Quantitative Sensory Testing and Mapping

A Review of Nonautomated Quantitative Methods for Examination of the Patient With Neuropathic Pain

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Objectives: Despite a growing interest in neuropathic pain, neurologists and pain specialists do not have a standard, validated, office examination for the evaluation of neuropathic pain signs to complement the neurologic, musculoskeletal, and general physical examinations. An office neuropathic pain examination focused on quantifying sensory features of neuropathic pain, ranging from deficits to allodynia and hyperalgesia, and evoked by a physiologically representative array of stimuli, will be an essential tool to monitor treatment effectiveness and for clinical investigation into the mechanisms and management of neuropathic pain. Such an examination should include mapping of areas of stimulus-evoked neuropathic pain and standardized, reproducible quantitative sensory testing (QST) of tactile, punctuate, pressure, and thermal modalities.

Methods: We review quantitative sensory testing methodology in general and specific tests for the evaluation of neuropathic pain phenomena.

Results: Numerous quantitative sensory testing techniques for dynamic mechanical, pressure, vibration, and thermal sensory testing and mapping have been described. We propose a comprehensive neuropathic pain evaluation protocol that is based upon these available techniques.

Conclusions: A comprehensive neuropathic pain evaluation protocol is essential for further advancement of clinical research in neuropathic pain. A protocol that uses tools readily available in clinical practice, when established and validated, can be used widely and thus accelerate data collection for clinical research and increase clinical awareness of the features of neuropathic pain.

Key Words: neuropathic pain, quantitative sensory testing, QST, hyperalgesia, pain testing, allodynia

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Interest in the study of neuropathic pain is growing rapidly. A PubMed search using the search term "neuropathic pain" identified 3525 articles in the 6 years from 2000 through 2006 compared with only 971 articles published in the decade of the 1990s. The typical clinical manifestations of neuropathic pain are sensory loss, spontaneous pain, such as burning, spontaneous paresthesiae, and stimulus-evoked pain.[1] This clinical observation is supported by the finding that, among 12 items in the Neuropathic Pain Questionnaire, numbness, tingling pain, and increased pain owing to touch are significant predictors of a neuropathic pain state.[2] It follows that, to study neuropathic pain as a clinical phenomenon, it is essential to evaluate sensory loss, spontaneous sensory symptoms, and stimulus-evoked pain in a systematic and reproducible fashion. There exist at present several clinical testing paradigms that each addresses this need at least in part, but all of which have important limitations. Neuropathic pain questionnaires and scales assess self-reported symptoms but do not measure perceptions elicited in response to predetermined sensory stimuli.

The standard neurologic examination is well designed for the evaluation of sensory loss but not for the evaluation of positive sensory signs. Commercially available computerized quantitative sensory testing (QST) devices have been designed to measure both sensory loss and thermal pain thresholds, and can thus be used to diagnose thermal allodynia and hyperalgesia,[3] though thus far there has not been a consensus about the standard for this determination. In addition these devices do not test mechanical pain thresholds, and are impractical as a method of routine testing, including bedside sensory and pain testing.

The most recent development in neuropathic pain evaluation, the comprehensive QST protocol of the German Neuropathic Pain Consortium (DFNS), represents the best effort to date to address this void.[4] Nonetheless, it is also limited by the inconvenience of reliance on time consuming laboratory testing devices, many of which are not commonly available. In addition, neither computerized QST tools nor the DFNS protocol are designed to map areas of sensory abnormality, another important component of the neuropathic pain quantitative evaluation.

In recognition of the limitations of existing techniques and protocols, one of the first goals of the recently formed Neuropathic Pain Research Consortium (NPRC) is the development of a sensitive, reproducible, and comprehensive neuropathic pain examination that includes psychophysical measures of both sensory loss and stimulus-evoked symptoms, provides information about the spatial distribution of both negative and positive sensory signs, and, like the standard neurologic examination, can be performed in the clinical or research setting with tools that are relatively inexpensive, widely available, and easy to use. The inclusion of existing neuropathic pain questionnaires will allow assessment of the relationship between reported and elicited sensory perceptions. We feel that this comprehensive yet clinically practical tool would pave the way for large scale, systematic evaluation of patients with neuropathic pain

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and, as a consequence, accelerate our ability to recognize clinical patterns in neuropathic pain disorders.

This review, prepared by NPRC members, summarizes the present state of nonautomated QST techniques, which can be easily adapted for bedside evaluation of patients with neuropathic pain. In recognition of their relevance to this discussion, we will make reference to established computerized QST protocols and the DFNS protocol. Nonetheless, the focus of this review is on available quantitative techniques which evolved from bedside approaches, meaning techniques that can be easily applied in the clinic with inexpensive, simple tools. In combination with the companion paper in this issue, it is intended to serve as a reference and a foundation for a comprehensive bedside neuropathic pain examination.

QST PARADIGMS

Threshold Detection Versus Stimulus Intensity Rating

Several testing paradigms can be used to quantitatively assess sensory abnormalities. The following discussion relies on literature developed in the context of computerized QST but applies to bedside techniques as well. First, one can establish sensory thresholds using a graded series of stimuli. This technique of threshold detection testing is usually performed at fixed, standard sites. Threshold detection testing is most commonly used to quantitate sensory loss (elevated sensory detection threshold); however, it can also be used to demonstrate allodynia or hyperalgesia (reduced pain thresholds). Threshold detection testing has traditionally used age-adjusted normative data for particular body sites.

Alternatively, one can use a standard stimulus of fixed intensity and instruct the individual to provide a quantitative rating of its intensity. This is known as stimulus intensity rating. Stimulus intensity rating most often uses a visual analog scale or a numeric 11 point (0 to 10) rating scale for rating of the perceived sensation from a stimulus with prespecified physical properties. This paradigm lends itself well to evaluation of positive sensory phenomena, such as hyperalgesia and allodynia, and negative sensory phenomena. When determining the pain threshold, threshold testing and intensity rating can be combined,[5] a paradigm that allows detection of hyperpathia.[6]

Conceptually, stimulus intensity rating would seem to have a greater flexibility of scoring owing to a wider range of rating scales, and may be a more intuitive way of rating pain for patients. Threshold detection testing paradigms have been in use longer, and several databases of normal values have been generated; however, only a limited number of sites have been studied, and the normal range for some modalities, such as cold pain, is broad. The most efficient and conceptually valid way to apply stimulus intensity rating in clinical research and practice is to use an area of the individual body that is unaffected by sensory abnormalities, including pain, as a reference site against which stimuli in the affected site(s) is (are) rated. Thus far we are aware of no studies comparing these two paradigms, and consequently comparative advantages and disadvantages are not known.

Threshold Detection Testing Paradigms

For modalities in which the stimulus intensity is a continuous variable, such as thermal and vibration sensation, threshold testing can be performed using either reaction time-inclusive tests, in which the individual threshold is determined during administration of a ramp stimulus of gradually increasing or decreasing intensity, or reaction time-exclusive tests, in which the determination is made after termination of the stimulus.

The most commonly used reaction time-inclusive test is the method of limits. When using the method of limits, the examiner triggers a ramp of increasing or decreasing stimulus intensity. In the case of a ramp of increasing intensity, the individual is asked to report when the sensation is first detected; in the case of a ramp of decreasing intensity, the individual is asked to report when the stimulus is no longer detected. Threshold is usually defined as the average result of a series of trials. In this method a reaction time artifact is inherently built in, wherein the reaction time results in artificially elevated thresholds. Reaction time-exclusive tests are the methods of levels,[7] generally employing a staircase[8] or a forced choice[9] algorithm. With the method of levels, a series of individual stimuli of predetermined intensity and duration are applied, and the individual is asked to report whether the stimulus was perceived. With a staircase algorithm, each stimulus that is perceived is generally followed by one of lower intensity, and each stimulus that is not perceived is generally followed by one of greater intensity. In this fashion, a method of levels protocol ultimately oscillates around the detection threshold. Null stimuli, in which no stimulus is in fact delivered, are often included in a random order. A test should be considered invalid if a individual repeatedly reports positive responses to null stimuli. The forced-choice algorithm is a variation of the method of levels in which stimuli are provided in pairs, one of which is always a null stimulus. The individual is told in advance that a pair of tests will be performed but that only one will be a true stimulus. They are asked to indicate which stimulus was the true stimulus. When a forced-choice algorithm is used, threshold is generally defined as the level at which a predetermined proportion of responses (eg, 75%) is correct. The forced choice algorithm can be helpful when positive responses to null stimuli are obtained with method of levels testing.

The method of limits is the least time-consuming. The disadvantage of the method of limits is that thresholds will be artificially altered by response time. Comparative studies have demonstrated that thermal thresholds using the method of limits are about 1 degree centrigrade higher than when the method of levels is used, presumably because of the influence of reaction time.[10,11] Reaction time depends upon, among other things, rate of change of the parameter being tested. When testing thermal thresholds, the effect of rate of change on reaction time is lessened at higher temperatures.[12] One study has demonstrated better test-retest reproducibility for thermal sensation with the method of levels.[9]

SENSORY MAPPING

A standard stimulus of fixed intensity can be used to determine the distribution of a positive or negative sensory abnormality on the skin surface. This is sensory mapping. Mapping of sensory deficits is a well-established part of the neurologic examination, where it is commonly used to establish the extent of a distal sensory polyneuropathy or to aid in diagnosis when the distribution of sensory loss can be of localizing value. In a neuropathic pain examination,

mapping of positive sensory findings such as allodynia or hyperalgesia provides quantitation of the geographic extent of the sign. Importantly, mapping of allodynia or hyperalgesia can also be performed repeatedly to monitor a patient's clinical course and to provide an outcome measure for treatment interventions[13] When mapping allodynia or hyperalgesia, it is suggested that sensory testing begin from outside the area of interest and move gradually towards the center along a series of at least 8 linear paths spaced evenly and arranged radially around the area of interest.[14,15] Along each path the margin of the sensory abnormality is marked with a marking pen, and the marks are then connected to form an outline of the outer margins of the deficit. This line can then be traced onto a translucent sheet or directly onto graph paper, and the size of the area of abnormality is then determined. This technique can be applied to the trunk or to a limb.

Bedside-derived QST of Specific Sensory Modalities

The following is a summary of published techniques of bedside testing which also have performance properties, which are conducive to QST when stimulus intensity rating is applied. The techniques are summarized in the Table 1.

MECHANICAL STIMULI

Sensory testing can be performed with a wide variety of mechanical stimuli. We will review methods of testing with light touch, punctate, pinprick, pressure, and vibration. The distinctions among some of these stimuli are not all precisely defined in the pain literature. Our operational definition of each type of stimulus is found in the corresponding section.

Light Touch

This term is used to refer to mechanical stimuli of very low intensity, often near the perception threshold, and often moving across the skin surface. Innocuous mechanical stimuli such as light touch displace tissue and activate a subset of highly specialized mechanoreceptors. These receptors respond to low threshold stimuli and signal tissue displacement through Ruffini endings, hair follicles with palisade endings, Merkel discs, or Meissner corpuscles. Classified collectively as low-threshold mechanoreceptors (LTMs), these receptors conduct along large myelinated A-β nerve fibers. LTMs are divided into slowly adapting mechanoreceptors, which transduce pressure on the skin, and rapidly adapting mechanoreceptors, which sense movement.

Light touch testing can be performed at the bedside with a cotton wisp, cotton-wool tip, Q-tip, foam brush, or paint brush.[14–18] Because the stimulus is usually moved across the skin surface, light touch testing lends itself well to sensory mapping to demarcate areas of abnormally decreased or abnormally increased sensitivity. In cases of decreased light touch, testing begins in the area of reduced or absent sensation and is slowly advanced until the sensate area is reached.

Increased sensitivity to light touch is most often manifest as mechanical allodynia. Mechanical allodynia is believed to represent pathologic activation of central pain transmission pathways by sensory inputs from LTMs owing to a cascade of biochemical events that increase dorsal horn neuronal excitability.[19,20] As a result, input from LTMs is perceived as painful. Mechanical allodynia can be classified as static or dynamic, depending upon the nature of the stimulus. Static mechanical allodynia is discussed below, in the sections devoted to punctate and pressure testing. Dynamic mechanical allodynia can be easily detected with tools used to test light touch, but the method of testing for dynamic mechanical allodynia is not standardized. Some use perpendicular strokes, stimulating first an area of normal sensitivity and moving towards the area of abnormal sensitivity, whereas others recommend

TABLE 1. Summary of Modalities, Receptors, and Testing Methods

Sensory Modality	Principal Receptors	Axon Type	Postulated Mechanism of Allodynia/Hyperalgesia	Testing Instruments
Dynamic mechanical	Meissner's	Aβ, some C[76]	Central sensitization	Brush
	Pacinian	Aβ		Cotton wisp
	Hair follicle	Aβ		Cotton swab
Cutaneous punctate (blunt)	Merkel	Aβ	Central sensitization	von Frey hair
	Ruffini	Aβ		
		Some Aδ		
Cutaneous punctate (sharp)	Unencapsulated	Aδ	Central sensitization	Pin
			Peripheral sensitization	
Deep pressure	Intramuscular afferents	Type III, IV	Unknown	Pressure algometer
Vibration	Pacinian	Aβ	Unknown	Tuning fork
Innocuous warm	Unencapsulated	C	Peripheral sensitization	Heated surface
Innocuous cool	Unencapsulated	Aδ	Unknown	Metallic surface at room temperature
Noxious heat	Unencapsulated	C	Peripheral sensitization	Heated surface
		Aδ		
Noxious cold	Unencapsulated	C	Reduced inhibition	Cooled surface
		Some Aδ	Central sensitization	Metallic surface in ice water
			Peripheral sensitization	

Postulated principal mechanisms of pathologic pain are listed. Some mechanisms are not fully accepted. Mechanisms of allodynia and hyperalgesia may vary depending upon the mechanism of injury.

moving from an area of abnormal sensitivity towards an area of normal sensitivity. The pressure applied depends on the testing instrument: it is 3 mN for a cotton wisp, 100 mN for a cotton swab fixed to an elastic strip, and 150 to 250 mN/cm^2 for a soft brush (3.5 cm diameter). Stimulus parameters vary widely and there is no consensus with respect to stroke number, length, duration, velocity, frequency, or interstimulus intervals.[16,17,21,22]

Punctate

The term "punctate" is generally applied to stimuli from small, fine-tipped probes[23] but is variably used to refer to either small blunt or sharp probes. The distinction is important, because depending upon the probe characteristics, punctuate probes may activate only LTMs, resulting in an innocuous pressure sensation, or high-threshold mechanoreceptors, in which case the perception is of a sharp, often mildly painful stimulus. We will discuss testing with non-noxious mechanical probes and testing with sharp, painful probes separately, and will refer to them as "punctate" and "pinprick," respectively.

Slowly adapting LTMs can be tested with von Frey hairs or Semmes-Weinstein monofilaments of varying thickness.[24] The technique for measuring tactile thresholds was first described by Max von Frey in 1895. He measured touch thresholds with horse-hair mounted inside a tube and pressed perpendicularly against the skin until it bent. Hairs of different thickness were calibrated with a balance to measure the applied force needed to bend the hair. These calibrated hairs are now known as von Frey hairs.[25] Tactile detection threshold is defined as the smallest force perceived by the patient. Today calibrated nylon monofilaments of different diameters are used for testing tactile thresholds according to the technique described by von Frey (Semmes-Weinstein monofilaments, Stoelting, IL, graded from 0.039 mN to 4386.40 mN). This technique has been adopted to screen diabetics for sensory neuropathy using 5.07/10 gm Semmes-Weinstein monofilaments.

In addition to their original purpose for determining sensory thresholds, von Frey hairs can be used to test for static mechanical allodynia in a small cutaneous region, or punctate allodynia. Although von Frey hairs can elicit a sharp and, at times, mildly painful sensation, punctuate allodynia testing using this stimulus should be distinguished from pinprick hyperalgesia, discussed below. Thresholds for punctate allodynia can be determined in a single location, using a graded series of von Frey hairs or similar stimuli of gradually increasing magnitude. von Frey hairs can also be used for sensory mapping of regions of punctate allodynia.

Pinprick

The adequate stimulus for high-threshold mechanonociceptors is strong mechanical stimulation. For practical reasons, mechanical stimulation with pinprick testing is the only test of nociceptors routinely used in the bedside neurologic examination. Commonly, pins or similar small-diameter probes are used, and participants are asked to determine whether the stimulus feels sharp. In this context, sharpness can be considered a surrogate for nociception because, whereas sharpness is not necessarily painful, mechanical thresholds for sharpness closely parallel those for pain. Furthermore, intraneural stimulation of human A-δ cutaneous nociceptors results in a sharp pain, suggesting that the sensation of sharpness is conveyed by nociceptors.[26] In patients with loss of nociceptors from neuropathy, sensation of sharpness may be lost in symptomatic areas. Conversely, relatively modest sharp stimuli may evoke an abnormal painful sensation, referred to as static mechanical hyperalgesia. This may reflect both peripheral and central sensitization. Evidence that static mechanical hyperalgesia persists after experimental ischemic block of myelinated fibers has been taken to indicate that this symptom is mediated via C fibers.[27]

Devices for pinprick testing vary in 2 respects: the shape of the probe tip and the force applied. The effect of probe size and shape on perception of sharpness and pain were studied systematically by Greenspan and McGillis.[28] In normal participants, thresholds for mechanical pain and sharp sensation rose rapidly as probe area increased from 0.1 mm^2 (probe diameter of about 0.36 mm) to 1 mm^2 (diameter of 1.3 mm). Thresholds also rose rapidly as the probe angle (the angle formed by the side of the probe's tip with a line drawn perpendicular to its shaft) increased from 120 degree to about 135 degree. Thus, probes with a diameter of less than 0.4 mm and an angle of less than 120 degree allowed testing of sharp sensitivity with minimal applied force. For small probes (tip diameter < 0.4 mm), Greenspan and McGillis found that thresholds are about 10 g for sharpness and 40 g for pain. Sharp and pain thresholds were relatively constant as a function of tension (force/linear dimension).

The device used for pinprick testing is not standardized. Physicians commonly use safety pins, straight pins, and, if no pins are available, the broken edges of a wooden applicator to test sharp sensation. The European Federation of Neurological Societies' task force on neuropathic pain stated that pinprick sensation is "best assessed… by a wooden cocktail stick."[29] Recently, two devices, the neuropen and the medipin, have been marketed for this purpose. A weighted needle has been described,[30] and weighted pins have been used by the DFNS.[4]

Safety pins, the neuropen, and the medipin all have probe (tip) diameters well less than 0.4 mm. Specifically, although all three seem to the naked eye to come to a point, safety pins and the medipin are seen to either come to a point or a short, flat surface at 20 × magnification, whereas the neuropen tip seems to consistently come to a point when viewed under 20 × magnification (unpublished observation).

The force used when applying these devices may vary. The force applied with a von Frey hair, which is generally used as a test of tactile sensation, is controlled by instructing the examiner to apply just enough force as is needed to allow the filament to bend. This principle is used when placing a sharp tip at the end of a flexible filament. There is no inherent way of standardizing the force applied when using a standard safety pin. The tip of the medipin rests on a flat surface or flange, which allows rough standardization of force if the examiner is careful to apply the pin so that the flange rests upon the skin surface without indenting it. Although the pin supplied with the neuropen can be used independently, with no standardization of force, the neuropen itself is a spring-loaded device into which the pin can be placed, with a guide allowing relative standardization of the degree of force applied. The force applied is about 40 g.[31]

Testing of pinprick sensation is generally performed by inquiring as to whether the sensation elicited by the test

probe is sharp or dull. Because patients with sensory deficits may recognize that the probe is sharp but perceive the sharpness as less than normal in the symptomatic skin, sharpness is often compared with an area of skin that is clinically unaffected. Some examiners apply either a sharp or dull object and ask the patient to indicate which sensation, sharp or dull, is evoked. This has the advantage of being relatively objective but does not identify a moderate decrease in pinprick sensitivity, wherein the patient recognizes the probe as sharp but finds it less sharp than it should be. Although patients often volunteer comments about the severity or nature of the sensation evoked, the severity of sharpness or pain evoked is not generally scored. However, such a scoring system for pinprick-evoked pain has been proposed and demonstrated recently by the DFNS.[4]

An alternative for scoring the severity of sharpness or pain evoked by a single stimulus type is to determine thresholds by the method of levels using a series of graded stimuli. The DFNS neuropathic pain protocol includes a test for pinprick pain threshold using a proprietary set of fine, blunt-tipped probes. In this method, the threshold force necessary to elicit a sensation of pain, rather than the intensity of sharpness or pain elicited by a single probe, is recorded. This is cumbersome, as it requires a series of stimuli with a set of test objects, but has the advantage of establishing a threshold value. Occasionally specific dysesthetic sensations are reported, and these can be recorded as well.

Pressure

The sensation of pressure is transduced primarily by slowly adapting mechanoreceptors. In the skin, these functions are subsumed by Merkel cell-neurite complexes near the dermal surface and, deeper in the dermis, by Ruffini endings.[32] Firm pressure likely activates mechanoreceptors in muscle and other deep structures as well. When referring to testing for allodynia to static mechanical stimuli, one must distinguish between stimuli that likely activate cutaneous receptors only and deep pressure stimuli. The von Frey hairs are the best-known stimuli for the application of static pressure to cutaneous mechanoreceptors. Pressure algometry is the most commonly used test for static mechanical allodynia in deep tissues. Pressure algometers deliver a firm and quantifiable pressure through a flat base applied to the skin. The force is generally applied as a gradually increasing stimulus, and the value of interest is the pressure pain threshold, defined as the force at which a subject first reports pain.[33–36] Pressure pain threshold testing has also been performed by using a gradually inflated sphygmomanometer.[37,38] The advantage of this technique is that it uses a commonly available tool; the disadvantage, of course, is that it can only be used in the limb.

Vibration

Vibration sensation represents a type of touch/pressure sensation that fluctuates rhythmically. Pacinian corpuscles are the specialized sensory receptors felt to be most important in transmitting vibration sensation from hairy skin.[39] Vibration sense is often tested with a tuning fork vibrating at 128 Hz and graded subjectively by the examiner. In an effort to improve the reliability and reproducibility of vibration sense testing, several computer assisted QST systems have been developed. These have been validated and norms have been established for their use.[5,40] Although quite valuable, computer-assisted QST is time-consuming and impractical in some clinical settings. In an effort to provide the convenience of testing vibration with a tuning fork with added reproducibility, two quantitative methods of testing vibration sensation at the bedside have been described: timed vibration and the Rydel-Seiffer (R-S) graduated tuning fork.

Reproducibility, as well as norms adjusted for age, sex, height, and education, have been published for timed vibration.[41] The authors trained examiners to strike a 128 Hz tuning fork "from a distance of about 20 cm… at a constant, medium-degree intensity." They demonstrated good interrater and intrarater reliability and age and sex-related norms for males and females. Findings with the R-S graduated tuning fork in control patients and patients with polyneuropathy have been reported by several authors.[42–46] Norms for the R-S tuning fork have been established for the hallux, the medial malleolus, the patella,[5] the distal interphalangeal joint of the second finger, the ulnar styloid, and the medial epicondyle of the humerus. R-S scores have been shown to correspond well with QST techniques[5] and with results of nerve conduction studies.[8]

Timed vibration and R-S scoring differ in several important respects. First, because scoring with the R-S tuning fork is based upon a graduated scale placed upon the fork, the scores obtained accurately reflect the amplitude of vibration of the tuning fork. This, along with a growing literature demonstrating validity and reproducibility, make the R-S method the more desirable method of bedside vibration sense testing. Second, the R-S tuning fork vibrates at 64 Hz when the weights with graduated scales are placed upon it, rather than 128 Hz. Perception thres holds are higher at 64 Hz.[47,48] Third, the vibration amplitudes of the two tuning forks differ. Because of these last 2 differences, patients who are insensate to stimulation with the R-S tuning fork may have a measurable response to 128 Hz timed vibration. Finally, the bases of the tuning forks are quite different. The base of the R-S tuning fork is broad, flat, and made of a hard plastic material. The base of the 128 Hz tuning fork in common usage is much narrower, has a circular ridge that is occasionally perceived as uncomfortable, and is made of metal.

Vibration allodynia has been described in several clinical settings. A psychophysical study of finger amputees with stump pain demonstrated vibration allodynia using a device with a 9 mm base vibrating at a frequency of up to 130 Hz.[49] The vibration amplitude is unclear, as the original publication reported it as 4.5 mm, whereas a follow-up report indicated it was 2.5 mm.[50] Vibration allodynia has also been described in a single patient with temporomandibular dysfunction, using a 25.4 mm base vibrating at 25 Hz with an 120 μm amplitude,[51] and in patients with whiplash, using an adjustable amplitude of up to 100 Hz and an adjustable frequency of up to 2.5 μm.[52] To our knowledge, vibration allodynia has not been measured using a hand-held tuning fork.

THERMAL STIMULI

The sensations of coldness or warmth when the skin is cooled or heated outside the thermoneutral zone (31 to 36°C) are due to the activation of Aδ and C thermoreceptors, respectively. Thermoreceptors have free nerve endings in the epidermis. The threshold for heat pain is approximately 45°C[53] and for cold pain varies from less than 0°C to >15°C.[54,55] Both A-δ mechanoheat

nociceptors and C polymodal nociceptors are believed to mediate painful thermal stimuli.[12,56–60]

Two pain qualities to thermal stimuli have been described. First pain is easily localized, sharp pricking pain mediated by myelinated cold-specific A-δ fibers, whereas second pain is poorly localized, burning pain mediated by unmyelinated warm-specific C-fibers.[12,60,61]

Thermal thresholds and thermal pain thresholds vary inversely with size and duration of the stimulus. These well-recognized features are referred to as spatial and temporal summation, respectively. Because of the phenomenon of spatial summation, it is important to maintain a constant probe size in any comparative study of thermal threshold.[62,63] Slow repeated stimulation of C fiber nociceptors results in exaggerated responses in dorsal horn neurons, a type of temporal summation referred to as wind-up. Wind-up occurs primarily with heat stimuli, and may be peculiar to C fiber activity.[64] Activity in both nociceptive and non-nociceptive systems is integrated for normal perception of thermal pain. When only one thermal sensory modality is intact, both innocuous and noxious stimuli acquire characteristics of the intact modality, resulting in paradoxical thermal sensations.[65]

Several methods have been used to alter skin temperature for psychophysical testing. These include application of hot or cold liquids to a skin surface,[66] immersion of a limb in a liquid,[67] exposure of skin to an intense focused light or laser beam,[58,68] or contacting the skin with a water circulating thermode,[69] an ohmic heating element[70–72] or a Peltier device.[73] Peltier devices can change temperature rapidly, accurately, and with a predictable rate of change without a circulating refrigerated coolant.

The two commercially available automated thermal QST machines use Peltier devices. Such devices offer great precision and can be used to test warm, cool, heat pain, and cold pain thresholds, but are cumbersome and expensive. Two simpler devices, the Lindblom roller and Minnesota thermal disks, allow testing of thermal sensitivity by taking advantage of the property of metals to conduct heat, thus feeling cool when placed against the skin. The Lindblom roller is a hand-held instrument with a stainless steel roller which, because it feels cool against the skin and moves easily across a surface, can be used to demarcate the margins of a region of cold hypoesthesia or allodynia.[74] Minnesota thermal disks, a set of small disks made of various materials of differing thermal conductivity, have also been designed to be placed against the skin to assess innocuous cold sensitivity.[75] The Lindblom roller or a 128 Hz tuning fork can be kept at room temperature, a regulated warm or hot water bath, or ice water, for the purpose of testing cool allodynia, warm allodynia, heat pain, and cold pain, respectively. In these applications, the examiner solicits a pain rating, whereas thermal pain threshold temperatures can be determined with a Peltier device.

COMPREHENSIVE QST NEUROPATHIC PAIN PROTOCOL

The complexity and range of manifestations observable in patients with neuropathic pain calls for a comprehensive, quantifiable testing protocol for sensory symptoms and signs in neuropathic pain disorders. After review of established techniques as outlined above, the NPRC has developed a neuropathic pain assessment protocol, which consists of the following components:

1. Neuropathic pain symptom-specific measurement tools and measurement of psychological symptoms via appropriate questionnaires, scales, or inventories.
2. Pain diagram. This would guide selection of the test site or sites.
3. Sensory mapping for margins of:
   (a) Sensory deficits to light brush or dynamic mechanical allodynia
   (b) Pinprick deficits or hyperalgesia
4. Quantitative testing using stimulus intensity ratings of evoked sensations, including pain, by recording either reduced or increased stimulus perception compared to a normal asymptomatic control site in response to the following stimuli:
   (a) Sensory deficit to light brush or dynamic mechanical allodynia
   (b) Vibration deficit or allodynia
   (c) Thermal deficit or allodynia to cool and warm stimuli
   (d) Pinprick deficit or hyperalgesia
   (e) Thermal pain deficit or hyperalgesia to noxious cold and noxious heat
   (f) Elevated or reduced pressure pain threshold
5. Record descriptions of any abnormal evoked sensations
6. Test for temporal summation or wind-up to repeated dynamic mechanical or punctate stimuli.

A more detailed description of the protocol is provided in Tables 1 and 2.

Quantitative testing of stimulus intensity ratings begins with the least noxious stimuli and proceeds to more typically noxious stimuli. Testing is first performed in an area of the individual body that is unaffected by sensory abnormalities, including pain, which serves as a reference site against which stimuli in the affected site(s) is (are) rated. A recognized protocol must be followed with respect to choosing this site. Wind-up, presenting as progressively increasing evoked pain with repeated stimulation, could occur and thereby influence each subsequent stimulus application; however, this has not occurred in our experience, perhaps in part because of a sufficient delay between application of stimuli, or perhaps because several different stimuli are used, beginning with those that stimulate Aβ fibers in the normal circumstance, whereas wind-up is a C-fiber mediated phenomenon. This issue requires further study.

This protocol could be performed easily in the clinical setting, including at the bedside, with tools that are commonly available. The protocol should be supplemented with a standard neurologic examination, to provide context and aid in interpretation of the findings of this quantitative testing protocol. We have found that such a protocol takes approximately 30 minutes to complete evaluation of up to 2 test sites, which we feel is the maximum number of sites that should be tested at one time. The protocol described here is a proposed approach to bedside-derived QST of neuropathic pain that is based upon several established techniques as described above. The combination of these techniques into a single comprehensive evaluation is novel and, as such, must be evaluated formally for reproducibility. Such studies are in progress. It is important to point out, however, that pain is a dynamic phenomenon. Therefore, not only is precise reproducibility not anticipated, but also the moment-to-moment variability of pain phenomenology is itself deserving of further study.

TABLE 2. Proposed Protocol for Neuropathic Pain Sensory Testing

- General steps and guiding points:
  - Administer a validated neuropathic pain symptoms tool, such as neuropathic pain questionnaire or scale, prior to performing QST
  - Record skin temperature and physical findings (eg, trophic changes, color or vascular changes) at test and control sites
  - Record overall pain rating at beginning and end of test
  - Perform testing in a quiet, comfortable setting free of distractions
  - Instruct patient with a practice examination of a single modality in a clinically unaffected area at start of test
  - Use written instructions to assure consistency
  - Score sensory deficits on a 0 to −100 scale and positive phenomena on a 0 to +100 scale
  - Test from least noxious to most noxious modality
  - Record any abnormal or paradoxical evoked sensations
  - Record participant's alertness, attention, cooperation, and relevant behavioral observations
- Choose testing site based upon history and pain diagram
- Choose a control site based upon a standard algorithm; eg,
  - Homologous contralateral site if pain is unilateral
  - Ipsilateral unaffected site if pain is bilateral
- Evaluate the following, in order, using control site for comparative ratings of perceived stimulus intensity:
  - Light brush in area of greatest pain
    - Hypesthesia, hyperesthesia, or allodynia to single stimulus
    - Summation, after-sensation after repeated stimuli
  - Map area of abnormal light brush sensation
    - Record map on transparency or body diagram
  - Vibration in area of greatest pain
    - Hypesthesia, hyperesthesia, or allodynia to single stimulus
    - Summation, after-sensation after repeated stimuli
  - Cool stimulus (eg, steel surface at room temperature) in area of greatest pain
    - Hypesthesia, hyperesthesia, or allodynia to single stimulus
    - Summation, after-sensation after repeated stimuli
  - Warm stimulus (eg, thermode at non-noxious temperature) in area of greatest pain
    - Hypesthesia, hyperesthesia, or allodynia to single stimulus
    - Summation, after-sensation after repeated stimuli
  - Pin in area of greatest pain
    - Hypesthesia, hyperesthesia, or allodynia to single stimulus
    - Summation, after-sensation after repeated stimuli
  - Map area of abnormal pin sensation
    - Record map on transparency or body diagram
  - Cold pain stimulus (eg, steel surface cooled in ice water)
    - Hypesthesia, hyperesthesia, or hyperalgesia to single stimulus
  - Heat pain stimulus (eg, thermode at noxious but nondamaging temperature)
    - Hypesthesia, hyperesthesia, or hyperalgesia to single stimulus
  - Pressure pain stimulus at area of greatest pain
  - Consider validated psychophysical tests of pain threshold at standard sites, eg, pressure point threshold at thumb nailbed

Unlike the DFNS protocol, this protocol does not include threshold detection testing with graded mechanical or thermal stimuli. We do not have specific information about the performance characteristics of our approach for quantification of sensory loss when compared with a threshold detection paradigm. The inclusion of a routine neurologic examination also allows for documentation of sensory loss in a systematic fashion. We feel that this protocol is more accessible in some clinical and research settings than the DFNS protocol. Furthermore, the applicability to the clinical problem presented by the patient in pain may be seen as more direct when testing pain ratings in response to fixed stimuli than when testing detection of sensory thresholds.

Adoption of a neuropathic pain examination is of critical importance for several reasons. First, the revised definition of neuropathic pain and accompanying grading algorithm include the identification of negative and positive sensory signs among the necessary criteria for a diagnosis of possible or definite neuropathic pain.[76] Under such a grading system, valid QST data become essential for the diagnosis of neuropathic pain. Second, our approach provides a tool for assessment of the progress of a patient's condition over time, much as serial neurologic examinations can document clinical worsening or improvement in sensory loss from neuropathy or stroke. This is needed for monitoring a patient's status and response to treatment and in research settings for measuring results of interventions. In particular, such a tool may lead to identification of interventions that have symptom-specific benefits, as in the demonstration that topical lidocaine reduces allodynia in postherpetic neuralgia,[77] or that a glycine antagonist reduces the area of allodynia.[14] Third, the adoption of standardized, practical office-based assessment of stimulus-evoked features of neuropathic pain is necessary when clinicians are learning the characteristics of neuropathic pain disorders, and will lead to insights which have heretofore been inaccessible because of the absence of such a tool. Here, too, the analogy of the neurologic examination applies. Most neurologic conditions are defined by their clinical features. Without a neurologic examination, such characterization would not be possible.

This last point is critical and merits elaboration. Medical knowledge is advanced through the rigorous testing of carefully framed hypotheses. Good hypotheses emerge from the interaction of established medical

knowledge and novel clinical observations. Novel clinical observations emerge from novel methods of observation and measurement. Therefore, the advancement of our understanding of neuropathic pain is dependent upon the development of tools to observe the phenomenon of neuropathic pain. As neuropathic pain is a fundamentally clinical physiologic phenomenon rather than a histologic, electrophysiologic, or laboratory phenomenon, the fundamental tools for the study of neuropathic pain must be clinical. All other modes of study are of inestimable value but at least one level removed from the clinical phenomenon of pain.

Finally, it should be noted that the potential for a tool to lead to valuable discoveries is in part proportional to the number of observers that have access to that tool. Simple clinical tools can be adopted by thousands of clinicians, who can in turn magnify the value of their observations by refining them through the inevitable information sharing that occurs when a substantial proportion of a community is using similar tools. Clinical tools are among the most powerful, and at times transformative, tools in biomedical science.

SUMMARY

The systematic, large-scale assessment of neuropathic pain awaits the development of a standardized, validated examination of negative and positive sensory phenomena that is sufficiently rapid and simple to be used routinely in the setting of an active clinical practice. We have summarized the available techniques that might contribute to such an examination. In addition to the accepted tests for sensory deficits, they include testing for dynamic mechanical allodynia, punctate allodynia, pinprick hyperalgesia, pressure pain threshold, vibration allodynia, thermal allodynia, and thermal hyperalgesia. We advocate use of a combination of threshold testing, pain ratings, and sensory mapping. A comprehensive QST and mapping protocol as presented here will provide a valuable complement to established QST techniques and allow wider use of QST in clinical and research settings, including the bedside evaluation of patients with neuropathic pain disorders.

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