Review Article

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 the pathogenesis, classification, differential diagnosis, and prognosis of chronic musculoskeletal pain.

Objectives. The objective of this paper is to discuss measurement properties of QST and potentials research and clinical applications in musculoskeletal pain.

Methods. This is a review of the current knowledge base on QST as it relates to musculoskeletal pain disorders. We based our summary on articles retrieved from Ovid MEDLINE (1946 to present) including EMBASE, AMED, and PsycINFO databases to search for all published literature focused on QST and musculoskeletal pain.

Results. QST has been shown to be related to neural sensitivity in musculoskeletal pain. QST measurement properties have been evaluated for multiple sensory evaluation modalities and protocols with no clear superior instrument or test protocol. The research evidence is incomplete, but suggests potential clinical benefits for predicting outcomes and subtyping pain. Threshold detection testing is commonly used to quantify sensory loss or gain, in current practice and has shown moderate reliability. Intensity/magnitude rating can be assessed on a wide range of rating scales and may be more useful for pain rating in a clinical context. Threshold detection-based testing and intensity/magnitude rating-based testing can be combined to determine pain threshold in clinical evaluation.

Conclusions. Musculoskeletal pain management may benefit from treatment algorithms that consider mechanism, pain quality, or neurophysiological correlates. Non-invasive QST may be helpful to find sensory array of altered nociceptive process. 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.

Key Words. Hyperesthesia; Hypoesthesia; Chronic Pain; Maladaptive Pain; Sensory Measurement
Introduction

Almost all adults have an episode of musculoskeletal pain from injury or overuse during their lifetime, and recurrent or chronic pain problems are common [1–3]. Chronic pain affects 33% of adults and accounts for 29% of lost workdays due to musculoskeletal pain [1,4]. Chronic musculoskeletal pain is a global health problem with significant economic impact [5,6], second only to cardiovascular disease [4].

The International Association for the Study of Pain (IASP) has defined “musculoskeletal pain” as a consequence of repetitive strain, overuse, and work-related disorders including a variety of disorders that cause pain in muscles, bones, joints, or surrounding structures (e.g., low back pain, neck pain, tendonitis, tendinosis, neuropathies, myalgia, and stress fractures) [1]. IASP also 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]. Chronic pain shares some common features of neuropathic pain [10–12], and the IASP redefined neuropathic pain (in 2011) as pain caused by a lesion or disease of the somatosensory nervous system [13]. This new definition opens a broader concept and shares common features of chronic musculoskeletal pain with other pain conditions (e.g., neuropathic, visceral) [14,15]. An example of this is cutaneous allostynia in neuropathic pain (assessed by brush), which may correspond to musculoskeletal pain (when evoked by weak muscle pressure). Pain biomarkers (pain assessment tools) related to hyperalgiesia/alldynia, referred pain, and spreading sensitization are phenomena that share many similarities between neuropathic and musculoskeletal chronic pain conditions [14,15].

Systematic reviews have demonstrated strong evidence for central hypersensitivity (abnormal pain response) as a prognostic factor for poor outcomes in chronic musculoskeletal pain [16,17]. The evolution of pain theory and evidence of a central component of post-injury pain hypersensitivity [12,18], 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 1 is a depiction of the stages of neurophysiologic mechanisms) suggesting that early detection of this involvement might allow clinicians to make a more accurate prognosis for their patients. Early identification would assist in allocating patients to the appropriate management strategies to alter this risk at an earlier stage.

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 fifth 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 altered pain sensitivity [19–21]. The aims of this paper are to 1) discuss the measurement properties of QST considering psychophysical principles that affect testing, and 2) provide the rationale of research and clinical benefits of QST with chronic musculoskeletal pain populations in light of mechanism based concepts of musculoskeletal pain.

QST Measurement Principles

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 [19,22]. The test protocol and interpretation can focus on the minimum threshold perceived, localization, threshold perceived as painful, tolerance, or differentiation of different sensory inputs [19,20,22,23]. 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] and other 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.

Figure 1 Stages of neural process in somatosensory system to produce pain hypersensitivity and chronicity (i.e., maladaptive pain). Adapted from Woolf & Salter, 2000 [36].
Weber–Fechner’s psychophysical law explains the logarithmic relationship between stimulus (physical magnitudes of stimuli) and perception (subjective sensation/perceived intensity of the stimuli) [25]. 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 [26–28]. They developed concepts of the mechanism underlying sensation, the nature of sensory damage following neural lesions, simple tests to analyze the loss of sensation and were pioneers in the history of quantifying sensation.

The developed 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 [29]. QST includes assessment of sensory threshold (detection threshold for innocuous stimuli and pain threshold) and sensations evoked by suprathreshold stimuli [20,30,31]. Tests are divided into 2 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 1 point on a scale of sensation within a complex pain processing system. To overcome this limitation, dynamic QST measures are suggested [32]. Dynamic QST measures are: tests of central integration (e.g., temporal and spatial summation) and tests of descending control (e.g., inhibitory conditioned pain modulation) [32]. Examples of test parameters for different QST are contained in Table 1.

Threshold detection and stimulus intensity rating (pain magnitude rating) are 2 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 [33]. 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 entire 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) [34]. The theory explains how changing the threshold affects the ability to distinguish.

Two distinct threshold measuring paradigms/methods (e.g., method of limits and levels, examples in Table 2) 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

Table 1  An example of stimulus modalities and pain measurement parameters in QST

<table>
<thead>
<tr>
<th>Stimulus Modalities</th>
<th>Pain Measurement Parameters</th>
</tr>
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<tbody>
<tr>
<td>Electrical</td>
<td>Pain Threshold/Tolerance, Temporal summation,</td>
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<tr>
<td></td>
<td>Noxious flexion response, Suprathreshold scaling (in VAS, NRS)</td>
</tr>
<tr>
<td>Contact thermal (heat, cold)</td>
<td>Pain Threshold/Tolerance, Temporal summation, Suprathreshold</td>
</tr>
<tr>
<td></td>
<td>scaling (in VAS, NRS)</td>
</tr>
<tr>
<td>Immersion thermal (heat, cold)</td>
<td>Temporal summation, Suprathreshold scaling (in VAS, NRS)</td>
</tr>
<tr>
<td>Mechanical (pressure, touch, vibration)</td>
<td>Pain Threshold/Tolerance, Temporal summation, Suprathreshold</td>
</tr>
<tr>
<td></td>
<td>scaling (in VAS, NRS)</td>
</tr>
<tr>
<td>Thermal, Ischemic Chemical (e.g., capsaicin,</td>
<td>Conditioned pain modulation</td>
</tr>
<tr>
<td>glutamate, hypertonic saline)</td>
<td>Pain rating, Pain area mapping, Cerebral responses (e.g., EEG,</td>
</tr>
<tr>
<td></td>
<td>fMRI, PET) Muscle reflexes (e.g., R3 reflex)</td>
</tr>
<tr>
<td>Light touch (e.g., monofilament)</td>
<td>Pain area mapping, Pain threshold</td>
</tr>
</tbody>
</table>
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 2).

Rationale for Research in QST Measures

QST has demonstrated potential benefits when compared with traditional neurological diagnostic tools. For example, around 80% of the peripheral nervous system consists of small nerve fibers [35], but traditional diagnostic methods for the peripheral nervous system (e.g., electromyography, nerve conduction velocity, and evoked potential) primarily focus on the large fibers [24,35]. Deep-tissue pain sensation transmits through small caliber A-delta (group III) and C fibers (group IV) [37]. QST can target these fibers by using frequencies that target small fibers (e.g., current perception threshold and vibratory perception threshold) 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 [32]. 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 functions (see Figure 3). Hyperesthesia and hypoesthesia (hypo and hyper sensory function) are fundamental features of neuropathic or maladaptive pain [20].

Table 3 contrasts an overview of bedside (clinical) examination and QST for evaluating small/pain fiber (A-delta and C fibers) function linked to spinal pathways. Bedside examinations are based on examiner interpretations of a qualitative nature and QST is based on patients’
Table 3 An overview of common clinical bedside examination and QST

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Bedside Exam</th>
<th>QST</th>
<th>Target Fiber (central pathway)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold Heat</td>
<td>Themoroller, test tube devices</td>
<td>Thermal testing QSTs</td>
<td>Aδ (spinothalamic)</td>
</tr>
<tr>
<td>Light touch (static) Vibration Pinprick Pressure (blunt)</td>
<td>Q-tip/cotton Tuning fork Pin Examiner's thumb</td>
<td>Calibrated monofilament Vibrometer Calibrated pin Algometer</td>
<td>C (spinothalamic) Aδ (Lemniscal) Aδ (Lemniscal) Aδ, C (spinothalamic)</td>
</tr>
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</table>

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 [48,49], 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 [10–12], and commonly is persistent, so it can also be considered as chronic pain [50].

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 [49]. 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 [19,20,23,51–53]
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 [20,23,32,51,54,55]. 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, and central (spinal or cerebral) nervous system [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 [56]. Clinical uses of QST in musculoskeletal pain management have already been suggested [52,54,58–61], as some QST modalities are found to be reliable and valid for clinical assessment of musculoskeletal pain disorders [57–59,62–69].

The Current Perception Threshold (CPT) measure is found very useful for assessing lower-extremity sensory functions in low back pain (both lumbar radiculopathy and discectomy) [70,71]. It has been demonstrated that CPT is reliable (consistent across occasions) and valid (associated with neck disability) for assessment of sensory detection threshold in patients with neck pain [62]. It has also been demonstrated that CPT testing has moderate discriminatory accuracy, specificity, and sensitivity for classification of neck pain categories into neck pain with or without neurological signs [55]. CPT might be useful for screening to classify patients with neck pain into clinically relevant subgroups [55]. 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 [55]. Evidence suggests that QSTs (psychophysical dimensions) and patient factors (gender, age and comorbidity) affect self-reported and performance-based outcome measures in shoulder disorder [72]. Another study suggests that pressure pain sensitivity may play a role in the self-reported outcome measures (e.g., pain and disability) of neck pain [69]. Although the studies [69,72] have indicated that gender and comorbidity are covariants in the relationship between pain detection threshold based QST and disability. Studies have suggested considering gender and comorbidity issues in QST measure [69,72]. A recent systematic review and meta-analysis demonstrated that QST of pressure pain thresholds demonstrated good ability to differentiate between people with osteoarthritis and healthy controls [73]. The study recommended that the “lower pressure pain thresholds in people with osteoarthritis in affected sites may suggest peripheral, and in remote sites, central sensitization” [73]. It is found that more than 90% of the QST tests of touch threshold 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 [63]. The study supports the reliability and specificity of these 2 QSTs (WEST and PSSD) [63]. Although multiple studies have suggested that QST is associated with multiple pain measures and outcomes, the size of the effect is sometimes small suggesting the need for better test methods and covariate controls.

It has been suggested that pain management should be based on a relational classification system of pain [74]. 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 [8,48]. QST can be used to categorize these subtypes of pain, and can provide a potential means to monitor change over time in response to treatment (outcome evaluation) [51].

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-stoke pain, whereas it cannot differentiate between pain of central origin (due to brain tissue damage) and musculoskeletal pain (due to 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-stoke pain) supports the first diagnosis (central pain).

QST has been shown to be useful for a wide range of clinical conditions including chronic musculoskeletal pain [19,23]. QST may 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 [55]. QST (pressure pain sensitivity test) may play a role in outcome measures of pain and disability in patients with chronic neck pain [69]. A recent consensus from the IASP expert panel [60], 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 [55,62] has similar reliability to other less costly tests such as Semmes Weinstein Monofilaments test (moderate cost) [63,75], ice-water immersion test (low cost) [54,59], or the ten test (no cost) [54,58,76]. 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 to justify the prognostic and evaluative properties of different sensory modalities; and to compare different sensory modalities, assessment protocols, indicators, and decision rules. There is a need to develop and test clinical decision rules that include QST and other relevant factors to allow clinicians to classify patients needing different treatment approaches based on the pain typology; and to allow clinicians to classify patients needing different treatment approaches based on the pain typology; and to trials to assess the efficacy of these decision rules. Since QST is not used consistently [77], there is a need for a knowledge translation strategy [61] to facilitate implementation of QST in clinical research and practice.

Conclusion

The evidence supports the ability of QST to assess processing of sensory and pain perceptions although the strength of the relationship between optimized QST and pain outcomes requires further study before we can be confident these assessments can lead to better outcomes.

Clinicians have to choose from a variety of test modalities and methods, although there is insufficient evidence to select between current options. Tests of threshold detection are readily available and used in current practice, but stimulus intensity rating testing may be useful for evaluating patient change over time [78]. Many test protocols have been described with moderate to high reliability; but there are insufficient head-to-head comparisons to select the best QST. Variable effect sizes for associations and discriminative accuracy have been reported.

QST may provide a semi-subjective method for examining sensation as a means 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 evaluative tool. QST may play a role in monitoring the disease prognosis and outcome evaluation in therapy intervention, but only continued research within homogenous parameters of QST will define this role. At present, clinicians should use standardized protocols based on tools and protocols reported in the literature, interpret QST findings in combination with standardized pain scales and clinical history/tests.

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