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The Role of Quantitative Sensory Testing in Clinical Medicine and Research

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ABSTRACT

A healthy peripheral nervous system allows for perception of temperature, touch and vibration at normal levels of stimulation without hypersensitivity or pain and is a key determinant of quality of life. Quantitative sensory testing (QST) describes an array of noninvasive methods for quantifying sensory function and monitoring sensory loss among patients with or at-risk for peripheral neuropathy (PN). Like audiometry, QST quantifies patients' subjective sensory experience with instrumentation that is precise and amenable to serial use. Thermal QST is the only diagnostic technology able to detect and quantify preclinical sensory deficit via direct patient feedback and merits wider use in clinical practice and research. A comprehensive QST assessment of 13 sensory parameters may be performed in an hour or less; abbreviated assessments take substantially less time. Although increasingly employed to evaluate sensation, define pain phenotypes, and predict outcomes in research studies and to monitor neurologic deficits in clinical practice, QST remains undervalued and underutilized possibly due to limited familiarity, experience, and understanding within the medical community and a lack of published standards regarding its use. This article is intended as a concise QST overview (with a focus on the use of thermal QST for the detection of small fiber abnormalities often associated with early PN) aimed at improving awareness of the unique role of QST in evaluating sensory function.

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Abbreviations

Quantitative Sensory Testing (QST), Peripheral Neuropathy (PN), Distal Sensory Peripheral Neuropathy (DSPN), Quality of Life (QoL), Activities of Daily Living (ADL), Nerve Conduction Studies (NCS), Cold Detection Threshold (CDT), Warm Detection Threshold (WDT), Cold-induced Pain Threshold (CPT), Heat-induced Pain Threshold (HPT), Thermal Sensory Limon (TSL) and Paradoxical Heat Sensations (PHS), Vibration Detection Threshold (VDT), Mechanical Detection Threshold (MDT) or Light Touch, Mechanical Pain Threshold (MPT), Mechanical Pain Sensitivity (MPS) to Pinprick Stimulation, Pressure Pain Threshold (PPT).

Introduction

Peripheral neuropathy (PN), a heterogeneous group of progressive neurologic disorders caused by damage to peripheral sensory and/or motor nerves, is common, potentially debilitating and currently medically incurable [1, 2]. While estimates vary widely by diagnostic criteria and population studied, PN likely affects between 21% and 50% of patients with HIV or diabetes during the course of their disease, a significant proportion of patients with pre-diabetes, and at least 40% of patients exposed to neurotoxic chemotherapeutic agents. PN may also be idiopathic [3-8].

Distal sensory peripheral neuropathy (DSPN) is among the most common types of PN patterns and characterized by progressive dysfunction of length-dependent sensory peripheral nerves. Symptoms typically start in the feet and may include pain, paresthesias such as tingling and prickling, hyper-reactivity, and loss of sensation to external stimuli [1, 9]. Patients consistently report a marked reduction in quality of life (QoL) related to difficulty standing, walking, driving, and performing activities of daily living (ADL) [1, 10]. Loss of sensation or balance puts patients at risk for falls, injuries, and wound infections. As temperature sensations shift, patients may have increased or decreased sweating and increased risk for burn injury [1, 11]. Physical symptoms and disabilities, social and work challenges, the stress of deteriorating QoL and the threat of loss of independence frequently contribute to depressed or anxious mood and feelings of hopelessness [3].

Research aimed at filling gaps in the knowledge base around PN—including pathogenesis, presenting patterns, risk factors, patient experience, diagnosis and management—must be a top priority across disciplines. An important area of emerging research is PN affecting small fiber (thinly myelinated A-*delta* fibers and unmyelinated C-fibers) neural networks, which is frequently missed in neurological work-ups as it evades detection with standard bedside neurologic examination as well as nerve conduction studies (NCS) [9, 12]. An initial manifestation of

small fiber PN is abnormal thermal sensitivity, ie., changes to the ability to feel heat and/or cold temperatures, commonly starting in the feet [12]. Small fiber neuropathy may occur as a component of mixed large- and small-fiber neuropathy, such as in diabetic peripheral neuropathy, or, as is being increasingly recognized, as an isolated, idiopathic disease [9].

In its earliest stages, lifestyle interventions and aggressive self-care have been shown to slow PN progression [13, 14]. Therefore prompt diagnosis of small fiber PN, even before the development of symptoms when possible, gives patients the best chance to forestall the development of serious consequences and live a healthy life [14].

Sensory abnormalities including thermal insensitivity are detectable by quantitative sensory testing (QST), which is sensitive, reliable and simple to perform [12]. QST is a set of tests that detect sensory loss (i.e., hypoesthesia, hypoalgesia) and sensory gain (i.e., hyperesthesia, hyperalgesia, and allodynia) due to damage in large (A-beta) fiber or small (A-delta and C) fiber peripheral nerve networks [15, 16]. A comprehensive battery of 13 parameters within 7 sensory categories was developed by the German Research Network on Neuropathic Pain for the evaluation of somatosensory function in the research of chronic pain [16].

Importance of Standard Practices

As small fiber neuropathy is increasingly recognized, thermal QST is being increasingly used in research and clinical practice as an individual entity [17]. However, standardization and guidelines regarding implementation and interpretation of QST are lacking, which has the effect of slowing progress in the field [14, 18]. The following is intended as a succinct review of current concepts and practices regarding clinical and research use of QST for assessment of sensory status, with a focus on the use of thermal QST for the detection of small fiber abnormalities.

Detecting and Evaluating PN

Subjective Techniques

The simplest method for assessing sensory perception is to query patients about their experience directly. Questionnaires and composite screening assessments (which capture symptoms and physical examination findings) impart structure and reproducibility to patient interviews and provide a basic means for quantifying neuropathic symptoms. There are a great many validated screening questionnaires in use in the evaluation of PN. The Leeds Assessment of Neuropathic Symptoms and Signs, Michigan Neuropathy Screening Instrument, Neurological Symptom Score, Toronto Clinical Neuropathy Score is some of the more popular questionnaires. The Utah Early Neuropathy Scale is a composite assessment specifically useful for uncovering evidence of small fiber neuropathy [9, 14, 19, 20].

A key benefit of questionnaires is they are direct, and provide immediate reflections of subjects' lived experience and as such, highly relevant. Other benefits include ease of administration, noninvasiveness, inexpensive cost and high patient acceptance, all of which make them proficient for serial administration and low-tech monitoring. Questionnaires however lack the ability to uncover pre-symptomatic stages of disease (patients cannot report what they do not themselves perceive) and are of limited sensitivity in general [19].

Objective Techniques

Objective tests used in the evaluation of PN are aimed at the assessment of neurophysiologic function or structural change related to the underlying disease. Such tests may be useful in identifying pathologic markers of PN, but do not deal with patients' experience of sensation specifically [21]. At best, objective tests are stand-ins for sensitivity. Purely objective tests are preferred by some researchers since they largely bypass the need for subject cooperation and reduce the human factor inherent in subjective scales and questionnaires. However, results of these tests must be correlated with patient symptoms to be clinically relevant; and correlations may be inexact or unknown depending on the state of research. While not a substitute for querying patients directly about their sensory symptoms and testing for sensory change via QST, the following tests play adjunctive roles in the evaluation of sensory PN.

Nerve conduction studies (NCS) and electromyography (EMG) is commonly used research tools in the assessment of neurophysiology and may be useful toward clinical diagnosis of PN, particularly mid-to-advanced stage diabetic peripheral neuropathy. These methods detect activity in large myelinated nerve fiber networks only, thus are unreliable for detecting small-fiber PN and mixed large- and small-fiber neuropathies at early stages. Other disadvantages include cost and the requirement for expertise and considerable time to administer, all of which limit their usefulness in clinical practice [22].

Skin biopsy may be used to assess for loss of intraepithelial nerve fiber density (IENFD) and abnormalities in nerve fiber morphology, hallmarks of some but not all types of PN [9]. In the diagnosis of small fiber neuropathy, skin biopsy IENFD is 61-97% sensitive and 64-95% specific and considered by some the "gold standard" [14]. Sensitivity varies depending on the approach and cut-off values used [23]. However, biopsies are invasive, take days to heal, and carry risk for bleeding and infection, which may be particularly hazardous among immunocompromised patients [22, 24]. It is also somewhat counterintuitive to deliberately disrupt tissues where nerve regeneration is the desired outcome. Further, interpretation of results is not clear-cut as extensive normative reference values are lacking and the relationship between IENFD and the clinical picture including NP severity is as yet unclear [14, 21, 24].

Corneal confocal microscopy (CCM) is a noninvasive ophthalmologic imaging technology that measures corneal nerve morphometric parameters, including fiber length, fiber density, branch density and inferior-whorl length. Corneal nerve metrics may be extrapolated and used as surrogate markers for peripheral nerve health in the diagnosis of PN [14, 24]. Peripheral neuropathy may be diagnosed by comparing CCM results to normative values from healthy individuals of the same age decade and sex, which has been shown to be 60-91% sensitive and 40-87% specific [14]. CCM has also been used to diagnose HIV neuropathy, idiopathic small fiber neuropathy, chemotherapy-induced neuropathy, and neuropathy associated with pre-diabetes [14, 24]. Severity of nerve fiber loss on CCM has been correlated with PN severity and, among patients with diabetes, risk for foot disease [14]. High costs, limited CCM availability, and the need for training to operate the device put CCM out of reach for many research teams. Additionally, interpretation of images requires understanding of clinical ophthalmology, further limiting its use within non-ophthalmologic fields [24].

Given limitations around CCM, some are looking for alternative PN biomarkers. Reflective confocal microscopy, for example, is a relatively new technology that measures the density of Meissner corpuscles in patients' fingertips and may be used to identify various forms of PN [8].

QST Bridges the Gap

Used widely by researchers and increasingly by clinicians, quantitative sensory testing (QST) is the gold standard for evaluating somatosensory function in human subjects [25]. QST is comprised of a battery of noninvasive somatosensory assessments that enables quantification (loss or gain) of sensory function at various areas of the body. Under controlled conditions, subjects undergoing QST respond to a series of stimuli delivered to the skin so that an "absolute sensory threshold" (AST) — defined as the "minimal energy reliably detected" of each study modality— may be determined [26]. Results are then compared to normal thresholds of healthy individuals of the same age and sex and recorded at the same anatomical site, which may be reported as a Z-score, ie., the sensitivity of the subject as a positive or negative deviation from a normal range [16]. An abnormally high AST indicates decreased sensitivity, ie., a greater stimulus is required for the patient to feel it. An abnormally low AST indicates hypersensitivity, ie., a patient feels the stimulus earlier than most people. Hypersensitivity may also be associated with spontaneous pain [25].

Like audiometry for detecting hearing loss, QST is a psychophysical metric, meaning it is neither entirely objective not entirely subjective, rather a combination of pertinent aspects of both. The objective ("physical") aspect of QST involves the delivery of a series of calibrated stimuli via a transducer to a specific area of the skin as per a predetermined protocol. The subjective ("psychological" or "psychoneurological") aspect is subjects' perception of and response to delivered stimuli. [18] QST may be thought of as occupying a category unto itself between subjective (e.g., patient-reported symptoms and symptom scales) and objective (e.g., NCV, CCM) testing. Multi-test QST may be administered alone or in combination with other measures [21, 26].

It is not uncommon for members of the scientific community to conflate objectivity with validity, two distinct concepts, including in the evaluation of an inherently subjective phenomenon such as sensation. Researchers may favor purely objective measurement techniques, for example CCM, over which they are able to exercise greater control as they do not depend on patient cooperation. However, in order to be clinically meaningful, results of CCM and other objective tests must be transposed onto sensory function as best as possible given the available science. In other words, in the study of sensation or other subjective phenomena, objective data are only as useful as the science correlating objective and subjective parameters is robust. Even then, the potential to misrepresent a patient's experience remains, as it is comprised of a complex array of neurophysiological aspects and is highly individualized. Thus, in the study of human sensory perception, patient involvement (subjectivity) should be thought of as a strength, as it allows for direct and immediate quantification of the study variable (perception) in a straightforward way without the need for abstraction or calculation. QST is a simple, mostly objective, validated means for quantifying sensory experience. Purely objective measures may support QST and patient-reports, but not replace them.

What QST Tests

Neurologic pathways of perception involve end-organ, peripheral and central nervous systems and have been well mapped. Perception of a sensation starts with receipt of a stimulus on sense receptors and free nerve endings of the skin or deep tissues, transformation of the stimulus into an electrical signal, then conduction along a network of afferent nerves and spinothalamic tract to the post-central gyrus of the cerebral cortex in the brain where it is consciously registered. Modulation of pain occurs in the prefrontal cortex, cingulate gyrus, pons, and other regions of the brain [24]. Different afferent nerve fibers conduct different sensations: mechanical sensations by large A-beta fibers, and pain and thermal sensations by small-fiber, thinly myelinated A-delta fibers and unmyelinated C-fiber types.

The full QST complement includes assessment of various distinct thermal and mechanical sensations a pain related to either thermal or mechanical stimuli. A comprehensive sensory evaluation involves the use of 7 methods to assess 13 sensory parameters performed bilaterally at several sites to allow for detection of positive (e.g., hyperesthesia, hyperalgesia, allodynia) and negative (e.g., hypoesthesia, hypoalgesia) signs and differentiation between small and large fiber disease and polyneuropathy and mononeuropathy [16, 27]. In some studies and clinical cases, such as population screenings or monitoring sensory status changes in longitudinal studies, a smaller battery of tests may be performed, e.g., at a single site, on one side, or using a focused subset of modalities [26]. The comprehensive QST assessment of 13 sensory parameters may be performed at two body sites in under an hour and abbreviated assessments in substantially less time [16].

Thermal QST: Temperature perception relies on the integrity of small, thinly myelinated A-delta and C- fiber nerves, which are typically the first nerves affected by many common types of PN. Thermal QST is of particular importance as it is the only modality that assesses the function of small nerves specifically. Abnormal thermal QST may be the first and only indication of subclinical neuropathy [28, 29]. Thermal QST has been shown to correlate with or be of greater sensitivity than skin biopsy IENFD [23, 30].

Pain perception relies on skin and end organ nociceptors and peripheral nerve C-fibers [26]. Like loss of temperature sensitivity, loss of pain sensation may go unnoticed by patients and place them at risk for injuries and, among those with diabetes, diabetic foot. Thus, pain and thermal QST provide valuable information to all at-risk patients, irrespective of neuropathy diagnosis, symptoms, and duration of time since primary diagnosis [28].

A full thermal QST protocol tests for 6 sub modalities related to temperature perception: cold detection threshold (CDT), warm detection threshold (WDT), cold-induced pain threshold (CPT), heat-induced pain threshold (HPT), thermal sensory limon (TSL) and paradoxical heat sensations (PHS) which may occur during the thermal sensory limen procedure [16, 27]. An abbreviated protocol that assesses cold detection, warm detection, and heat-induced pain thresholds may be substituted if time or technology is limited or in the interest of efficiency.

Mechanical QST: A full mechanical QST protocol tests for 7 sub modalities: vibration detection threshold (VDT), mechanical detection threshold (MDT) or light touch, mechanical pain threshold (MPT) and mechanical pain sensitivity (MPS) to pinprick stimulation, pressure pain threshold (PPT) to blunt pressure, allodynia to soft tactile stimulation, and wind-up ratio [16, 27].

Vibration perception relies on the integrity of Meissner and Pacinian corpuscles and their associated large diameter nerve fibers; these sites are affected by polyneuropathy, particularly in later stages [26]. Vibration detection thresholds (VDT) may be measured by delivering a static vibratory frequency (between 60 and 125Hz, depending on the device) via a vibrational device or biothesiometer to the skin of the fingers or toes. Voltage is subsequently increased or decreased according to a protocol, and

the subject reports their perceptions [31]. Vibrational QST has been shown to perform comparably but not better than the Rydel-Seiffer tuning fork (used in neurologic physical examination) in predicting the detection of neuropathy [32]. Therefore, the tuning fork, the simpler method, may be preferred [16].

Light touch relies on the integrity of Merkel touch domes, Meissner corpuscles and associated large-diameter fibers [26]. Light touch may be semiquantitatively assessed by a pressure aesthesiometer based upon methodology originated by von Frey (von Frey hairs) and refined by Semmes and Weinstein [33]. Modified von Frey filaments or Weinstein-Semmes pressure aesthesiometer measures sensitivity to touch by assessing subjects' response (felt or not felt) to nylon filaments of varying thicknesses pressed against the skin with standardized pressure until the filament bows [16, 31] . For a more detailed discussion of mechanical QST please see Rolke et al and Mucke et al [16, 27].

QST Advantages

Compared with other direct and indirect methods for quantifying sensory perception, QST offers several advantages [26]. A main clinical advantage is that, unlike questionnaires, QST may detect sensory loss in advance of the development of symptoms. Second, unlike biomarker techniques such as CCM, QST is a direct measure of patients' experience and unquestionably relevant. Other than questionnaires and composite screening assessments, QST is the only available sensory evaluation method that accounts for the complexity with which individual patients process and experience their pain, neurologic symptoms and sensations in response to stimuli.

Third, the delivery of stimuli and recording of responses are objective and quantified making QST precise, reproducible, and well suited for research. Quantification makes it plain to see if a patient is improving or worsening. QST precision is further optimized by adherence to standard practices that reduce variability and promote consistency: training testing personnel, scripted or recorded subject instruction, standard application of the device, and controlled testing environments. Fourth, QST is noninvasive and generally nonaversive to patients, with the caveat that pain testing involves a brief experience of pain extinguished by the patient immediately upon perception. Fifth, QST may be performed by a nurse or other qualified member of the clinical or research team after a brief training. Device manufacturers typically offer such trainings. And lastly, QST is relatively inexpensive compared with other techniques.

QST in Research

QST may be employed to facilitate a wide range of research objectives. In epidemiological studies, QST may be used to screen large heterogenous populations or smaller well-defined populations for sensory abnormality. QST results may contribute to an understanding of disease presentation, natural history or pathogenesis, or be used to refine and quantify pain definitions. In an example of the latter, Felix and colleagues demonstrated that heat-induced pain as determined by QST was a marker for chronic pain severity among patients with spinal cord injury [34]. Understanding sensory correlates of pain may be of useful toward determining and ultimately targeting underlying pain mechanisms. A main indication for QST is monitoring sensory status of patients enrolled in clinical trials. Thermal and/or pain QST, for example, may be used to monitor therapeutic response in trials of medications or interventions aimed at treating pain or neuropathic symptoms. QST modalities, including cold detection thresholds and heat-pain thresholds, have been correlated with acupuncture-induced analgesia [35]. In addition, QST may be used in clinical trials of potentially neurotoxic medications or combinations of medications to monitor for the development adverse events, e.g., chemotherapy-induced peripheral neuropathy [36].

QST in Precision Pain Management

QST is taking a central role in the developing field of precision pain management, which attempts to define phenotypic profiles of chronic pain-based patterns of psychological, social and physiologic determinants [37]. Phenotypic profiles of pain are used to understand patients' pain patterns, their potential to respond to various treatments, predict the transition from acute to chronic pain, and ultimately to guide pain management choices and improve outcomes.

For example, Baron and colleagues used QST to perform a cluster analysis of over 900 patients with chronic pain. They identified three clusters or subgroups of chronic pain with distinct QST patterns across 13 modalities and symptom profiles [38]. Their findings suggest that the physiology of chronic pain may be less related to etiology and more to a patient-specific pain phenotype or profile and supports a phenotypic model of chronic pain [37, 38].

Wang and colleagues used QST to predict which patients would develop chronic pain following thoracic surgery [39]. Similarly, Dursteler and colleagues showed that low descending pain inhibition, i.e., low conditioned pain modulation (CPM), as assessed by QST was associated withincreased risk for persistent pain following knee replacement surgery [40]. Zaferio and colleagues used QST findings to predict which participants would complete a pain management program and get relief [41]. And Stark weather and colleagues were able to differentiate patients with sustained low back pain from those whose pain resolved based on their results of thermal QST [42]. These studies illustrate ways QST has been employed in pain phenotype research and are not intended, of course, as a comprehensive review of the subject.

QST in Clinical Medicine

In the clinical management of PN, QST is an important adjunct to history-taking and questionnaires and may be understood as an extension of sensory aspect of clinical neurologic examination [26]. As mentioned in the introduction, a critical and underused indication for QST is in the detection of preclinical and/or early diabetic neuropathy and other suspected neuropathies [14]. Research shows that patients with diabetes without documented neuropathy have significantly higher thermal thresholds than patients without diabetes, which indicates that a diagnosis of diabetes implies the presence of subclinical neuropathy [28]. Further, patients with diabetes and DSPN of the feet may also demonstrate signs of DSPN in their hands despite not having symptoms in their hands [43]. In patients with diabetes, researchers have shown a linear correlation between thermal insensitivity as demonstrated by QST and hemoglobin A1C elevation (indicating worse glycemic control) [44]. In the same study, QST abnormalities predicted symptomatic neuropathy [44]. In a separate study among patients with type 2 diabetes who had neither overt neuropathy nor cardiovascular disease, abnormal thermal thresholds in the feet were associated with peripheral artery disease, indicating a heightened risk for diabetic foot [45]. Abnormal thermal thresholds have also been associated the presence of cardiac autonomic neuropathy among patients with diabetes [46].

Taken together, there is ample evidence that patients at every stage of diabetes would be well served to undergo thermal QST,

as detection of sensory abnormalities at an earliest possible stage enables timely intervention and should be the goal [14]. Clinicians should consider conducting warm and cold QST when PN is present or simply suspected, even if examination and nerve conduction studies are normal or near normal [12, 14]. QST is also indicated for patients at risk for PN (e.g., patients with metabolic syndrome, pre-diabetes, diabetes, or receiving chemotherapy) including those in whom symptoms are lacking [14, 28, 44].

Administering Thermal QST

Thermo-testing devices capable of performing complete or partial thermal QST assessments include The Sensory Analyzer (TSA)-II and Q-Sense (Medoc Ltd., Israel) and MSA Thermal Stimulator (Somedic SenseLab AB, Sweden) [27, 31]. A highly practical approach to thermal QST involves testing three key thermal parameters—warm detection, cold detection, and heat-induced pain thresholds—via the Q-Sense (Medoc, Ltd.)

Q-Sense is popular among researchers for its precision, reproducibility, portability, ease of use, and relative affordability. Q-Sense has been shown to be comparable to TSA-II for hot and cold detection and heat-induced pain thresholds among healthy individuals and patients with diabetes [30]. TSA-II was superior to Q-Sense only for loss of cold sensation for males over the age of 60 [30]. The device uses a small metal plate called a thermode to deliver a warm or cold stimulus to subjects' skin (e.g., dorsal aspect of the foot), then raises or lowers the temperature at a standard rate (1 degree C per second) until the subject reports perception of temperature (hot or cold) and stops the test using a handheld response unit [47]. The Q-Sense is pre-calibrated and pre-programmed with Medoc Main Station (MMS) software enabling efficient interpretation and reporting of results against age-, gender-, and anatomy-matched normative data [47]. Results are reported as Z-transformed QST data (also called Z-scores) which represent the difference between the subjects's mean score and a normal range for a cohort of age-, gender- and anatomical site-matched normative values [16]. Z-score is calculated as [mean value per patient] X [mean value per matched controls] / [standard deviation of matched controls] [16]. Temperature change or ramp rate of 1 degree Celsius/second and temperature cut-off points are also programmed into the system's standard protocol [47].

For studies to be reliable and reproducible, stimulus delivery must be standardized and exact. In the past that meant that the following variables had to be kept constant: make and model of QST instrument, anatomical site, size of skin area, ramp rate, stimulus intensity and duration [31]. While it is still important to use the same device and anatomical location, current technology such as Q-Sense eliminates the need for the researcher to control other variables, e.g., ramp rate, stimulus size (which is thermode size), intensity and duration, as they are already incorporated into the software of the instrument [47].

Researchers must choose between the *method of limits or method of levels* to deliver the stimuli, and input that decision into the instrument. Using the *method of limits*, which is the more common, a stimulus is applied, then gradually increased at a standard rate until felt and reported by the subject. Advantages of this method are efficiency and the need for fewer stimulations; a disadvantage is that the variable of reaction time must be factored into the result [31]. Using the *method of levels*, a stimulus is applied which terminates on its own, and the subject is asked if it was felt. If it was felt the stimulus is reduced; if it was not the stimulus is increased. The process continues until a detection threshold can be deduced based upon the cumulative inputs [24, 27]. An advantage of method of levels is that it is independent of human reaction time. Disadvantages include the need to revisit and compare against a baseline sensation each time in order to accurately say whether a stimulus has been added and the need for a greater number of tests, which makes the assessment longer to perform and may cause patients to become sensitized (which may reduce accuracy) [31, 24, 27].

Standard Technique

As a psychophysical method, QST must be administered using rigorous, standardized technique for each patient at each visit so that results of individual studies are accurate, meaningful and reproducible and so that cumulative studies may be understood and interpreted as a whole. At a minimum, every effort should be made to standardize the following: staff training, gathering of participants' demographic data, participant instruction, testing environment, and methods and technique for delivery of stimuli [26, 44]. In addition, study design methodology, including stimulus delivery method (method of limits vs. method of levels etc.,) and comparative normative database, should be reported.

Staff training: Staff members who administer QST should have medical and technical expertise, the latter of which may be developed through brief training specific to the device and protocol intended for use. Nurses are well suited for the role as their expertise equips them to recognize physical issues that may confound results, e.g., skin conditions that may interfere with delivery of stimuli, and work effectively with patients. Nurses with research experience are ideal as they are already well versed on the importance of patient and investigator blinding, adherence to protocol, using scripted language to instruct participants, and other aspects of research that are distinct from regular clinical care.

Examiners should be trained to ensure operational competence, understanding of procedures and protocols, ability to communicate testing instructions clearly for each modality (typically via a script), insight to clear up participants' misunderstandings without introducing bias, ability to identify artifacts in the testing procedure, and proficiency to correct calibration errors or malfunctions in the unit [26]. In longitudinal studies, whenever possible, an effort should be made to have the same examiner administer each assessment to further reduce risk for examiner-related bias [26]. For their own edification, examiners should understand the distinction between method of limits and method of levels in the study algorithm. However, only one method is likely to be used per protocol, and it is not necessary or advisable that study methodology be communicated to the patient.

Gathering participant data: Demographic data and other relevant baseline data points should be collected and reported on all subjects in studies in which QST is performed [26].

Participant prescreening and instruction: Subjects should be screened with mini-mental exam prior to enrollment to assess ability to understand and follow instructions. Interactions between staff and study subjects should be kept to the minimum necessary to instruct the subject and optimize their participation. When instructing patients about use of the device and setting expectations regarding procedure, nursing staff may be asked to adhere to a preset script, which should be simple, clear and standardized. A standard instruction script is available from Medoc for use with the Q-Sense device. Examiners should refrain from explaining more than is necessary; for example, the hypothesis of the study should not be disclosed to participants. Testing environment: Ambient room temperature should be documented and maintained at

standard in QST studies. Baseline skin temperature and condition should be thoroughly documented [26].

Methods and technique for delivery of stimuli: Study design should include delivery of stimuli via reaction-time inclusive method of limits or reaction-time exclusive method of levels. (See above.)

According to the Medoc website, in addition to the aforementioned, the following variables must remain constant between subjects and between visits for the most accurate results [47].

- Instrument make and model should be consistent
- Thermode size should be consistent
- Anatomical placement of the thermode, e.g., dorsal aspect (top) of foot (selected as per the needs of the study)
- Baseline skin temperature should be 32 degrees C
- Rate of temperature increase should be 1 degree C/second (preprogrammed into the device)
- Interval between sequential stimuli, the inter-stimuli interval (ISI) should be consistent
- Number of stimuli (generally 4 for warm threshold and cold threshold and 3 for heat induced pain)

Calibration and Interpretation: In the past, it was necessary to calibrate QST devices and interpret results against normative data using complex algorithms following completion of the studies [26]. Current technology is much simpler. State of the art QST devices such as Q-Sense no longer require calibration; and normative data sufficient for some studies are already programmed into the system. For each modality and test, an interpretive report is generated in which subject results are automatically compared to normative data (if that is the design) and prior tests, so that patient-specific longitudinal data are available at the time of testing.

Comparisons and Normative Values

Proper interpretation of QST results varies according to purpose, population, and methods of the individual study. For comparison, normal values have been determined for cold perception threshold, warm perception threshold and pain perception stratified by sex, age (by decade, between 6 and 79), site of stimulation (including mandible, medial forearm, hand and foot), and method (limits or levels), and incorporated into the Q-Sense algorithm [48-50]. These data reflect populations based in Germany, Australia and Israel; race and ethnicity are not known but may be presumed to be mostly Caucasian based on geographic demography. QST results may also be compared with normative values published elsewhere or gathered during current research, ie., researchers' own normative data, which may be uploaded into the software for ease of use. For example, vibratory and thermal normative values have been published that are specific to Mexican-born Latin American Hispanic and African-American populations, either or both of which may be imported into the Medoc system [17, 51, 52]. Results may also be compared against normative values for individuals with a specific disease, eg., sickle cell disease, if available [53].

Intra-subject comparisons may also be made. For example, in a cohort of patients with unilateral neuropathic complaints, researchers may choose to compare QST findings on the affected side to those on the unaffected side. Alternatively, results may be compared solely with baseline values in lieu of or in addition to comparisons with normative values. A statistician should be employed for evaluation of data regardless of study design.

Conclusion

Greater use of QST using standard methods for administration, interpretation and reporting would advance research in the areas of neuropathy, chronic pain and neurotoxicity. Broader application of thermal QST in clinics, including abbreviated protocols, would be of value in assessing small fiber neuropathology consistent with subclinical and early neuropathy.

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Declaration Conflicts of Interest

No conflict of interest

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