, Ward MM, Atroshi I: The shortened disabilities of the arm, shoulder and hand questionnaire (QuickDASH): validity and reliability based on responses within the full-length DASH. *BMC Musculoskelet Disord.* 2006;7:44
40. Riddle DL, Lee KT, Stratford PW: Use of SF-36 and SF-12 health status measures: a quantitative comparison for groups versus individual patients. *Med Care.* 2001;39: 867-878.
41. Chesterton LS, Sim J, Wright CC, Foster NE. Interrater reliability of algometry in measuring pressure pain thresholds in healthy humans, using multiple raters. *Clin J Pain.* 2007;23(9):760-766.
42. Bernhardt O, Schiffman EL, Look JO. Reliability and validity of a new fingertip-shaped pressure algometer for assessing pressure pain thresholds in the temporomandibular joint and masticatory muscles. *J Orofac Pain.* 2007;21(1):29-38.
43. Kosek E, Ekholm J, Nordemar R. A comparison of pressure pain thresholds in different tissues and body regions. Long-term reliability of pressure algometry in healthy volunteers. *Scand J Rehabil Med.* 1993;25:117-124.
44. Walton DM, Macdermid JC, Nielson W, Teasell RW, Nailer T, Maheu P. A descriptive study of pressure pain threshold at 2 standardized sites in people with acute or subacute neck pain. *J Orthop Sports Phys Ther.* 2011 Sep;41(9):651-7.
45. Finocchietti S, Andresen T, Arendt-Nielsen L, Graven-Nielsen T. Pain evoked by pressure stimulation on the tibia bone—Influence of probe diameter on tissue stress and strain. *European Journal of Pain.* 2012;16(4):534-42.
46. Hubbard MC, MacDermid JC, Kramer JF, Birmingham TB. Quantitative vibration threshold testing in carpal tunnel syndrome: analysis strategies for optimizing reliability. *J Hand Ther.* 2004;17(1):24-30.
47. Uddin Z, MacDermid JC, Galea V, Gross AR, Pierrynowski J. The Current Perception Threshold Test Differentiates Categories of Mechanical Neck Disorder. *J Orthop Sports Phys Ther:* in press.
48. Katims JJ, Rouvelas P, Sadler BT, Weseley SA. Current perception threshold. Reproducibility and comparison with nerve conduction in evaluation of carpal tunnel syndrome.

ASAIO Trans. 1989;35:280-284.

49. Katims JJ, Patil AS, Rendell M et al. Current perception threshold screening for carpal tunnel syndrome. Arch Environ Health. 1991;46:207-212.

50. Nishimura A, Ogura T, Hase H et al. Evaluation of sensory function after median nerve decompression in carpal tunnel syndrome using the current perception threshold test. J OrthopSci. 2003;8:500-504.

51. Pitei DL, Watkins PJ, Stevens MJ, Edmonds ME. The value of the Neurometer in assessing diabetic neuropathy by measurement of the current perception threshold. Diabet Med. 1994;11:872-876.

52. Prendergast JJ, Miranda G, Sanchez M. Improvement of sensory impairment in patients with peripheral neuropathy. Endocr Pract. 2004;10:24-30.

53. Rendell MS, Katims JJ, Richter R, Rowland F. A comparison of nerve conduction velocities and current perception thresholds as correlates of clinical severity of diabetic sensory neuropathy. J Neurol Neurosurg Psychiatry. 1989;52:502-511.

54. Weseley SA, Sadler B, Katims JJ. Current perception: preferred test for evaluation of peripheral nerve integrity. ASAIO Trans. 1988;34:188-193.

55. Katz JN, Chang LC, Sangha O, Fossel AH, Bates DW. Can comorbidity be measured by questionnaire rather than medical record review? Med Care. 1996;34(1):73-84.

56. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis Rheum. 2003;;49(2):156-163.

57. Kumta P, MacDermid JC, Mehta SP, Stratford PW. The FIT-HaNSA demonstrates reliability and convergent validity of functional performance in patients with shoulder disorders. J Orthop Sports Phys Ther. 2012;42(5):455-464.

58. Luo X, George ML, Kakouras I, et al. Reliability, validity, and responsiveness of the short form 12-item survey (SF-12) in patients with back pain. Spine. 2003;28(15):1739-1745.

59. Salyers MP, Bosworth HB, Swanson JW, Lamb-Pagone J, Osher FC. Reliability and validity of the SF-12 health survey among people with severe mental illness. Med Care. 2000;38(11):1141-1150.

60. Hübscher M, Moloney N, Leaver A, Rebbeck T, McAuley JH, Refshauge KM. Relationship between quantitative sensory testing and pain or disability in people with spinal pain—a systematic review and meta-analysis. *Pain*. 2013 154(9):1497–1504.
61. Costantini M, Tunks K, Wyatt C, Zettel H, MacDermid JC. Age and upper limb tension testing affects current perception thresholds. *J Hand Ther*. 2006;19(3):307-317.
62. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the german research network on neuropathic pain (DFNS): Standardized protocol and reference values. *Pain*. 2006;123(3):231-243.
63. Berkley KJ. Sex differences in pain. *Behav Brain Sci*. 1997; 20(3): 371-380.
64. Uddin Z, MacDermid JC, Galea V, et al. Reliability Indices, Limits of Agreement and Construct Validity of Current Perception Threshold Test in Mechanical Neck Disorder. *Crit Rev Phys Rehabil Med*. 2013;25(3-4):25–37.
65. Sandén H, Wallin BG, Hagberg M. Chronic pain has a small influence and mood has no influence on vibrotactile perception thresholds among working women. *Muscle Nerve* 2010;42(3):401-409.
66. Wideman TH, Asmundson GG, Smeets RJ et al. Rethinking the fear avoidance model: toward a multidimensional framework of pain-related disability. *Pain*. 2013;154(11):2262-2265.
67. Wideman TH, Sullivan MJ. Differential predictors of the long-term levels of pain intensity, work disability, healthcare use, and medication use in a sample of workers' compensation claimants. *Pain*. 2011;152(2):376-383.
68. Uddin Z, MacDermid JC, Galea V, Gross AR, Pierrynowski MR. The Current Perception Threshold Test Differentiates Categories of Mechanical Neck Disorder. *J Orthop Sports Phys Ther*. 2014: in press.

Figures



Figure 1. The set-up for the pressure pain threshold and tolerance test (by a computerized Algometer) procedure is depicted. The test was done on the shoulder (left) and shin bone (right).



Figure 2. Set-up of Vibrometer with 50 Hz stimulus. The test was done on the middle and little fingers.

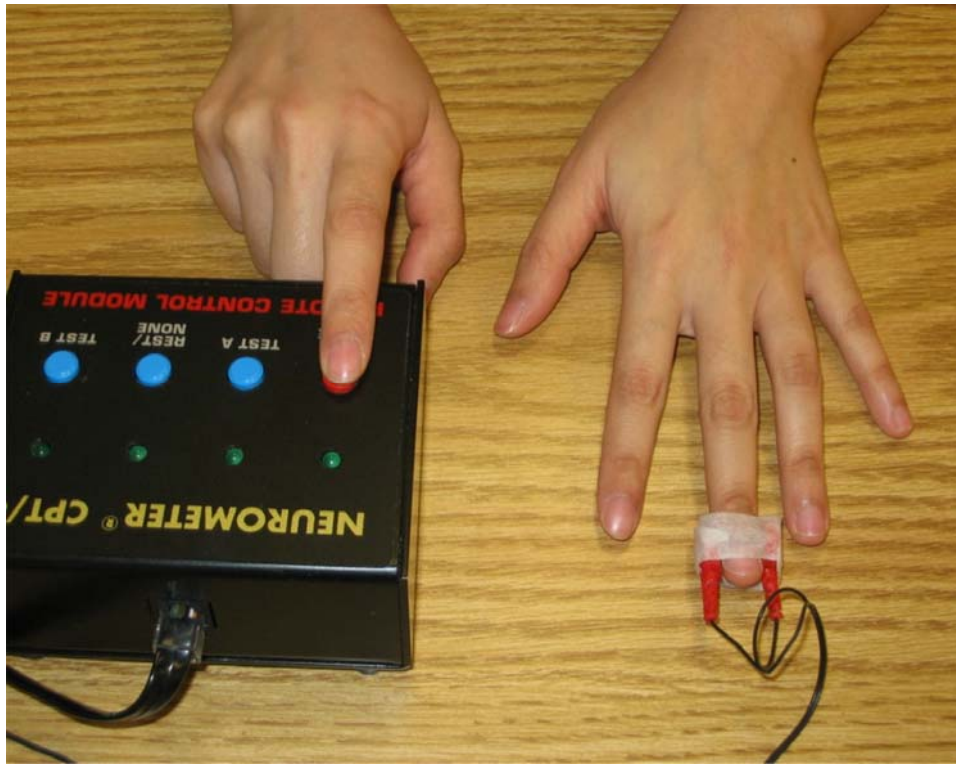


Figure 3. The set-up for the current perception threshold (CPT) test procedure is depicted. The Rapid-CPT values (1 to 25) is obtained from the minimal strength of alternating current (between 0 to 10 mA) stimulus that the patient could detect. The test was performed at the 5Hz frequency on the tip of the middle (D3) and little (D5) fingers, as well as at the shoulder (mid deltoid).

Tables

Table 1. Summary of the Study Measures

<i>Construct</i>	<i>Perspective of Score</i>	<i>Measuring Tool</i>	<i>Score Unit/Range</i>	<i>Reliability</i>
Outcome (Dependent) Variables				
Pain	Self-report	Shoulder Pain and Disability Index (SPADI) – Pain Subscale [24-26]	0-10 (5 pain items)	ICC $\geq$ 0.89, α > 0.90 [26]
	Self-report	Numeric rating scale (NRS) of Pain [27-29]	11 grade (0-10) pain rating scale	Sensitivity=71% (for score of 1) [27,28], ICC=.74 [29]
	Self-report	Pain Catastrophizing Scale (PCS) [30]	0-4 (13 items)	α = 0.92 (with outpatients) [33]
Functional	Timed performance	FIT-HaNSA (Functional Impairment Test-Head and Neck, Shoulder, Arm) [32]	Average time in second for the 3 tasks that require lifting at waist-level, lifting at eye-level or overhead manipulation for up to 5 minutes.	ICC have ranged from .79-.98 [10]
	Self-report	Shoulder Pain and Disability Index (SPADI) – Disability Subscale [24-26]	0-10 (8 disability items)	ICC $\geq$.89, α > .90 [26]
	Self-report	QuickDASH (Disabilities of the Arm, Shoulder and Hand) [29,34-39]	Disability/symptom (11 items, scored 1-5)	ICC=.90-.94 [36,37]
Health Status	Self-report : Physical and Mental Component Summary (PCS and MCS)	SF-12 (v2 health survey) [40]	0-5 (12 items), finally PCS and MCS scores are converted range of 0 to 100	ICC $\geq$.77, α > .77 [58,59]
Predictor (Independent) Variables: Psychophysical factors				
Pressure Pain Sensitivity	Pressure pain threshold and pain tolerance	Computerized JTech algometer [43]	Pressure level at uncomfortable and intolerable are determined in muscle and bone	ICC range = .73-.99 [41,42]
Vibration Sensation Threshold	Threshold value of vibration sensation	JTech vibrometer [46]	50Hz Ramped protocol and threshold determined in micrometers.	ICC = .86- .89 [46]
Current Perception Threshold	Threshold value of current perception	Neurometer CPT/C [47,48,54]	1-25 (R-CPT protocol, 5Hz)	Sensitivity = 73-92% [47,48,54]
Patient factor (Covariate)				
Comorbidity	Self-report	Katz comorbidity index [10]	0-3 (12 items score)	ICC = .91 [55]

Table 2. Participant Demographics and Measures (Mean $\pm$ Standard Deviation)

Construct	Measure	Surgical group (n=34)	Non-Surgical group (n=10)	Overall (n=44)
PAIN	SPADI-Pain	57.1 $\pm$ 27.1	37 $\pm$ 17	52.5 $\pm$ 26.4
	NRS of Pain	2.21 $\pm$ 2.3	2.00 $\pm$ 1.6	2.2 $\pm$ 2.1
	PainCS	16.7 $\pm$ 15.6	13.7 $\pm$ 16	16 $\pm$ 15.5
FUNCTION	FIT-HaNSA	158.5 $\pm$ 95.1	183.3 $\pm$ 65.4	164.2 $\pm$ 89
	SPADI-Disability	36.4 $\pm$ 27.9	19.4 $\pm$ 14	32.5 $\pm$ 26.3
	QuickDASH	38.2 $\pm$ 21.8	23.9 $\pm$ 19.4	34.8 $\pm$ 21.9
HEALTH STATUS	SF12-PCS	39.5 $\pm$ 9.8	47.8 $\pm$ 8.5	41.4 $\pm$ 10.1
	SF1-2MCS	49.5 $\pm$ 12.3	45.1 $\pm$ 12.1	48.5 $\pm$ 12.2
Psychophysical QSTs	PPT _h Sh	8.4 $\pm$ 5.9	4.5 $\pm$ 1.9	7.5 $\pm$ 5.5
	PPT _o Sh	16.5 $\pm$ 11.9	9.2 $\pm$ 3.4	14.8 $\pm$ 11
	PPT _h T	7.1 $\pm$ 3.6	4.9 $\pm$ 2.2	6.6 $\pm$ 3.5
	PPT _o T	11.5 $\pm$ 6.1	6.5 $\pm$ 2.2	10.3 $\pm$ 5.8
	VTD3	11.7 $\pm$ 8.5	7 $\pm$ 2.1	10.7 $\pm$ 7.8
	VTD5	16.7 $\pm$ 25.6	17.6 $\pm$ 30.2	16.9 $\pm$ 26.3
	CPTD3	10.6 $\pm$ 2.9	8.6 $\pm$ 3.6	10.1 $\pm$ 3.1
	CPTD5	10.9 $\pm$ 2.4	10 $\pm$ 1.8	10.7 $\pm$ 2.3
	CPT _h Sh	8.6 $\pm$ 2.2	8.1 $\pm$ 2.6	8.5 $\pm$ 2.3
PATIENT FACTORS	Age (years)	46 $\pm$ 16.4, Min-Max =18-79	44.2 $\pm$ 17.5, Min- Max =21-67	45.6 $\pm$ 16.4, Min- Max =18-79
	Gender	M= 25 (74%), F= 9 (26%)	M= 2 (20%), F= 8 (80%)	M=27 (61%), F=17 (39%)
	Comorbidity	4.1 $\pm$ 4.2	3.9 $\pm$ 1.9	4.1 $\pm$ 3.8
OTHER DEMOGRAPHICS	Dominant side	R=29 (85%), L=5 (15%)	R=10 (100%)	R=39 (89%), L=5 (11%)
	Affected side	R=13 (38%), L=21 (62%)	R=5 (50%), L=4 (40%), B=1(10%)	R=18 (41%), L=25 (57%), R+L=1(2%)

Abbreviations : CPTD3, Current Perception Threshold at digit 3 (middle finger); CPTD5, Current Perception Threshold at digit 5 (little finger); CPT_hSh, Current Perception Threshold at Shoulder (mid-deltoid); DASH, Disabilities of the Arm, Shoulder and Hand; F= female; FIT-HaNSA, (Functional

Impairment Test-Head and Neck, Shoulder, Arm); L, Left; M, Male; MCS, Mental Component Summary; NRS, Numeric Rating Scale; n, number of participants; PainCS, Pain Catastrophizing Scale; PCS, Physical Component Summary; PPT_{Sh}, Pressure Pain Threshold at Shoulder (mid-deltoid); PPT_T, Pressure Pain Threshold at Tibia (Shinbone); PPT_{Sh}, Pressure Pain Tolerance at Shoulder (mid-deltoid); PPT_T, Pressure Pain Tolerance at Tibia (Shinbone); QST, Quantitative Sensory Testing; R, Right; SF12, Short Form 12-item health survey version 2; SPADI, Shoulder Pain and Disability Index; VTD₃, Vibration Threshold at digit 3 (middle finger); VTD₅, Vibration Threshold at digit 5 (little finger).

Table 3. The relationships between Psychophysical QSTs and Patient Factors with either Pain, Function or Health Status (n=44)

	PAIN			FUNCTION			HEALTH STATUS	
	SPADI-Pain	NRS of Pain	PainCS	FIT-HaNSA	SPADI - Disability	Quick-DASH	SF12-PCS	SF12-MCS
<i>QST variables</i>								
PPT _{Sh}	-.07	-.01	-.11	.31*	-.23	-.24	.11	.17
PPT _{Sh}	-.24	-.24	-.29	.32*	-.36*	-.34	.22	.19
PPT _{Th}	-.08	-.07	-.10	.40**	-.25	-.22	.11	.18
PPT _{ToT}	-.14	-.14	-.20	.44**	-.32*	-.23	.07	.29
VTD ₃	.14	-.24	-.12	-.25	.09	.07	-.11	.19
VTD ₅	.16	.50**	-.10	-.34*	.17	.22	-.24	.17
CPTD ₃	.04	.06	-.16	-.02	-.06	.16	-.16	.01
CPTD ₅	.12	.21	-.14	.21	.004	-.07	.13	.16
CPT _{Sh}	.16	.10	.14	-.22	.21	.18	-.22	-.15
<i>Patient Factors</i>								
Age	.31*	.38*	-.001	-.48**	.57**	.40**	-.30	.08
Comorbidity	.31*	.31*	.37*	-.35*	.46**	.42**	-.40**	-.43**

Abbreviations and Symbols: CPTD₃, Current Perception Threshold at digit 3 (middle finger); CPTD₅, Current Perception Threshold at digit 5 (little finger); CPT_{Sh}, Current Perception Threshold at Shoulder (mid-deltoid); DASH, Disabilities of the Arm, Shoulder and Hand; FIT-HaNSA, (Functional Impairment Test-Head and Neck, Shoulder, Arm); MCS, Mental Component Summary; NRS, Numeric Rating Scale; PainCS, Pain Catastrophizing Scale; PCS, Physical Component Summary; PPT_{Sh}, Pressure Pain Threshold at Shoulder (mid-deltoid); PPT_{Th}, Pressure Pain Threshold at Tibia (Shinbone); PPT_{ToSh}, Pressure Pain Tolerance at Shoulder (mid-deltoid); PPT_{ToT}, Pressure Pain Tolerance at Tibia (Shinbone); QST, Quantitative Sensory Testing; SF12, Short Form 12-item health survey version 2; SPADI, Shoulder Pain and Disability Index; VTD₃, Vibration Threshold at digit 3 (middle finger); VTD₅, Vibration Threshold at digit 5 (little finger); ** Correlation (Pearson's r) is significant at 0.01 level; * Correlation is significant at 0.05 level. Significant correlations are bolded.

Table 4. Regression models describing Psychophysical QSTs predictors of Pain, Function and Health Status (n=44)

Construct Measure	Dependent Variable	QST Variables in the regression model: beta (p values) are shown									Model	
		PPT _{Sh}	PPT _{Sh}	PPT _T	PPT _T	VTD ₃	VTD ₅	CPTD ₃	CPTD ₅	CPT _{Sh}	R ²	p value
PAIN	SPADI-Pain	.31 (.40)	-.54 (.16)	-.18 (.68)	.15 (.75)	.12 (.50)	.18 (.30)	.04 (.82)	.14 (.45)	.18 (.35)	.21	.53
	NRS of Pain	.57 (.09)	-.55 (.12)	-.38 (.35)	.04 (.92)	-.28 (.08)	-.28 (.08)	-.05 (.77)	.11 (.50)	.11 (.53)	.33	.15
	PainCS	.37 (.36)	-.68 (.09)	-.14 (.75)	.19 (.69)	-.19 (.29)	.05 (.77)	-.03 (.88)	-.10 (.58)	.28 (.14)	.22	.51
FUNCTION	FIT-HaNSA	.13 (.69)	-.05 (.88)	.09 (.81)	.22 (.60)	-.10 (.51)	-.24 (.12)	-.08 (.64)	.13 (.42)	-.21 (.21)	.34	.11
	SPADI-Disability	.18 (.61)	-.51 (.16)	-.26 (.54)	.18 (.69)	.03 (.88)	.20 (.23)	-.03 (.87)	.11 (.54)	.29 (.12)	.27	.28
	QuickDASH	.09 (.80)	-.54 (.16)	-.40 (.34)	.38 (.39)	-.06 (.73)	.05 (.76)	.24 (.19)	-.16 (.38)	.30 (.11)	.28	.29
HEALTH STATUS	SF12-PCS	-.34 (.38)	.69 (.07)	.66 (.13)	-.72 (.11)	-.04 (.82)	-.02 (.90)	-.17 (.33)	.29 (.11)	-.36(.05)*	.30	.22
	SF12-MCS	.36 (.36)	-.26 (.50)	-.51 (.25)	.68 (.13)	.32 (.07)	.23 (.17)	-.22 (.23)	.21 (.25)	-.25 (.17)	.28	.28

Abbreviations and Symbol: CPTD₃, Current Perception Threshold at digit 3 (middle finger); CPTD₅, Current Perception Threshold at digit 5 (little finger); CPT_{Sh}, Current Perception Threshold at Shoulder (mid-deltoid); DASH, Disabilities of the Arm, Shoulder and Hand; FIT-HaNSA, (Functional Impairment Test-Head and Neck, Shoulder, Arm); MCS, Mental Component Summary; NRS, Numeric Rating Scale; PainCS, Pain Catastrophizing Scale; PCS, Physical Component Summary; PPT_{Sh} , Pressure Pain Threshold at Shoulder (mid-deltoid); PPT_T , Pressure Pain Threshold at Tibia (Shinbone); PPT_{Sh} , Pressure Pain Tolerance at Shoulder (mid-deltoid); PPT_T, Pressure Pain Tolerance at Tibia (Shinbone); QST, Quantitative Sensory Testing; R², Coefficient of determination; SF12, Short Form 12-item health survey version 2; SPADI, Shoulder Pain and Disability Index; VTD₃, Vibration Threshold at digit 3 (middle finger); VTD₅, Vibration Threshold at digit 5 (little finger); * beta is significant at 0.05 level and bolded.

Table 5. Regression models describing Patient's Factors predictors of Pain, Function and Health Status (n=44)

Construct Measure	Dependent Variable	Covariates in the model: <i>beta (p values) are shown</i>			Model	
		Age	Gender	Comorbidity	R ²	p value
PAIN	SPADI-Pain	.15 (.38)	.20 (.21)	.32 (.07)	.15	.10
	NRS of Pain	.27 (.11)	-.08 (.62)	.16 (.37)	.16	.08
	PainCS	.20 (.22)	.16 (.30)	.52(.004)**	.19	.04*
FUNCTION	FIT-HaNSA	-.42 (.01)	.04 (.81)	-.15 (.37)	.27	.01**
	SPADI-Disability	.43(.004)**	.06 (.65)	.30 (.06)	.36	<.001**
	QuickDASH	.26 (.11)	.14 (.37)	.37 (.04)*	.25	.01**
HEALTH STATUS	SF12-PCS	-.16 (.32)	-.20 (.20)	-.40(.02)*	.21	.03*
	SF1-2MCS	.33 (.04)*	.07 (.63)	-.55(.002)**	.28	.005**

Abbreviations and Symbols: DASH, Disabilities of the Arm, Shoulder and Hand; FIT-HaNSA, (Functional Impairment Test-Head and Neck, Shoulder, Arm); MCS, Mental Component Summary; NRS, Numeric Rating Scale; PainCS, Pain Catastrophizing Scale; PCS, Physical Component Summary; QST, Quantitative Sensory Testing; R², Coefficient of determination; SF12, Short Form 12-item health survey version 2; SPADI, Shoulder Pain and Disability Index; ** beta and R² are significant at 0.01 level; * beta and R² are significant at 0.05 level. Significant beta and R² are bolded.

Table 6. Effect of Gender on Psychophysical/QST measure and Pain reporting (n=44)

<i>Variables</i>	<i>Male, Mean ± SD</i>	<i>Female, Mean ± SD</i>	<i>Mean Difference (Male-Female)</i>	<i>P value</i>
<i>QST</i>				
PPT _{Sh}	10 ± 5.7	3.8 ± 2	6.2	<.001
PPT _{Sh}	19.7 ± 11.2	7.1 ± 3.9	12.6	<.001
PPT _T	8.1 ± 3.2	4.1 ± 2.3	3.9	<.001
PPT _T	13.3 ± 5.3	5.7 ± 2.8	7.6	<.001
VTD ₃	12.5 ± 9.2	7.8 ± 3.3	4.6	.06
VTD ₅	15.1 ± 22.1	19.7 ± 32.5	-4.5	.60
CPTD ₃	11 ± 2.5	8.7 ± 3.6	2.3	.02
CPTD ₅	11.1 ± 2.6	10.2 ± 1.5	.9	.21
CPT _{Sh}	9.1 ± 1.8	7.5 ± 2.7	1.6	.02
<i>Pain</i>				
SPADI-Pain	52.9 ± 25	52 ± 29.3	.87	.92
NRS of Pain	1.8 ± 2.2	2.7 ± 1.9	-.90	.18
PainCS	16.1 ± 14.7	15.9 ± 17.2	.14	.98

Abbreviations: CPTD₃, Current Perception Threshold at digit 3 (middle finger); CPTD₅, Current Perception Threshold at digit 5 (little finger); CPT_{Sh}, Current Perception Threshold at Shoulder (mid-deltoid); DASH-Pain, Disabilities of the Arm, Shoulder and Hand-pain subscale; NRS, Numeric Rating Scale; PainCS, Pain Catastrophizing Scale PPT_{Sh} , Pressure Pain Threshold at Shoulder (mid-deltoid); PPT_T , Pressure Pain Threshold at Tibia (Shinbone); PPT_{Sh} , Pressure Pain Tolerance at Shoulder (mid-deltoid); PPT_T , Pressure Pain Tolerance at Tibia (Shinbone); QST, Quantitative Sensory Testing; SD, Standard Deviation; VTD₃, Vibration Threshold at digit 3 (middle finger); VTD₅, Vibration Threshold at digit 5 (little finger). Significant mean differences and p values are bolded.

CHAPTER 6: Study 5

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The Effect of Pressure Pain Sensitivity and Patient Factors on Self-reported Pain-Disability in Patients with Chronic Neck Pain

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Abstract:

The study was conducted to estimate the extent to which pressure pain sensitivity (PPS) and patient factors predict pain-related disability in patients with neck pain (NP), and to determine if PPS differs by gender. Forty-four participants with a moderate level of chronic NP were recruited for this cross sectional study. All participants were asked to complete self-reported assessments of pain, disability and comorbidity and then underwent PPS testing at 4-selected body locations. Pearson's r were computed to explore relationships between the PPS measures and the self-reported assessments. Regression models were built to identify predictors of pain and disability. An independent sample t -test was done to identify gender-related differences in PPS, pain-disability and comorbidity. In this study, greater PPS (threshold and tolerance) was significantly correlated to lower pain-disability ($r = -.30$ to $-.53$, $p \leq .05$). Age was not correlated with pain or disability but comorbidity was ($r = .42$ -. $.43$, $p \leq .01$). PPS at the 4-selected body locations was able to explain neck disability ($R^2 = 25$ - 28%). Comorbidity was the strongest predictor of neck disability ($R^2 = 30\%$) and pain ($R^2 = 25\%$). Significant mean differences for gender were found in PPS, disability and comorbidity, but not in pain intensity or rating. This study suggests that PPS may play a role in outcome measures of pain and disability but between-subject comparisons should consider gender and comorbidity issues.

Key Words: Pain threshold, Pain tolerance, Neck pain sensitivity, Neck disability, Gender, Comorbidity

Abbreviations: Neck Pain (NP); Quantitative Sensory Testing (QST); Pressure Pain Sensitivity (PPS); Cervical spine level two (C2), Cervical spine level six (C6), Short Form of the McGill Pain Questionnaire (SF-MPQ), Pain Rating Index (PRI)

Introduction

Neck pain (NP) is a common musculoskeletal pain disorder [1,2]. Almost everyone experiences NP at some point in his or her lifetime [3] with a yearly prevalence estimated at roughly 30-50% in the general population [4-7]. Reported incidence and prevalence figures of NP may vary according to patient factors (e.g. age, gender, and comorbidity). The prevalence of pain is reportedly greater among females and older persons [5,8]. A recent review suggested that gender can influence pain [9] and being female might be associated with higher prevalence and pain intensity. A systematic review reported that the prevalence of NP declines after middle age [10]. Another study suggests an important association between comorbidities and NP [11]. Moreover, it has been demonstrated that accumulated comorbid load is independently associated with chronic pain [12]. This provides a rationale for considering patient factors, including comorbidity, in the assessment of pain-related disability in patients with chronic NP.

NP and its associated disability are a tremendous financial burden to most industrialized nations [13]. The under pinning etiology of NP can be illusive [1]. Evidence suggests it is more closely associated with sensory disturbances than degenerative and radiological findings [14-17]. A large community based British study [18] supported the importance of neurological factors in NP. Poor recovery in NP is associated with widespread sensory hypersensitivity [19,20]. Research studies [21,22] and a systematic review [23] have demonstrated evidence of central hyperexcitability in musculoskeletal pain. Generalized sensory hyposensitivity (hypoesthesia)

and/or hypersensitivity (hyperesthesia) is a feature in a subset of chronic NP [24]. Abnormal sensory findings are prognostic of poorer clinical outcomes for chronic pain conditions [25,24] thereby providing substantial rationale for including sensory evaluation in the assessment of patients with NP.

Psychophysical quantitative sensory testing (QST) provides a means for semi-objective measurement of both hypo and hyper-sensory function [25,26]. QST has the potential to contribute to the assessment of NP conditions if it can be shown to help with diagnosis, treatment selection, or prognosis. Mapping of the anatomical distribution of sensory changes (e.g. hypoesthesia) may be one factor identifying the pathological source in peripheral nerve, plexus, root and central tissues (spinal or cerebral) [26]. QST was associated with neck disability in patients with NP [27]. QST has many demonstrated uses in clinical practice [28-30].

Pressure pain sensitivity (PPS) measures are a reliable QST technique for the assessment of pressure (mechanical) pain sensitivity of deep somatic structures in the neck area [31,32]. PPS measure using algometry is relatively inexpensive and feasible test method. The PPS test protocol is based on the “method of levels” parameter of QST techniques where pressure level is determined by a forced choice option (e.g. yes/no). In this way PPS can target peripheral small fiber based sensory/pain channels (e.g. A δ , C nerve fibers) [25,33,34]. Alterations of pain processing mechanisms (both peripheral and central) may manifest as a reduction in PPS [35].

There are two common test sites on the cervical spine for somatosensory characterization of patients with NP [36-38] - the C2 paraspinal muscles and the upper trapezius muscle. Self-reported physical activity of NP population was related to PPS at these two common testing sites

of neck muscles [39]. The upper trapezius pressure pain threshold value has high reliability (minimum detectable change = .48 kg/cm²) in patients with NP [40]. PPS measures over the C2-C3 and C5-C6 cervical zygapophyseal joints correlate with lower activation of the semispinalis cervicis muscle as quantified by intramuscular electromyography (at the levels of C2 and C5 during NP)[41]. Studies of PPS indicate that women were more sensitive than men to pressure pain stimulation in cervico-thoracic areas [42]. Pressure pain threshold was positively associated with muscle strength in healthy individuals [43]. Clinically, PPS measures over bony sites (e.g. tibia) were lower in patients with musculoskeletal pain compared to the healthy population [44] and were used to indicate central sensitization. Moreover, since the periosteum (innervated by unmyelinated small fibers) is sensitive to pressure stimulation [45,46], the tibial shaft was used to assess periosteum sensitivity.

At present there is insufficient evidence about the relationship between PPS and pain-related disability and which patient factors (e.g. age, gender, and comorbidity) might mediate the relationship. The main objective of this study was to estimate the extent to which the PPS test (threshold and tolerance in selected locations) and patient factors predict pain-related disability in patients with chronic NP. The second objective was to estimate the effect of gender on PPS measures, particularly threshold and tolerance, for this patient population. The final objective was to determine if there were gender differences for self-reported pain-disability and comorbidity in this patient population.

Materials and Methods

Study design and participants

In a cross-sectional study design, 44 participants (33 female and 11 male) were recruited. All participants were adults with moderate levels of chronic (> 3 months) NP who were actively seeking treatment from local physiotherapy clinics. Recruitment of participants was done through advertisements posted at the clinics. The Hamilton Health Sciences/McMaster University Faculty of Health Sciences Research Ethics Board approved the study protocol and informed consent was obtained from all participants prior to testing. All participants were asked to complete self-reported outcome measures (for pain, disability and comorbidity) and then underwent QST (PPS tests) at the MacHAND clinical research lab at McMaster University.

Participant *inclusion criteria* included: age between 18-85 years, fluency in English (reading and speaking), ability to complete all assessments, complaints of pain in the neck area for more than 3 months, minimum score of 3/10 on visual analogue scale of pain specifically in the neck, documented (physical examination or imaging evidence) of suspected neck pathology.

Exclusion criteria were: 1) any neurological disorders or pre-existing neuropathic pain as indicated by specific neuropathic pain treatment/diagnostic procedures, 2) scheduled for neck surgery or current pain complaints from prior neck surgery, 3) history of recent neck fracture or any history of tumor or cancer, 4) a history of chronic pain disorder (previously diagnosed), 5) current psychiatric management (from history of medication), 6) a high risk of surgery due to any comorbid condition, and 7) patients unable to complete the test procedures.

According to the patient reported symptom diagram, pain distribution included either 1) symptoms localised to neck/shoulder region (Occiput to the inferior angle of Scapula) or 2) two or more of a) Headache, b) Neck/shoulder, c) Hand/arm symptoms. Participant's characteristics and demographics are described in Table 1.

Study Measures

A. NP-Disability Measure:

1. *Short Form of the McGill Pain Questionnaire (SF-MPQ)*. The MPQ was developed to assess pain as a multidimensional phenomenon [47]. The SF-MPQ, introduced in 1987, contained a total of 15 descriptors (11 sensory and 4 affective) each of which are rated on a 4-point (0 to 3) intensity scale [48]. In total, five dimensional pain scores were derived from SF-MPQ: (i) Sensory Pain Rating Index (PRI) was derived from the sum of the intensity rate values for sensory words chosen, (ii) Affective PRI was derived from the sum of the intensity rate values for the affective words chosen, (iii) Total PRI was derived from the sum of the total descriptors (both sensory and affective), (iv) Present Pain Intensity was derived from a visual analog scale, (v) Evaluative Overall Intensity of total pain experience was derived from a 6-point numeric scale (0 to 5).

2. *NP and disorder measure*. The Neck Disability Index was developed to assess self-reported neck-specific disability and included 10 items (e.g. pain intensity, personal care, lifting, reading, headache, concentration, work, driving, sleeping, and recreation) [49,50]. Each item was scored out of 5 and a total score of 50 was computed; the lower the score the less the self-rated disability [49,50].

B. Pressure Pain Sensitivity (PPS)

Pain threshold and pain tolerance (51-53) for pressure stimuli was measured using the computerized JTech algometer (JTECH Medical, Salt Lake City, UT, USA). The hand-held device of the algometer contains a 1cm² circular probe, and it was used to create pressure on the selected body locations using a standardized protocol. Pressure was applied over the posterior cervical spine at the level of the second (C2) and sixth (C6) vertebrae, upper trapezius muscle (UpTrap) and anterior aspect of the tibia (shin bone) bilaterally. The unaffected side was tested first. In cases of bilateral involvement, the less affected side was tested first. The applied algometric pressure at “uncomfortable” (for pain threshold) and “intolerable” (for pain tolerance) levels were determined by patient response using a standard protocol [40,54,55]. The test was repeated 3 times at each site, and the average of these measures was used for data analysis.

C. Patient Factor (Comorbidity Status)

The Katz comorbidity scale was used to detect the number and severity of 12 co-morbid conditions [56,57]. Participants were asked to indicate if they currently had the condition (at the time of assessment), whether or not they were receiving treatment for it, and whether their level of physical activity was limited by the condition. Patient can receive a maximum of 3 points for each condition (1 point if they have been diagnosed with the comorbid health, 1 point if it requires treatment, and 1 point if it causes activity limitation) [56]. The total score was calculated by summing across 12 items [58].

Data Analysis

All data were entered into SPSS 17.0 software (SPSS Inc., Chicago, IL). Descriptive statistics (e.g. skewness, kurtosis) and test of normality (Kolmogorov-Smirnov, Shapiro-Wilk, Histogram, and QQ-Plot) were conducted on all variables. Scatter plots were generated to check violation of assumptions (linearity and homoscedasticity) before performing bivariate correlation (Pearson's) analysis. Assumptions of multiple regressions (e.g. multicollinearity and singularity, outliers, normality, linearity, homoscedasticity) were checked prior to the regression analysis.

Mean and standard deviation were calculated for all variables (e.g. PPS, pain-disability, comorbidity) and then for gender subgroups. Pearson correlation coefficients were computed to determine the relationships between PPS and self-reported NP-disability. Four regression models were built to analyze the relative impact of different PPS measures as predictors of neck disability. We built four further regression models to analyze patients' factors as predictors of NP-disability. An independent sample t-test (equal variance assumed) was used to evaluate the effect of gender on PPS measure, pain-disability reporting and comorbidity status. Significant level was determined by $p < 0.05$ for all interpretation of data.

Results

The bivariate relationships between PPS and pain-disability are shown in Table 2. These correlations indicate that greater PPS (both threshold and tolerance) was significantly associated with less pain-disability ($r = -.35$ to $-.53$, $p \leq .01$). PPS at the level of C2 was significantly correlated with the total pain rating index of SF-MPQ ($r = -.31$ to $-.40$, $p \leq .05$). Age was not correlated with pain-disability, whereas greater comorbidity was correlated with higher pain-disability ($r = .42$ -. $.43$, $p \leq .01$).

Table 3 indicates that when multiple PPS test variables were entered as potential predictors of neck disability outcomes all PPS variables (at 4-selected test locations) were significant predictors ($p < .03$). The total variability explained by all PPS variables range from 25% to 28%. Table 4 indicates that when patient factors (age, gender and comorbidity) were considered in a multivariate model of NP-disability outcomes, comorbidity was the most common predictor that was significantly related to neck disability and evaluative pain. In these multivariate models, comorbidity ($p < .01$) was associated with higher pain (in rating, intensity and evaluation). The amount of variability explained by the overall R^2 for these models range from 13% to 30%.

Significant mean differences in gender (male-female) were found in most PPS tests (1.2-5.4, $p < .05$), with a few exceptions (mainly at C2 level) (Table 5). Significant mean differences for gender (male-female) were found in the self-reported disability (18.5, $p = .003$) and comorbidity score (2.1, $p = .03$) (Table 6). However, self-reported pain dimensions (SF-MPQ) were independent of gender.

Discussions

This study provided preliminary evidence suggesting that both pain threshold and tolerance affect pain-disability, as indicated by medium to large size bivariate correlations. The impact of PPS was further evident in multivariate modeling where individual PPS (at four test locations) explained 25 to 28% of neck disability. Conversely, when age, gender and comorbidity were entered into multivariate models, although higher R^2 's were not achieved, comorbidity was the primary determinant of pain-disability. This suggests that the role of

comorbidity in pain-related disability may partially be related to the extent to which it *sensitizes* the pain-neurophysiology of the individual.

Male participants demonstrated higher pain threshold and tolerance. However, gender was not associated with differences in pain dimensions when multivariate modeling was considered. Previous studies found that pressure pain threshold was lower in women than men [59,60]. Moreover, it was demonstrated that self-reported NP was higher among women than men [4,5]. Our study suggested that pressure pain tolerance was also gender dependent. Gender was acknowledged as an important consideration in NP conditions because of differences in prevalence of different NP conditions by gender. For example, prevalence and incidence of NP was reported to be higher in females than males [65]. Furthermore, gender differences in pain threshold and tolerance was well accepted [66,67]. This study also demonstrated that PPS measures (threshold and tolerance) was more sensitive (lower threshold and tolerance) in females. Females also had more pain-related disability and comorbid health conditions. As gender influences the PPS scores obtained, multivariate models should be powered sufficiently to allow for separate modeling of males and females to identify the true impact of PPS on outcomes or, at minimum, sufficient power to allow for gender interactions to be tested. The relatively small sample precluded testing interactions between PPS and other variables in a gender specific analysis.

Prevalence of NP declined after middle age (i.e. 60 years of age) [10], with middle-aged individuals having more than a two-fold risk of developing NP compared to younger aged individuals [61]. A recent study reported that age was an important moderator between pain and

cognition relationships [62]. Although, we did not assess cognition in this study, we did not find age to be related to pain or disability. Similarly, whereas others have found age to be associated to QST [63] and pressure pain threshold [60], we did not find a similar relationship.

Dominick et al. demonstrated that accumulated comorbid load was independently associated with chronic pain in a large population based study [12]. Recently, Johansen et al. speculated that painful comorbid conditions influence pain sensitivity based on findings from their large population-based study of pain and health status determined by medical examination [60]. That study and our findings concur about the potential importance of comorbid health conditions to “prime” the pain system.

One of the main limitations of this study was that our sample was too small to explore more variables and their interactions. PPS measures provide somatosensory information based on stimulus-response parameters, and are limited by semi-objective psychophysical evaluation. A recent review suggested that it was preferable to assess both sensory and modulatory elements of pain sensitivity [9]. The type of stable threshold-based pain sensitivity measure used in this study provided limited information on complex pain processing since the measure was based on the static parameter of QST [26,64]. It was suggested that dynamic QST may be better at assessing spatial and temporal summation as well as descending modulation of pain [9,26]. In addition, suprathreshold pain processing can be assessed by the magnitude rating for a suprathreshold stimulus [9,26]. We used threshold and tolerance parameters for the QST measures in this study because these are commonly used in clinical practice. Our findings reaffirmed the importance of

PPS and patient factors in explaining pain-disability. Stimulus intensity/magnitude rating parameters of QST may be more relevant to clinical features (e.g. pain, disability).

The greater sensitivity of females to pain threshold and tolerance may reflect differences in how sensory inputs are received at the tissue level or how they are processed from the periphery to the brain. However, this study indicated that gender differences in pain threshold and tolerance was not necessarily indicative of gender differences in all NP-related health outcomes, including pain. This differential suggested that gender needs to be carefully considered when examining NP, and that all hypotheses should be tested separately between male and female subjects to assure that conclusions made apply across genders. Again, these requirements suggested the need for larger sample sizes; and prespecified gender analyses.

Conclusion

This descriptive cross-sectional study suggested that PPS (both threshold and tolerance) may play a role in self-reported outcome measures (e.g. pain and disability) in NP. However, given the findings that PPS tests was gender dependent, and comorbidity also affected these outcomes, these observations must be considered with caution until larger samples are used to confirm any interactions between comorbidity and PPS measures. Gender-specific analyses are necessary to determine if these relationships hold true across genders. This is certainly important before the potential role for PPS to provide useful information in managing NP can be determined particularly because gender was shown to relate to pain threshold and tolerance, but not to pain (rating, intensity and evaluation) in this study. Future studies should focus on the determination of these more complex relationships and may consider using alternative sensory

evaluations including dynamic QST and pain magnitude ratings (for a suprathreshold stimulus) to elucidate the relationship between suprathreshold pain processing, descending control or central integration of pain and other clinical features of NP.

References

- [1] Borghouts JAJ, Koes BW, Vondeling H, Bouter LM. Cost-of-illness of neck pain in The Netherlands in 1996. *Pain*. 1999;80(3):629-636.
- [2] Bot S, Van der Waal J, Terwee C, et al. Incidence and prevalence of complaints of the neck and upper extremity in general practice. *Ann Rheum Dis*. 2005;64(1):118-123.
- [3] Haldeman S, Carroll L, Cassidy JD, Schubert J, Nygren Å. The Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders. *European Spine Journal*. 2008;17:5-7.
- [4] Bovim G, Schrader H, Sand T. Neck pain in the general population. *Spine*. 1994;19(12):1307-9.
- [5] Côté P, Cassidy JD, Carroll LJ, Kristman V. The annual incidence and course of neck pain in the general population: a population-based cohort study. *Pain*. 2004;112(3):267-273.
- [6] Fejer R, Kyvik KO, Hartvigsen J. The prevalence of neck pain in the world population: a systematic critical review of the literature. *European spine journal*. 2006;15(6):834-848.
- [7] Hogg-Johnson S, van der Velde G, Carroll LJ, et al. The burden and determinants of neck pain in the general population. *European Spine Journal*. 2008;17:39-51.
- [8] Tsang A, Von Korff M, Lee S, Alonso J, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *The journal of pain*. 2008;9(10):883-891.
- [9] Hashmi JA, Davis KD. Deconstructing sex differences in pain sensitivity. *Pain*. 2014;155(1):10-3.
- [10] Fejer R, Leboeuf-Yde C. Does back and neck pain become more common as you get older? A systematic literature review. *Chiropr Man Therap*. 2012;20:24.
- [11] Côté P, Cassidy JD, Carroll L. The factors associated with neck pain and its related disability in the Saskatchewan population. *Spine*. 2000;25(9):1109-1117.

- [12] Dominick CH, Blyth FM, Nicholas MK. Unpacking the burden: understanding the relationships between chronic pain and comorbidity in the general population. *Pain*. 2012;153(2):293-304.
- [13] Ferrari R, Russell AS. Neck pain. *Best Practice & Research Clinical Rheumatology*. 2003;17(1):57-70.
- [14] Abdulkarim J, Dhingsa R, L Finlay D. Magnetic resonance imaging of the cervical spine: frequency of degenerative changes in the intervertebral disc with relation to age. *Clin Radiol*. 2003;58(12):980-984.
- [15] van der Donk J, Schouten JS, Passchier J, van Romunde LK, Valkenburg HA. The associations of neck pain with radiological abnormalities of the cervical spine and personality traits in a general population. *J Rheumatol*. 1991;18(12):1884-1889.
- [16] Pettersson K, Hildingsson C, Toolanen G, Fagerlund M, Björnebrink J. MRI and neurology in acute whiplash trauma: No correlation in prospective examination of 39 cases. *Acta Orthopaedica*. 1994;65(5):525-528.
- [17] Karlsborg M, Smed A, Jespersen H, Stephensen S, Cortsen M, Jennum P, et al. A prospective study of 39 patients with whiplash injury. *Acta Neurol Scand*. 1997;95(2):65-72.
- [18] Coggon D, Cyrus Cooper D. Prevalence and occupational associations of neck pain in the British population. *Scand J Work Environ Health*. 2001;27(1):49-56.
- [19] Sterling M, Jull G, Vicenzino B, Kenardy J, Darnell R. Physical and psychological factors predict outcome following whiplash injury. *Pain*. 2005;114(1-2):141-148.
- [20] Sterling M, Jull G, Kenardy J. Physical and psychological factors maintain long-term predictive capacity post-whiplash injury. *Pain*. 2006;122(1-2):102-108.
- [21] Sterling M. Differential development of sensory hypersensitivity and a measure of spinal cord hyperexcitability following whiplash injury. *Pain*. 2010;150(3):501-506.
- [22] Desmeules J, Cedraschi C, Rapiti E, Baumgartner E, Finckh A, Cohen P, et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis & Rheumatism*. 2003;48(5):1420-1429.
- [23] Lim EC, Sterling M, Stone A, Vicenzino B. Central hyperexcitability as measured with nociceptive flexor reflex threshold in chronic musculoskeletal pain: a systematic review. *Pain*. 2011 Aug;152(8):1811-1820.

- [24] Chien A, Eliav E, Sterling M. Whiplash (grade II) and cervical radiculopathy share a similar sensory presentation: an investigation using quantitative sensory testing. *Clin J Pain*. 2008;24(7):595.
- [25] Backonja M, Attal N, Baron R, Bouhassira D, et al. Value of quantitative sensory testing in neurological and pain disorders: NEUPSIG consensus. *Pain*. 2013;154(9):1807-19.
- [26] Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *The Journal of Pain*. 2009;10(6):556-572.
- [27] Uddin Z, MacDermid JC, Ham HH. Test–retest reliability and validity of normative cut-offs of the two devices measuring touch threshold: Weinstein Enhanced Sensory Test and Pressure-Specified Sensory Device. *Hand Therapy*. 2014;19(1):3-10.
- [28] Courtney CA, Kavchak AE, Lowry CD, O'HEARN MA. Interpreting joint pain: quantitative sensory testing in musculoskeletal management. *J Orthop Sports Phys Ther*. 2010;40(12):818-825.
- [29] Uddin Z, MacDermid J, Packham T. Clinical implementation of two quantitative Sensory Tests: Cold Stress Test and the Ten Test. *Physiotherapy Practice and Research*. 2014;35(1):33-40.
- [30] Uddin Z, MacDermid J, Packham T. The ten test for sensation. *Journal of Physiotherapy* 2013 Jun;59(2):132-32.
- [31] Ylinen J, Nykänen M, Kautiainen H, Häkkinen A. Evaluation of repeatability of pressure algometry on the neck muscles for clinical use. *Man Ther*. 2007;12(2):192-197.
- [32] Ylinen J, Takala E, Kautiainen H, et al. Effect of long-term neck muscle training on pressure pain threshold: A randomized controlled trial. *European Journal of Pain*. 2005;9(6):673-673.
- [33] Chong PST, Cros DP. Technology literature review: quantitative sensory testing. *Muscle Nerve*. 2004;29(5):734-747.
- [34] Hansson P, Backonja M, Bouhassira D. Usefulness and limitations of quantitative sensory testing: clinical and research application in neuropathic pain states. *Pain*. 2007;129(3):256-259.
- [35] Hogeweg JA, Kuis W, Oostendorp RA, Helders PJ. General and segmental reduced pain thresholds in juvenile chronic arthritis. *Pain*. 1995;62(1):11-17.
- [36] Chien A, Eliav E, Sterling M. Hypoaesthesia occurs with sensory hypersensitivity in chronic whiplash—further evidence of a neuropathic condition. *Man Ther*. 2009;14(2):138-146.

- [37] Johnston V, Jimmieson NL, Jull G, Souvlis T. Quantitative sensory measures distinguish office workers with varying levels of neck pain and disability. *Pain*. 2008;137(2):257-265.
- [38] Sterling M, Treleaven J, Edwards S, Jull G. Pressure pain thresholds in chronic whiplash associated disorder: further evidence of altered central pain processing. *Journal of Musculoskeletal Pain*. 2002;10(3):69-81.
- [39] Cheung J, Kajaks T, Macdermid JC. The relationship between neck pain and physical activity. *The open orthopaedics journal*. 2013;7:521-529.
- [40] Walton D, Macdermid J, Nielson W, Teasell R, Chiasson M, Brown L. Reliability, standard error, and minimum detectable change of clinical pressure pain threshold testing in people with and without acute neck pain. *J Orthop Sports Phys Ther*. 2011;41(9):644-650.
- [41] Schomacher J, Boudreau SA, Petzke F, Falla D. Localized Pressure Pain Sensitivity is Associated With Lower Activation of the Semispinalis Cervicis Muscle in Patients With Chronic Neck Pain. *Clin J Pain*. 2013;29(10):898-906.
- [42] Binderup A, Arendt-Nielsen L, Madeleine P. Pressure pain sensitivity maps of the neck-shoulder and the low back regions in men and women. *BMC musculoskeletal disorders* 2010;11(1):234.
- [43] Henriksen M, Klokke L, Bartholdy C, Graven-Nielsen T, Bliddal H. The associations between pain sensitivity and knee muscle strength in healthy volunteers: a cross-sectional study. *Pain research and treatment*. 2013; 787054.
- [44] Tunks E, Crook J, Norman G, Kalaher S. Tender points in fibromyalgia. *Pain*. 1988;34(1):11-19.
- [45] Finocchietti S, Andresen T, Arendt-Nielsen L, Graven-Nielsen T. Pain evoked by pressure stimulation on the tibia bone—Influence of probe diameter on tissue stress and strain. *European Journal of Pain*. 2012;16(4):534-542.
- [46] Grönblad M, Liesi P, Korkala O, Karaharju E, Polak J. Innervation of human bone periosteum by peptidergic nerves. *Anat Rec*. 1984;209(3):297-299.
- [47] Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain*. 1975;1(3):277-299.
- [48] Melzack R. The short-form McGill pain questionnaire. *Pain*. 1987;30(2):191-197.
- [49] Vernon H, Mior S. The Neck Disability Index: a study of reliability and validity. *J Manipulative Physiol Ther*. 1991;14(7):409-415.

- [50] MacDermid JC, Walton DM, Avery S, Blanchard A, et al. Measurement properties of the neck disability index: a systematic review. *J Orthop Sports Phys Ther.* 2009;39(5):400-417.
- [51] Chesterton LS, Sim J, Wright CC, Foster NE. Interrater reliability of algometry in measuring pressure pain thresholds in healthy humans, using multiple raters. *Clin J Pain.* 2007;23(9):760-766.
- [52] Bernhardt O, Schiffman EL, Look JO. Reliability and validity of a new fingertip-shaped pressure algometer for assessing pressure pain thresholds in the temporomandibular joint and masticatory muscles. *J Orofac Pain.* 2007;21(1):29-38.
- [53] Kosek E, Ekholm J, Nordemar R. A comparison of pressure pain thresholds in different tissues and body regions. Long-term reliability of pressure algometry in healthy volunteers. *Scand J Rehabil Med.* 1993;25(3):117-124.
- [54] Finocchietti S, Andresen T, Arendt-Nielsen L, Graven-Nielsen T. Pain evoked by pressure stimulation on the tibia bone—Influence of probe diameter on tissue stress and strain. *European Journal of Pain.* 2012;16(4):534-542.
- [55] Walton DM, Macdermid JC, Nielson W, Teasell RW, Nailer T, Maheu P. A descriptive study of pressure pain threshold at 2 standardized sites in people with acute or subacute neck pain. *J Orthop Sports Phys Ther.* 2011;41(9):651-657.
- [56] Katz JN, Chang LC, Sangha O, Fossel AH, Bates DW. Can comorbidity be measured by questionnaire rather than medical record review? *Med Care.* 1996;34(1):73-84.
- [57] Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The self-administered comorbidity questionnaire: A new method to assess comorbidity for clinical and health services research. *Arthritis Care & Research.* 2003;49(2):156-163.
- [58] Tashjian RZ, Henn RF, Kang L, Green A. The effect of comorbidity on self-assessed function in patients with a chronic rotator cuff tear. *The Journal of Bone & Joint Surgery.* 2004;86(2):355-362.
- [59] Castro-Sánchez AM, Matarán-Peñarrocha GA, López-Rodríguez MM, et al. Gender differences in pain severity, disability, depression, and widespread pressure pain sensitivity in patients with fibromyalgia syndrome without comorbid conditions. *Pain Medicine.* 2012;13(12):1639-1647.
- [60] Johansen A, Schirmer H, Stubhaug A, Nielsen CS. Persistent post-surgical pain and experimental pain sensitivity in the Tromsø study: Comorbid pain matters. *Pain.* 2014;155(2):341-8.

[61] Cagnie B, Danneels L, Van Tiggelen D, De Loose V, Cambier D. Individual and work related risk factors for neck pain among office workers: a cross sectional study. *European Spine Journal*. 2007;16(5):679-686.

[62] Oosterman J, Gibson S, Pulles W, Veldhuijzen D. On the moderating role of age in the relationship between pain and cognition. *Eur J Pain*. 2013;17(5):735-741.

[63] Costantini M, Tunks K, Wyatt C, Zettel H, MacDermid JC. Age and upper limb tension testing affects current perception thresholds. *Journal of Hand Therapy*. 2006;19(3):307-317.

[64] Hübscher M, Moloney N, Leaver A, et al.. Relationship between quantitative sensory testing and pain or disability in people with spinal pain—a systematic review and meta-analysis. *Pain*. 2013;154(9):1497-504

[65] Cassou B, Derriennic F, Monfort C, Norton J, Touranchet A. Chronic neck and shoulder pain, age, and working conditions: longitudinal results from a large random sample in France. *Occup Environ Med*. 2002;59(8):537-544.

[66] Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain*. 2006;123(3):231-243.

[67] Berkley KJ. Sex differences in pain. *Behav Brain Sci*. 1997;20(3):371-380.

Table 1. Participants Demographics (N = 44)

<i>Construct</i>	<i>Variable</i>	<i>Characteristic</i>
PATIENT FACTOR	Age (years)	Mean = 40.1 ± 13.9 (Female = 41.6 ± 13.4 and Male = 35 ± 15)
	Gender	Female = 33 (75%), Male = 11 (25%)
	Comorbidity	Mean = 4 ± 2.8
NP-DISABILITY	McGill Total Pain Rating Index (0-45)	Mean = 12.5 ± 6.9
	Pain Intensity: VAS (0-10 mm)	Mean = 4.5 ± 2.0
	Neck Disability Index (%)	Mean = 31.4 ± 17.8
OTHER DEMOGRAPHICS	Dominant Side	Right = 40 (90.9%), Left = 4 (9.1%)
	Affected side	Right = 8 (18.2%), Left = 9 (20.5%), Bilateral = 27 (61.4%)
	Body Weight (lbs)	Mean = 158.0 ± 33.6

Abbreviation/Symbol: ± = standard deviation; N = number of participants; VAS, Visual Analogue Scale; lb = pounds

Table 2. Relationship between PPS and Patient Factors with either Disability or Pain dimensions

Test location		Neck Disability Index	Short Form of the McGill Pain Questionnaire				
			Sensory -PRI	Affective -PRI	Total-PRI	Pain Intensity-VAS	Evaluative overall pain
PPS Variables							
Cervical spine at level of C2	Left Threshold	-.50**	-.28	-.29	-.31*	-.14	-.12
	Left Tolerance	-.51**	-.32*	-.30	-.33*	-.13	-.15
	Right Threshold	-.51**	-.36*	-.33*	-.37*	-.15	-.14
	Right Tolerance	-.52**	-.40**	-.35*	-.40**	-.17	-.15
Cervical spine at level of C6	Left Threshold	-.47**	-.22	-.27	-.28	-.11	-.05
	Left Tolerance	-.44**	-.28	-.28	-.30*	-.12	-.07
	Right Threshold	-.47**	-.27	-.23	-.26	-.05	-.01
	Right Tolerance	-.43**	-.33*	-.24	-.29	-.10	-.06
Upper Trapezium muscle	Left Threshold	-.40**	-.21	-.18	-.20	.00	-.06
	Left Tolerance	-.43**	-.27	-.22	-.24	-.05	-.14
	Right Threshold	-.49**	-.16	-.20	-.21	-.10	-.14
	Right Tolerance	-.46**	-.21	-.18	-.20	-.12	-.18
Anterior Tibia (shine bone)	Left Threshold	-.48**	-.20	-.19	-.21	-.28	-.21
	Left Tolerance	-.49**	-.25	-.24	-.26	-.36*	-.30
	Right Threshold	-.38**	-.12	-.27	-.25	-.40**	-.25
	Right Tolerance	-.35**	-.24	-.24	-.26	-.46**	-.26
Patient Factors							
	Age	.16	.03	.09	.06	.07	.04
	Comorbidity	.42**	.31	.20	.31	.30	.43**

Abbreviation/Symbol: PPS, Pressure Pain Sensitivity; PRI, Pain Rating Index; VAS, Visual Analogue Scale;

** Correlation (Pearson's r) is significant at 0.01 level; * Correlation is significant at 0.05 level. Significant correlations are bolded.

Table 3. Regression models describing Pressure Pain Sensitivity predictors of Neck Disability (Depended Variable =Neck Disability Index, N=44)

Test locations	Pressure Pain Sensitivity in the model: beta (p values) are shown				Model	
	Left Threshold	Left Tolerance	Right Threshold	Right Tolerance	R ²	p value
Cervical spine at level of C2	-.13 (.79)	-.11 (.85)	-.13 (.83)	-.19 (.79)	.28	.02*
Cervical spine at level of C6	.01 (.99)	-.62 (.32)	-1.02 (.20)	1.12 (.24)	.26	.03*
Upper Trapezium muscle (UpTrap)	.38 (.54)	-.27 (.68)	-.66 (.22)	.08 (.88)	.25	.03*
Anterior aspect of Tibia (shine bone)	.23 (.66)	-.91 (.13)	-.45 (.34)	.64 (.23)	.28	.02*

Abbreviation/Symbol: * R² are significant at 0.05 level. Significant R² are bolded.

Table 4. Regression models describing Patient's Factors predictors of Pain-Disability (n=44)

Construct	Dependent Variable	Patient factors in the model: beta (p values) are shown			Model	
		Age	Gender	Comorbidity	R ²	p value
NP-DISABILITY	McGill Total Pain Rating Index	-.22 (.28)	-.05 (.78)	.43 (.04)*	.13	.17
	Pain Intensity: VAS	.19 (.36)	-.08 (.64)	.44(.04)*	.12	.22
	Evaluative overall pain	-.32 (.09)	-.01 (.94)	.62 (.01)**	.25	.02*
	Neck Disability Index	-.15 (.43)	.35 (.03)*	.39 (.05)*	.30	.007**

Abbreviation/Symbol: PRI, Pain Rating Index; VAS, Visual Analogue Scale; ** beta and R² are significant at 0.01 level; * beta and R² are significant at 0.05 level. Significant beta and R² are bolded.

Table 5. Effect of Gender on PPS measure (n=44). Both threshold and tolerance tests were done on 4 locations (C2, C5, UpTrap and Shin bone) in each side of neck-shoulder and leg area.

<i>Test Variables</i>	<i>Male, Mean $\pm$ SD</i>	<i>Female, Mean $\pm$ SD</i>	<i>Mean Difference (Male-Female)</i>	<i>P value</i>
Test location: Cervical spine level two (C2)				
Left Threshold	5.3 $\pm$ 2.2	3.9 $\pm$ 1.6	1.4	.02
Left Tolerance	9.4 $\pm$ 4.2	6 $\pm$ 2.5	3.3	.03
Right Threshold	5.7 $\pm$ 3.0	4.2 $\pm$ 1.7	1.5	.14
Right Tolerance	9.3 $\pm$ 5.5	5.9 $\pm$ 2.5	3.5	.07
Test location: Cervical spine level six (C6)				
Left Threshold	6.1 $\pm$ 2.5	4.2 $\pm$ 1.8	1.9	.01
Left Tolerance	9.9 $\pm$ 5	6.5 $\pm$ 3.3	3.4	.06
Right Threshold	7.1 $\pm$ 3.7	4.5 $\pm$ 1.8	2.6	.04
Right Tolerance	10.8 $\pm$ 4.6	6.4 $\pm$ 3.0	4.1	.05
Test location: Upper Trapezium muscle (UpTrap)				
Left Threshold	10.8 $\pm$ 4.6	7.7 $\pm$ 3.4	3.1	.02
Left Tolerance	16.8 $\pm$ 7.2	11.9 $\pm$ 5.3	4.9	.02
Right Threshold	11.4 $\pm$ 5	7.7 $\pm$ 3.8	3.7	.01
Right Tolerance	17.5 $\pm$ 7.3	12.2 $\pm$ 6.7	5.4	.03
Test location: Anterior aspect of Tibia (Shin bone)				
Left Threshold	6 $\pm$ 1.9	4.2 $\pm$ 1.9	1.8	.01
Left Tolerance	9.5 $\pm$ 3.5	6.5 $\pm$ 3.4	2.9	.02
Right Threshold	5.8 $\pm$ 2	4.6 $\pm$ 1.6	1.2	.05
Right Tolerance	8.4 $\pm$ 3.4	6.7 $\pm$ 2.9	1.7	.12

Abbreviation/Symbol: SD = Standard Deviation;. Significant mean differences and p values are bolded.

Table 6. Effect of Gender on self-reported Pain-Disability and Comorbidity status (n=44)

<i>Variables</i>	<i>Male, Mean ± SD</i>	<i>Female, Mean ± SD</i>	<i>Mean Difference (Female-Male)</i>	<i>P value</i>
Short Form of the McGill Pain Questionnaire				
Sensory Pain Rating Index (0-33)	8.8 ± 5.9	11.1 ± 5.9	2.26	.29
Affective Pain Rating Index (0-12)	1.8 ± 1.39	2 ± 1.8	.23	.75
Total Pain Rating Index (0-45)	10.6 ± 6.9	13 ± 6.9	2.4	.34
Present Pain Intensity-Visual Analog Scale (0-10)	4.4 ± 1.5	4.6 ± 2.1	.15	.83
Evaluative overall intensity of total pain experience (0-5)	2.1 ± 0.6	2.3 ± 0.9	.23	.46
Disability and Comorbidity				
Neck Disability Index (in %)	17.4 ± 9	35 ± 17.6	18.5	.003
Comorbidity Status (0-39)	2.4 ± 2.3	4.5 ± 2.7	2.1	.03

Abbreviation/Symbol: SD, Standard Deviation; Significant mean differences and p values are bolded.

CHAPTER 7: Discussion

Overall, the studies under this thesis demonstrated that both methods (limits and levels) components of quantitative sensory testing (QST) are reliable and valid in neck and shoulder disorders and as well as in healthy hands. QST evaluated in this thesis included different modalities (electrical, vibration, touch, pressure), protocols and test devices. The studies indicated that QST demonstrates moderate to high reliability, and moderate discriminative validity including good specificity and moderate sensitivity across different subgroups of patients with musculoskeletal pain disorders. QST was found to be related to self-reported (e.g. pain and disability) and performance-based measures. Pain and disability were significantly related to pain detection threshold based QST (e.g. pressure pain sensitivity). However, findings also indicated that gender and comorbidity were covariants in the relationship between pain detection threshold based QST (by algometry) and pain-disability. Gender impacted on self-reported disability, whereas it was not a determinant of pain reporting (e.g. pain intensity, rating and catastrophizing) or functional performance.

Theoretically, the pressure pain sensitivity test (method of levels in QST) is capable of providing more stable responses. Originally, the psychophysical “method of levels” paradigm was developed from the theoretical concept of sensory threshold and it is supported by the signal detection theory (Green & Swets, 1966). Nevertheless, a recent systematic review and meta-analysis demonstrated that QST poorly explains pain and disability (Hübscher et al., 2013). QST includes a wide variety of stimulus modalities with different protocols. It is difficult to find multiple studies with homogeneous QST protocols and outcome measures. In addition, patient cohorts vary across different research laboratories. This first systematic review of QST is useful

to chart the literature, but without a sufficient number of homogenous studies, it is difficult to determine whether particular QST measures are more useful than others. This thesis adds to the body of evidence by evaluating different QST methods across different musculoskeletal disorders. While these studies may contribute to improving the depth of evidence for future systematic reviews. The determination of an optimal role for QST remains elusive because the findings are not sufficiently conclusive.

Comorbid conditions were found to be negatively related to pain or disability in two studies of this thesis (study 4 and 5, in chapter 5 and 6). This is in agreement with a previous study that reported that comorbidities negatively impact on pain or function (Tashjian, Henn, Kang, & Green, 2004). Comorbidity has been strongly associated with the intensity of pain in a large population based study of subjects with persistent pain (Johansen, Schirmer, Stubhaug, & Nielsen, 2014). That study and this thesis work reflected the importance of recognizing the contribution of comorbid conditions with chronic/persistent pain. Dominick et al. demonstrated that accumulated comorbid load is independently associated with chronic pain in a large population based study (Dominick, Blyth, & Nicholas, 2012). Recently, Johansen et al. speculated that painful comorbid conditions influence pain sensitivity in another large population based cross-sectional survey that included a follow-up medical examination (Johansen et al., 2014). That study did not include disability measures. This thesis (study 5, in chapter 6) demonstrated that comorbidity is significantly related to pain sensitivity and to neck pain-disability. Thereby, suggesting that pain sensitivity may be important whether arising as a result of the condition being treated or as a result of pre-existing comorbidity.

From the evidence presented, it is clear that gender as an important factor for QST. Gender differences in pain sensitivity occurred despite a lack of gender differences in disability or other health outcomes. The importance of gender in pain was summarized in a landmark review by Berkley in 1997 (Berkley, 1997). This review highlighted that gender is sometimes included as a descriptor in pain research, but is rarely investigated in a comprehensive manner. Gender differences exist in many different sensory experiences (Hashmi & Davis, 2013; Velle, 1987). Women have been shown to be more perceptive in sensory function than men across multiple sensory modalities or domains (Hashmi & Davis, 2013). Earlier pain studies often focused on measuring pain responses in men, and it was assumed that findings could be generalized to both genders. A psychophysical study conducted in 1940 reported gender differences in metabolic responses to temperature (Hardy & Du Bois, 1940). Subsequent studies were more inclusive. However, how sex, gender, and gender roles expectations affect pain responses, pain interference and disability is not yet well defined.

A recent consensus from the expert panel of the International Association for the Study of Pain (IASP) reported that QST has the capacity to provide important and unique information from somatosensory system, which would be valuable to assess functional status in the clinical context (Backonja et al., 2013). The IASP consensus recommended using static pain thresholds of QST (mechanical or thermal) for characterization of allodynia and hyperalgesia before and after initiation of treatment (Backonja et al., 2013). Study 5 (in chapter 6 of this thesis) demonstrated that static mechanical pain threshold is a predictor of neck disability and significantly related to pain-disability.

A recent review (Cruz-Almeida & Fillingim, 2014) indicated that QST has the potential to become a cost-effective and clinically useful tool of pain assessment and diagnosis but that further research is needed to define this role. QST may enable the goal of personalized pain management (Woolf, 2004) based on sound psychophysical and physiological principles. A recent study illustrates the uniqueness of the QST investigative technique by showing the use of QST to interpret the categories of complex regional pain syndrome (Gierthmühlen et al., 2012). Study 2 (in Chapter 3 of this thesis) demonstrated a potential role for a component of QST in assessing prognostic studies that target neurologically focused therapy interventions as the study found that the current perception threshold test is capable of differentiating categories of mechanical neck disorder (e.g. neck pain with or without neurological signs) (Uddin et al, 2014c). Previous evidence (Cruz-Almeida & Fillingim, 2014) and this thesis work suggest that QST might be a clinically useful technique in the classification of pain.

Now, the question is how QST might be applied to best improve pain rehabilitation? People suffering from chronic musculoskeletal pain disorders are frequently referred for rehabilitation with goals of reducing pain and or improving function. Rehabilitation therapy generally involves a multimodal approach (e.g. exercise, manual therapy, physical modalities and other techniques). Currently it is not possible to predict which type of patient will respond positively to rehabilitation or to specific options for intervention. A recent systematic review (Chester et al., 2013) found inconsistent evidence about the prognostic factors associated with the outcome of rehabilitation therapy in the management of musculoskeletal pain. QST may play a role in monitoring the disease progression and outcome evaluation in rehabilitation therapy intervention but only continued research will define this role.

The studies outlined and published from this thesis add to the number of the growing literature applying the QST approach and is an important knowledge building block on the way to creating a scientific foundation for better understanding many challenging musculoskeletal pain disorders. Multidimensional assessment, including QST, may help identify the clinical features that predispose to the development of neuropathic pain syndrome (i.e. a common entity of chronic pain) in the clinical context.

Limitations

The findings must be considered inconclusive until a larger sample that tests interactions between age and comorbidity with psychophysical QST measures is used. Gender-specific analysis analyses must be conducted to determine if the relationships hold true across genders is needed before the potential role for QST to provide useful information in managing musculoskeletal disorders. The relatively small sample (in 2 studies of this thesis) precluded testing interactions between QST and other variables for doing a gender specific analysis. This may have contributed to the lack of prediction.

There is an "inverse problem" in QST measures as in other sciences such as physics, computing vision and remote sensing. QST provides somatosensory information based on stimulus-response parameters, and it is difficult to quantify absolute objectively or via direct observation. The static QST measures (used in this thesis studies) provide a limited perspective on a complex pain processing system (Arendt-Nielsen & Yarnitsky, 2009). It has been suggested that dynamic QST is better at assessing the spatial and temporal summation as well as the descending modulation of pain (Arendt-Nielsen & Yarnitsky, 2009). In addition, suprathreshold pain processing can be assessed by magnitude rating for a suprathreshold stimulus (Arendt-

Nielsen & Yarnitsky, 2009). Threshold and tolerance parameters for QST measures were used in this thesis because these have been used in research and clinical practice. However, stimulus intensity/magnitude rating parameters of QST may be more relevant to clinical features (e.g. pain, function). Conceptually, stimulus intensity ratings may have a greater flexibility on a wider range of rating scales and might be an intuitive way of pain rating in the clinical context. An efficient and valid way to apply stimulus intensity rating (in both clinical research and practice) is to use an unaffected body area (free of sensory abnormalities or pain), as a reference test site. In fact, more studies are needed to compare these two paradigms with their advantages and disadvantages.

Candidates of QST evaluation need to be selected carefully; they must be able to understand and follow the test protocol. The clinician should consider relevant medical and psychological comorbid conditions. The studies of this thesis have been followed those by setting eligible criteria for the participants, whereas other rule setups might improve the quality of QST measure. Such as few null stimuli application and observation during the testing may enhance to identify the issues related to attention and participation in the clinical research context.

Implications for Practice and/or Policy

The outcome of this thesis work suggests that QST is clinically useful in musculoskeletal pain as the detection thresholds were reliable and pain thresholds were valid in the clinical context. On the basis of research studies (i.e. reproducibility of detection and pain thresholds) an IASP consensus report (Backonja et al., 2013) recommended using QST for clinical practice in the following pathologies: diabetic neuropathy, small fiber neuropathies and pain conditions

including musculoskeletal pain. It is recommended that QST be used as a screening test for the assessment of small and large nerve fibre pathologies and monitoring of sensory deficit/gain over time. Specifically QST would be helpful for documenting and monitoring hypo/hyper-sensitivity phenomena (i.e. magnitude of sensory abnormalities). However, to outline the region of sensory abnormalities bedside/routine neurological assessment is required before using QST for outlining the region of sensory deficit/gain (hypo/hyper-sensitivity). The site of QST stimuli should be determined based on the clinical context. The response of QST should be interpreted in a broader clinical context by taking into account the specific musculoskeletal pain condition, and clinicians should consider negative influence of cognitive and affective factors of patients.

The observations outlined in this thesis and other pain study literatures support the existence of significant differences in pain treatment and outcome measures between women and men. The IASP consensus working group on gender and pain (Greenspan et al., 2007) already recommended that: 1) Both sexes should be included in clinical trials (including psychological, physical medicine, and medication treatments) in sufficient numbers to detect sex or gender effects, 2) Report of outcomes in each sex (sex differences) should also be mandated in treatment/clinical trials. However, these recommendations (Greenspan et al., 2007) have not yet been implemented widely even in research (Hashmi & Davis, 2013). The reason for this failure of the implementation strategy might be a gap between knowledge and evidence. This gap should be identified for appropriate knowledge translation and implementation in clinical research, practice and as well as in policy making.

QST demonstrates colonization of sensory sign and pain. However, QST has not yet gained acceptance in clinical practice as compared to conventional neurophysiological tests and

other psychophysical sensory techniques (e.g. visual field assessment, visual acuity, and audiometry). Databases of normal values have been provided (Rolke et al., 2006) but the normal range for some modalities (e.g. cold pain) are quite broad. In addition, insufficient numbers of sites have been studied. One of the main reasons why the adoption of QST has been slow in clinical context is probably insufficient knowledge translation about its standard protocol and lack of information about its utility. Further refinements of standard protocol for conducting QST and accumulated knowledge about its potential utility will contribute to better evaluation and diagnosis of musculoskeletal pain disorders. The issue of cost versus benefit of QST in clinical practice has yet to be well addressed.

Recommendation for Implementation and Future Research

This thesis work recommends that gender needs to be carefully considered when examining physical disorders and that all hypotheses should be tested separately between women and men to assure that conclusions made apply across genders. Again, these requirements suggest the need for larger sample sizes; and prespecified gender analyses. Due to the multivariate nature of musculoskeletal disorders future study should include large homogenous samples to identify the most important predictors of QST for the specific musculoskeletal pain condition.

This thesis work also recommends that all pain and sensation related research should consider testing their hypotheses in both genders. Since pain sensitivity comprises elements from both the sensory (peripheral and ascending nociceptive pathways) and modulatory mechanism (descending modulation pathways and top-down controls (Hashmi & Davis, 2013). Future

investigations should consider the concept of pain “sensitivity” and interpret their findings within a conceptual framework.

The following developments may make QST more applicable in the musculoskeletal clinical setting: First, there is a need to develop QST protocols that require less time and inexpensive portable equipment. Second, normative values of different sites are needed for various QST protocols. Third, there is a need to develop QST batteries for musculoskeletal pain assessment that are broadly implemented. Fourth, there is a need for more evidence regarding the clinical predictive value of QST for classification/diagnosis, treatment prognosis. Finally, for implementation at the policy level, evidence will be needed to justify cost reimbursement since third-party payers are more likely to cover QST fees if clinical utility is demonstrated. With these development plans, QST could become a clinically feasible and cost-effective measurement tool.

An illustration that cost-effectiveness affects choices of QST tool is reflected in comparing current perception threshold test (Uddin et al., 2013a, 2014c) to other potential tools screening tools currently used by clinicians including Semmes Weinstein Monofilaments (*moderate cost*) (MacDermid, Kramer, & Roth, 1994; Uddin et al., 2014b) or ice-water immersion test (*low cost*) (Uddin et al., 2013c, 2014a) or the ten test (*no cost*) (Uddin et al., 2013b, 2014a). Head to head comparisons of these tests as screening, diagnostic, or evaluative tools will be needed to determine which tools are best for different practice and research applications. Future research should also focus on longitudinal prospective studies with a large cohort of patients. These will be required to justify the prognostic and evaluative properties of different sensory modalities; and to compare different sensory modalities, assessment protocols, indicators, and decision rules. Accuracy and cost-benefit should be weighed when implementing

new tests. In future, the gap between different level of knowledge users should be identified for appropriate knowledge translation strategy and implementation of QST in clinical research, practice and as well as in policy making.

References

- Arendt-Nielsen, L., & Yarnitsky, D. (2009). Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *The Journal of Pain*, 10(6), 556-572.
- Backonja, M., Attal, N., Baron, R., Bouhassira, D., Drangholt, M., Dyck, P., Haanpaa, M. (2013). Value of quantitative sensory testing in neurological and pain disorders: NEUPSIG consensus. *Pain*,
- Berkley, K. J. (1997). Sex differences in pain. *Behavioral and Brain Sciences*, 20(3), 371-380.
- Chester, R., Shepstone, L., Daniell, H., Sweeting, D., Lewis, J., & Jerosch-Herold, C. (2013). Predicting response to physiotherapy treatment for musculoskeletal shoulder pain: A systematic review. *BMC Musculoskeletal Disorders*, 14, 203.
- Cruz-Almeida, Y., & Fillingim, R. B. (2014). Can quantitative sensory testing move us closer to Mechanism-Based pain management? *Pain Medicine*, 15(1), 61-72.
- Dominick, C. H., Blyth, F. M., & Nicholas, M. K. (2012). Unpacking the burden: Understanding the relationships between chronic pain and comorbidity in the general population. *Pain*, 153(2), 293-304.
- Gierthmühlen, J., Maier, C., Baron, R., Tölle, T., Treede, R., Birbaumer, N., . . . Lauchart, M. (2012). Sensory signs in complex regional pain syndrome and peripheral nerve injury. *Pain*, 153(4), 765-774.
- Green, D. M., & Swets, J. A. (1966). *Signal detection theory and psychophysics* Wiley New York.
- Greenspan, J. D., Craft, R. M., LeResche, L., Arendt-Nielsen, L., Berkley, K. J., Fillingim, R. B., Mayer, E. A. (2007). Studying sex and gender differences in pain and analgesia: A consensus report. *Pain*, 132, S26-S45.
- Hardy, J. D., & Du Bois, E. F. (1940). Differences between men and women in their response to heat and cold. *Proceedings of the National Academy of Sciences of the United States of America*, 26(6), 389.
- Hashmi, J. A., & Davis, K. D. (2013). Deconstructing sex differences in pain sensitivity. *Pain*;155(1):10-3.

- Hübscher, M., Moloney, N., Leaver, A., Rebeck, T., McAuley, J. H., & Refshauge, K. M. (2013). Relationship between quantitative sensory testing and pain or disability in people with spinal pain—a systematic review and meta-analysis. *Pain*,
- Johansen, A., Schirmer, H., Stubhaug, A., & Nielsen, C. S. (2014). Persistent post-surgical pain and experimental pain sensitivity in the tromsø study: Comorbid pain matters. *PAIN®*, 155(2), 341-348.
- MacDermid, J. C., Kramer, J. F., & Roth, J. H. (1994). Decision making in detecting abnormal semmes-weinstein monofilament thresholds in carpal tunnel syndrome. *Journal of Hand Therapy : Official Journal of the American Society of Hand Therapists*, 7(3), 158-162.
- Rolke, R., Baron, R., Maier, C., Tölle, T., Treede, R. D., Beyer, A., . . . Bötefür, I. (2006). Quantitative sensory testing in the german research network on neuropathic pain (DFNS): Standardized protocol and reference values. *Pain*, 123(3), 231-243.
- Tashjian, R. Z., Henn, R. F., Kang, L., & Green, A. (2004). The effect of comorbidity on self-assessed function in patients with a chronic rotator cuff tear. *The Journal of Bone & Joint Surgery*, 86(2), 355-362.
- Uddin, Z., MacDermid, J. C., Galea, V., Gross, A. R., & Pierrynowski, M. (2013a). Reliability indices, limits of agreement and construct validity of current perception threshold test in mechanical neck disorder. *Critical Reviews™ in Physical and Rehabilitation Medicine*, 25(3-4), 173-185.
- Uddin, Z., MacDermid, J., & Packham, T. (2013b). The ten test for sensation. *Journal of Physiotherapy*, 59(2), 132.
- Uddin Z, MacDermid JC, Packham T. (2013c) Ice-water (cold stress) immersion testing. *Journal of Physiotherapy*, 59(4):277-277.
- Uddin, Z., MacDermid, J., & Packham, T. (2014a). Clinical implementation of two quantitative sensory tests: Cold stress test and the ten test. *Physiotherapy Practice and Research*, 35(1), 33-40.
- Uddin Z, MacDermid JC, Ham H. (2014b) Test-Retest Reliability and Validity of Normative Cut-offs of the Two Devices Measuring Touch Threshold: Weinstein Enhanced Sensory Test and Pressure Specified Sensory Device. *Hand Therapy*, 19(1):3-10.
- Uddin Z, MacDermid JC, Galea V, Gross AR, Pierrynowski MR. (2014c). The Current Perception Threshold Test Differentiates Categories of Mechanical Neck Disorder. *Journal of Orthopaedic & Sports Physical Therapy*: In press.
- Velle, W. (1987). Sex differences in sensory functions. *Perspect Biol Med*. 1987;30(4):490-522.
- Woolf, C. J. (2004). Pain: Moving from symptom control toward mechanism-specific pharmacologic management. *Annals of Internal Medicine*, 140(6), 441-451.

Appendix 1

Hamilton Integrated Research Ethics Board approval/renewal Letter (Study 4)



Hamilton Integrated Research Ethics Board RENEWAL FORM

Review of an Active Study (to be completed by HIREB Chair only)

REB Project #: 10-654

Principal Investigator: Dr. Joy MacDermid

Project Title: Clinical prediction rule for chronic pain after shoulder surgery

☒ **Approved for Continuation**

☐ **Approved conditional on changes noted in "Conditions" section below**

Type of Approval:

☒ **Full Research Ethics Board**

☐ **Research Ethics Board Executive**

REB Approval Period: Approval period covers December 21-2013 to December 21-2014

☐ **New Enrolment Suspended**

☐ **Suspended pending further review**

Conditions:

The Hamilton Integrated Research Ethics Board operates in compliance with and is constituted in accordance with the requirements of: The Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans; The International Conference on Harmonization of Good Clinical Practices; Part C Division 5 of the Food and Drug Regulations of Health Canada, and the provisions of the Ontario Personal Health Information Protection Act 2004 and its applicable Regulations; for studies conducted at St. Joseph's Hospital, HIREB complies with the health ethics guide of the Catholic Alliance of Canada.

Suzette Salama PhD., Chair
Raelene Rathbone, MB BS, MD, PhD, Chair

12/17/2013
Date of REB Meeting

All Correspondence should be addressed to the HIREB Chair(s) and forwarded to:
HIREB Coordinator
293 Wellington St. N, Suite 102, Hamilton ON L8L 8E7
Tel. 905-521-2100 Ext. 42013 Fax: 905-577-8378

Appendix 2

Hamilton Integrated Research Ethics Board approval/renewal Letter (Study 5)



R E S E A R C H E T H S B O A R D



RENEWAL FORM

*Research Ethics Board Review of an Active Study
(to be completed by REB Chair only)*

REB Project #: 06-272

Principal Investigator: Ms. Linda Woodhouse

Project Title Proposal to Evaluate the Efficacy of the InterX 5000 in the Treatment of Chronic Neck and Shoulder Pain

☒ Approved for Continuation

☐ Approved conditional on changes noted in "Conditions" section below

Type of Approval:

☒ Full Research Ethics Board

☐ Research Ethics Board Executive

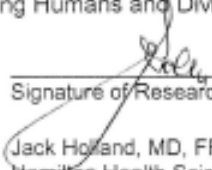
REB Approval Period: Approval period covers July 15-2009 to July 15-2010

☐ New Enrolment Suspended

☐ Suspended pending further review

Conditions:

The Hamilton Health Sciences/McMaster University Research Ethics Board operates in compliance with the ICH Good Clinical Practice Guidelines and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans and Division 5 Health Canada Food and Drug Regulations.


Signature of Research Ethics Board Chair

21-Jul-09

Date of REB Meeting

Jack Holland, MD, FRCP, FRCP(C), Chair
Hamilton Health Sciences/McMaster Health Sciences Research Ethics Board

All Correspondence should be addressed to the REB Chair and forwarded to:
REB Coordinator, Hamilton Health Sciences
1057 Main Street West, Suite 1, Hamilton ON L8S 4B7
Tel: 905-521-2100 Ext. 42013 Fax: 905-577-8378

Appendix 3

Information letter and consent for participants: MacHAND clinical research lab, McMaster University (Study 1 and 2)



MacHAND Laboratory



**McMaster University Institute for Applied Health Sciences
Room 310A, 1400 Main Street West, Hamilton, Ontario L8S 1C7**

CONSENT FORM

Role of Sensory, Motion, and Function Assessments when Evaluating Patients with Neck Disorders

Vickie Galea, Ph.D., (905) 525-9140 x 22189

Therapists treat patients with neck pain. At the present time there are few tests that measure sensation and body motion changes that could be caused by neck pain. Given this situation it is difficult for the therapist to prove that these problems exist and how severe they are. In addition, problems in the neck sometimes result in problems in the shoulder and down the arm. For this reason, a team of clinicians and movement scientists are working to investigate sensation and body motion changes in patients with neck pain. We are including those patients with neck pain with or without headache, shoulder pain, and “nerve” signs. Thus, therapists will be able to measure these problems and offer patients better treatment options.

You are being invited to participate in a research study that will assess volunteers with neck pain. If you do not wish to participate in this research study, your clinical care will not be affected.

I agree to visit the MacHAND Laboratory for muscle and nerve tests. Specifically, I will be invited to:

1. answer questions about my clinical history as it relates to my head and neck, shoulder & arm,
2. complete questionnaires that will ask me questions about headaches, and neck, shoulder and arm movements,
3. undergo strength testing of the hand and fingers via a grip and pinch force measurement,
4. complete a dexterity task involving objects of various sizes,
5. have my upper limb nerves and muscles tested by applying small vibration, pressure and electrical impulses to the surface of my hand and fingers,
6. visit the MacHAND Laboratory for two hours. Potentially, I may be asked to visit the Laboratory a second

Ph.D. Thesis - Zakir Uddin; McMaster University - Rehabilitation Science
time, approximately one week later.

During these assessments there are the following known **MINIMAL RISKS**,

- a. temporary muscle tiredness after completing the strength testing.

CONSENT

1. I hereby agree to undergo upper extremity sensory and motor control evaluations as part of a series of studies being undertaken in the School of Rehabilitation Science at McMaster University.
2. I understand that I may not immediately benefit from this testing, but I am volunteering my time in order that the implications of neck pain to the rest of the body's functioning may be better understood.
3. I have been informed that I have the option of stopping any assessment anytime. If I stop the assessment, I am aware that there will be no penalty, treatment consequence, nor loss of benefits to which I am otherwise entitled.
4. The assessment procedures, risks, and my options have been explained to me by a principal investigator or designate.
5. I have been provided ample time to ask any questions I may have. If I have any further questions, anytime, I can contact Vickie Galea at 905-525-9140 x 22189 to have these resolved.
6. I am aware that the information collected from me will be kept confidential always unless written permission is obtained from me in advance.
7. If I have questions regarding my rights as a research participant I may contact the Hamilton Health Sciences Patient Relations Specialist at (905) 521-2100, Ext 75240.
8. I will be provided with a signed copy of this consent form.

Volunteer's Printed Name

Signature

I have explained the nature of the study to the above-named individual.

Investigator's Printed Name

Signature

Dated in Hamilton, Ontario

Appendix 4

Information letter and consent for participants: MacHAND clinical research lab, McMaster University (Study 3)



Letter of Information / Consent Form

Reliability and Concurrent Validity of Two Methods of Measuring Functional Sensibility

Local Principal Investigator: Dr. Joy C MacDermid
School of Rehabilitation Sciences
McMaster University
Hamilton, Ontario, Canada
(905) 525-9140 ext. 22524

Student Investigator: Hyungjoo Ham and Jay Wang,
BHSc Level IV, McMaster University

Research Sponsor: N/A

You are being invited to participate in a student research study conducted by Hyungjoo Ham and Jay Wang, under the supervision of Dr. Joy C. MacDermid, about functional sensibility. This study will help the student in learning more about the topic area, research design, data collection, analyses, and interpretation, and writing of a research paper.

Why is this research study being done?

Functional sensibility is an important method of measuring sensory nerve function. Further, it can be used to follow the progression of patient illnesses affecting sensory nerves and to evaluate rehabilitation. It is important to find simple and accurate methods to measure functional sensibility that can be used in clinical settings.

In this study, we will use two different methods of measuring the ability to identify unseen objects with the fingertips. The two tests are the Moberg Pick-up Test and Shape Texture Identification (STITM) Test. , we wish to find out whether the two tests can consistently produce same results, and whether the two tests can produce accurate results.

What is the procedure involved in the study?

This is a two-part research study to be completed over two test days. Each test day should take about 30 – 45 minutes of your time

The procedures involved in the first test day are as follows:

- randomly decide on the order in which you will be taking the two tests (most likely done by

the flip of a coin)

- Take the first test (either STI™ Test or the Moberg Pick-up Test). Details of the tests will be explained.
- Take the second test (either STI™ Test or the Moberg Pick-up Test). Details of the tests will be explained.

The procedure involved in the second test day

- Repeat of the first test day, with the randomization of the order to be done again in the beginning.

What are the possible risks and discomforts?

The tests are non-invasive, and shall inflict minimal to no risks and discomforts.

How many people will be in this study?

Approximately 40 – 60 people will be participating in this study.

What is/are the potential benefit(s) of this research study?

On the personal level, the study participant may benefit from the study by obtaining the knowledge of his/her functional sensibility in more quantified measures. On a social level, the result obtained from this research study may serve as evidence for the reliability and concurrent validity of the Moberg Pick-up Test and the STI™ Test.

Will my confidential information be protected?

We appreciate your participation in the study, and will respect your personal privacy. The data collected will be stored on a password protected computer, and any other information written on paper which may disclose your identity will be stored in a locked cabinet. This ensures that no one other than the study investigators will have access to the information.

What if I change my mind about participating in this study?

Your participation in this study is voluntary. Even after signing the consent form, you can still withdraw from the study **at any time** throughout the study. Withdrawing from the study does not result in any consequences to you, and any information that you do not wish to be used for research will be destroyed.

You will be notified if any new information, which may affect your decision in participating in the trial, becomes available.

What if I want to learn about the result of the study?

If you are interested in the research findings after the study you may obtain information by contacting the investigators listed above. A written summary may be provided for you.

What if I have more questions?

Feel free to contact the study investigator, Jay Wang, via e-mail, for further information.

Information about Participating as a Study Subject

If you have questions or require more information about the study itself, please contact Dr. Joy C MacDermid, School of Rehabilitation Sciences, McMaster University, Hamilton, Ontario, Canada, (905) 525-9140 ext. 22524.

If you have any questions regarding your rights as a research participant you may contact the **Office of the Chair of the Hamilton Health Sciences / Faculty of Health Sciences Research Ethics Board at 905-521-2100, Ext. 42013.**

CONSENT

I have read the information presented in the information letter about a study being conducted by Dr. Joy C MacDermid and her students (listed above). I have had the opportunity to ask questions about my involvement in this study. I have received the additional details that I wanted to know about the study. I understand that I may withdraw from the study at any time. I have read and understood the information above. I agree to participate in the study. I will receive a copy of this form.

Name of Participant (please print)

Signature of Participant

Date

In my opinion, the person who has signed above is agreeing to participate in this study voluntarily, and understands the nature of the study and the consequences of participation in it.

Name of Researcher or Witness

Signature of Researcher or Witness

Date

Appendix 5

Information letter and consent for participants: MacHAND clinical research lab, McMaster University (Study 4)



PARTICIPANT INFORMATION SHEET

Title of Study:	Clinical prediction rule for chronic pain after shoulder surgery
Principal Investigators:	Dr. Joy MacDermid, PhD, McMaster University Dr. Jaydeep Moro, MD, FRCS(C), St. Joseph's Healthcare
Co-Investigators:	Dr. Krishan Rajaratnam, MD, FRCS(C), Hamilton General Hospital
Student Investigators:	Zakir Uddin, PhD (Candidate), McMaster University Jennifer Poon, BHSc. (Student), McMaster University
Sponsor:	McMaster University Surgical Associates Grant

You are being invited to participate in a research study because you have a shoulder problem.

In order to decide whether or not you want to be a part of this research study, you should understand what is involved and the potential risks and benefits. This form gives detailed information about the research study which will be discussed with you. Once you understand the study, you will be asked to sign this form if you wish to participate. Please take your time to make your decision. Feel free to discuss it with your friends and family, and/or your family physician.

why is this research being done?

Shoulder diseases are common and disabling. Common surgical procedures which stop the shoulder tendons from rubbing against the bone; repair torn tendons in the shoulder; or replace the damaged shoulder joint with a metal and plastic implant, can help stop shoulder problems. While the majority of patients are successfully treated with surgery, there is a small number of patients who develop chronic disabling pain after surgery.

What is the purpose of this study?

The purpose of this study is to try to identify the combination of factors—psychological, behavioural, health and nerve sensitivity—that will predict which patients are at risk of developing an increase in pain following surgery. We will also compare the baseline responses of the surgical patients versus the non-surgical patients.

What will happen to participants in this study?

If you volunteer to participate in this study, we will ask you to come in to the MacHAND clinical research lab at McMaster University. The visit will take 1.5 hours.

During the lab visit, you will be asked to:

- do tests that measure how you feel vibration, electrical impulses, and pressure applied to your fingers and/or shoulder;
- do 3 repetitive arm tasks where you move objects between 2 shelves.
- answer surveys on your quality of life, general health status, pain, arm/shoulder function, and physical activity

You may be asked to have video markers placed on your neck, shoulder and arm during the 3 repetitive arms tasks so that we can record your movements.

How many people will be in this study?

The study will have a total of 158 participants: 108 surgical patients and 50 non-surgical patients.

What are the possible risks?

During some of the testing, you may experience mild discomfort and pain. Temporary muscle tiredness may occur after the repetitive arm tasks. We will work with your tolerance level and you can stop testing at any time if you are experiencing any undue pain or discomfort.

What are the possible benefits?

You may not personally benefit from the study, however, your participation would help clinicians and researchers better understand the chronic pain that may develop after shoulder surgery. This research may also provide physicians a window of opportunity to prevent the increase in pain after surgery by helping them identify at-risk individuals.

What will happen to my personal information?

Your data will not be shared with anyone except with your consent or as required by law. All personal information such as your name, address, phone number will be removed from the data and will be replaced with a number. A list linking the number with your name will be kept in a secure place, separate from your file. The data, with identifying information removed, will be securely stored in a locked office in the research office. The data for this research study will be retained for 10 years following final publication of results.

For the purposes of ensuring the proper monitoring of the research study, it is possible that a member of the Hamilton Health Sciences/Faculty of Health Sciences Research Ethics Board may consult your research data.

However, no records which identify you by name or initials will be allowed to leave the institution/university/hospital. By signing this consent form, you authorize such access.

If the results of the study are published, your name will not be used and no information that discloses your identity will be released or published without your specific consent to the disclosure. However, it is important to note that this original signed consent form and the data which follows may be included in your health record.

Can participation in the study end early?

If you volunteer to be in this study, you may withdraw at any time without any effect on the quality of your medical care. If you wish to withdraw during or after the study, you have 2 options:

- 1) Continue to contribute the data collected prior to withdrawal
- 2) Request that all your information and data be withdrawn completely from the study.

You may also refuse to answer any questions you don't want to answer and still remain in the study. The investigator may withdraw you from this research if circumstances arise which warrant doing so.

Will I be paid to participate in this study?

If you volunteer to participate, you will be given a \$10 Tim Horton's gift card as honorarium for your participation. You will be reimbursed for your parking expenses when you come for your lab visit.

What happens if i have a research-related injury?

If you are injured as a direct result of taking part in this study, no compensation will be provided to you by Hamilton Health Sciences/McMaster University, St. Joseph's Healthcare or the Researchers.

You still have all your legal rights. If you sign this consent form it does not mean that you are releasing the investigator(s), institution(s) and/or sponsor from their legal and professional responsibilities.

If I have any questions or problems, whom can I call?

If you have any questions about the research now or later, please contact:

Margaret Lomotan, Research Assistant, at 905-525-9140 ext. 27328 or lomotam@mcmaster.ca on behalf of:

Dr. Joy MacDermid at the School of Rehabilitation Science at 905-525-9140 ext. 22524.

This study has been reviewed by the Hamilton Integrated Research Ethics Board (HIREB). The HIREB is responsible for ensuring that participants are informed of the risks associated with the research, and that participants are free to decide if participation is right for them. If you have any questions about your rights as a research participant, please call the Office of the Chair, Hamilton Integrated Research Ethics Board at 905.521.2100 x 42013.

CONSENT STATEMENT

SIGNATURE OF RESEARCH PARTICIPANT

I have read the preceding information thoroughly. I have had the opportunity to ask questions, and all of my questions have been answered to my satisfaction. I agree to participate in this study. I understand that I will receive a signed copy of this form.

Name of Participant

Signature of Participant

Date

Do you wish to be contacted to participate in future studies on hand/arm problems?

Please check one: YES ☐ NO ☐

Person obtaining consent:

I have discussed this study in detail with the participant. I believe the participant understands what is involved in this study.

Name, Role in Study

Signature

Date