Handbook of Clinical Neurology, Vol. 81 (3rd series)
Pain
F. Cervero, T.S. Jensen, Editors

Neurophysiological examinations in neuropathic pain

Chapter 27

Quantitative sensory testing

*DAVID YARNITSKY AND MICHAL GRANOT
Rambam Medical Center, Haifa, Israel

27.1. Introduction

27.1.1. General

The need to quantify is central to any scientific process; one cannot make any valid conclusion about disease mechanism, epidemiology, natural history or response to therapy without quantifying the relevant parameters. The pain research and therapy community has been in search of quantification methods for pain ever since pain has become an issue for scientific research. Although the classical psychophysicists of the late 19th century did not deal specifically with pain, but rather with the non-painful sensations, they formulated the basic concepts of threshold, tolerance and stimulus–response relationship. Some measurement instruments introduced during that era are still (!) in use, such as the von Frey filaments. The advent of microcomputers has made more sophisticated computer-based devices available to clinicians and researchers, allowing for the accumulation of a large body of data regarding pain measurement. In this chapter, we will summarize the methodological issues related to pain measurement and its clinical applications.

Quantitative sensory testing (QST) evaluates the integrity of the entire sensory neuraxis receptor to the cortex and it is a reliable and relatively reproducible test. However, it is subjective and is affected by distraction, boredom, mental fatigue, drowsiness or confusion. Moreover, its results can also be deliberately misreported by patients with an interest in altered QST results (Dyck, 1998; Siao and Cros, 2003; Chong and Cros, 2004; Gibbons and Freeman, 2004). The use of appropriate testing methodology and careful attention to the technical details of test performance are of utmost importance in order to obtain meaningful results.

QST has been criticized for being subjective. However, recent brain imaging studies, using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), provide strong evidence that subjective pain magnitude scores are associated with objectively measured neural activity in cortical and subcortical regions that are known to be involved in pain processing including anterior cingulate and insular cortexes (Derbyshire et al., 1997; Porro et al., 1998; Coghill et al., 1999; Coghill and Eisenach, 2003). These studies have confirmed that interindividual differences in subjective pain reports correlate with the degree of activation in these brain regions. Moreover, the stimulus intensity of experimentally induced pain is correlated to quantifiable objective parameters, such as neural traffic in peripheral nerves, pain-evoked potentials (EPs) and QST measures, supporting the validity and reliability of pain psychophysics (Yarnitsky et al., 1992; Chen et al., 2001).

The issue of repeatability of pain psychophysical parameters is a major concern for all practitioners in the field, as low repeatability severely limits the long-term usefulness of the method. Clinical applications, such as follow-up on the natural history of a certain clinical situation or assessment of the response to therapy, depend on the repeatability of the measurement. Data for heat pain repeatability were presented by Yarnitsky et al. (1995), allowing interpretation of heat pain data that defines the framework for establishing protocols in the clinical set-up of the individual patients along time.

Clinically, QST has relevancy to several contexts. Diagnostically, the availability of computerized tomography (CT) and MRI for definitive imaging of central nervous system (CNS) disorders of an anatomical nature and the availability of electrodiagnostic tests (nerve

*Correspondence to: David Yarnitsky, Department of Neurology, Rambam Medical Center, Haifa, Israel 31096. E-mail: davidy@techunix.technion.ac.il, Tel: +972–48542605, Fax: +972–48542944.

conduction and electromyography) for the assessment of peripheral large-fiber associated disorders, as well as of somatosensory EPs for their central connections, define the fields unique for QST in the diagnostic context: (i) disorders related to peripheral small fibers, which are not detectable by electrodiagnosis and (ii) disorders of sensation, both peripheral and central, where the demonstration of an anatomical lesion by imaging is not sufficient for diagnosis or follow-up and an assessment of the sensory *function* is required. An example is the case of central post-stroke pain, where the mere presence of a brain infarct, evidenced by CT or MRI, is not sufficient to differentiate between musculoskeletal pain subsequent to physical disability due to the stroke and pain of central origin subsequent to brain tissue damage. The finding, by QST, of decreased sensory function in the painful hemibody supports the latter diagnosis. Beyond diagnosis, QST is most useful in assessing the extent of the sensory disorder, for both painful and nonpainful sensory modalities, in clarifying disease mechanisms and in assessing natural history and response to therapy.

QST has been the focus of several consensus papers by American and European scientific authorities. The San Antonio consensus (1988, 1992) recommended QST as a valid tool for the early detection of diabetic neuropathy. The task force on QST of the American Academy of Neurology has recently published its recommendations (Shy et al., 2003). The clinical utility, efficacy and safety of QST were assessed by a meta-analysis that was based on the use of normal values and the degree of reproducibility between the same and different systems. Findings demonstrated that because of differences between systems, normal values from one system cannot be transposed to others. In addition, there is no consensus on how reproducibility of results should be defined. The authors identified no adequately powered class I studies demonstrating the effectiveness of QST in evaluating any particular disorder. A number of class II and III studies demonstrated that QST is probably or possibly useful in identifying small- or large-fiber sensory abnormalities in patients with diabetic neuropathy, small-fiber neuropathies, uremic neuropathies and demyelinating neuropathy.

The consensus is that QST is a potentially useful tool for measuring sensory impairment for clinical and research studies. However, QST results should not be the sole criteria used to diagnose pathology. Because other nonorganic factors or malingering can influence the test results, QST is not currently useful for the purpose of resolving medicolegal matters. The committee commented that well-designed studies comparing different QST devices and methodologies are needed, including patients with abnormalities detected solely by QST. In assessing the usefulness of QST in the diagnostic process of neuropathic pain, the EFNS (European Federation of Neurological Societies) expressed some reservations: "QST abnormalities, because also found in non-neuropathic pains, cannot be taken as a conclusive demonstration of neuropathic pain. Furthermore, QST depends on expensive equipment, it is time consuming and thus difficult to use in clinical practice." Although QST is not yet officially accepted as a clinical diagnostic tool, it seems to be on the verge of gaining recognition as a useful clinical test, pending further experimentation and data collection.

In addition to its common use in adults, QST has been suggested for clinical neurological assessment in children as well. Values of cold and warm sensations, cold and heat pains and vibration sensation detection thresholds were determined in the hand and foot with the methods of limits and levels. Measurements were well accepted by children with good reproducibility between sessions (Hilz et al., 1998a,b). Based on these results, the use of QST was recommended for documenting and monitoring the clinical course of sensory abnormalities in children with neurological disorders or neuropathic pain (Meier et al., 2001).

Since this volume's focus is on pain, most of the following will emphasize pain sensory testing, although references will be made to nonpainful sensory testing as well. For further elaboration on nonpainful sensory testing, the reader is referred to a recent book (Yarnitsky and Pud, 2004) and a slightly older review article (Zaslansky and Yarnitsky, 1998).

27.2. Methodology and normative data

27.2.1. General

QST encompasses several modalities of stimulation – thermal, with low or high temperatures provoking cold and hot sensations; mechanical and electrical; ischemic and chemical. Each modality can produce several measures including parameters related to (i) nonpainful sensations, such as detection thresholds – the point of transition between lack of any sensation to a minute sensation evoked by a stimulus, and to (ii) painful sensations. The spectrum of pain experience ranges from threshold, through the suprathreshold intensities, and ends at tolerance level. Thus, we can measure pain thresholds, the point of transition between a detectable, yet nonpainful, stimulation and a painful one, as well as magnitude estimation of suprathreshold pain, which represents pain sensitivity and tolerance to pain. Neurophysiology has clarified that nonpainful and painful sensations are provoked by different sets of peripheral and central neurons.

The assessment of pain via QST can be applied in two settings – the assessment of endogenous pain that the patient experiences due to the disease process or the assessment of experimentally induced pain inflicted on a patient or a normal subject in order to experiment on pain mechanisms or therapy. For the first, only slight progress has been achieved over the years, as several scales have been developed for subjective quantification by the individual regarding the magnitude of the pain sensation. For the second, a much larger body of knowledge has been accumulated, using various stimulation paradigms and parameters. Most QST practitioners are well experienced with cutaneous stimulation and indeed, most of the relevant literature deals with somatic stimulation. Some experience has been accumulated in recent years on visceral stimulation and will be briefly reviewed at the end of this section. Notwithstanding this knowledge and experience, one needs to remember that as elegant as these reports may be, they still represent an artificial pain situation. Extrapolating to clinical pain scenarios might not always be straightforward (Gracely, 1999).

27.2.2. Measurement of spontaneous (nonexperimental) pain

Several pain scales have been developed and introduced to clinical practice. First and foremost is the visual analog scale (VAS), representing a continuum between the two anchors of no pain on one side and the worst imaginable pain on the other. Usually, the continuum is presented to subjects as a line or an elongated rectangle and subjects are requested to put a mark at a point appropriate to their subjective sensation between the two ends. The examiner then translates the marked point to a numerical value, usually between 0 (= no pain) and 100 (= the worst imaginable pain). The major advantages of the VAS are: (i) the relative value of its readings, that is, if pain at baseline was 6 and subsequent to therapy it was 3, then one can say that it was halved (Price et al., 1983, 1987); and (ii) its continuous character allows the use of parametrical statistics on the results. The major disadvantage is the requirement for abstract thinking, which is not universal to all patients.

The numeric pain rating scale (NRS) uses a set of numbers, usually 0, 1, 2, up to 10, with the same anchors as previously. The use of this scale is simpler and is more intuitive to most populations. The disadvantage is the noncontinuous character of the data collected, causing diminished sensitivity of the scale and requiring the use of nonparametrical statistics for analysis. The verbal pain (rating) scale (VRS) is a list of words that describe the gradual increase in intensity of a stimulus, covering the spectrum from no pain to maximal pain. People that find difficulty in translating their sensations to numbers can use the VRS. The disadvantages of this scale include dependence on the level of language proficiency of subjects, the differences within a given population regarding the interpretation of various adjectives, and the need to pretest the scale on a large normal population in order to give each word a numerical value relevant to the local population for purposes of data analysis (Price et al., 1983, 1987).

Several studies have examined agreement and estimated differences in sensitivity between the three pain assessment scales as well as between pain behavior and pain rating (Dirks et al., 1993). In acute and chronic pain models, the sensitivity of the VAS and NRS was approximately equal and was correlated with the global impression of change in pain. Therefore, it has been suggested that the choice between the VAS and NRS can be based on subjective preferences (Breivik et al., 2000; Farrar et al., 2001). In addition to measuring spontaneous pain, these scales are used routinely for the assessment of experimental pain, as described later.

27.2.3. Measurement of experimental pain

Several parameters can be obtained in response to a simple or a complex set of experimental noxious stimuli. The simpler and routinely used ones are pain thresholds, tolerance and magnitude estimation of suprathreshold pain intensities. More multifaceted parameters, which are mainly used in research, are those of temporal and spatial summation and methods to assess endogenous analgesia.

27.2.3.1. Thresholds

Threshold is defined as the minimal energy required to elicit a sensation. Receptor or "absolute" threshold is the energy required to elicit response in the primary afferent, whereas the psychophysical threshold or "sensory" threshold in clinical parlance, is the minimal energy required to reach perception. An example of the psychophysical and receptor thresholds being the same is the observation that following a simple, discrete light touch stimulus, an impulse from a single afferent unit in the fingertip may be consciously detected (Johansson and Vallbo, 1979; Ochoa and Torebjörk, 1983). However, with most sensations and with pain in particular, the receptor threshold is lower than the perception threshold (Van Hees and Gybels, 1981). Serving as a discrimination task, psychophysical thresholds are a convenient parameter – the point of transition from a nonpainful stimulus to a painful one along a continuum of increasing stimulation intensity. This is an obvious point to most

people and is therefore an easy criterion for the subject to follow and easy for the examiner to understand and manipulate.

Several intuitive methodologies are available for such measurement, the most common of which is the method of limits. In this method, a stimulus is gradually increased to a point at which the subject experiences the onset of pain. This method can be used with all conventional stimulation modalities and usually the average is taken of a few stimulus trial results. The major disadvantage of this method is the reaction time artifact, which is included in the measurement. The stimulus continues to increase after sufficient energy has been given to the stimulation site, in accordance with the time needed for transmission of the neural data to the CNS, the central processing time and the time needed to transmit efferent data down to the signaling hand. Thus, patients who are slow to respond, such as those with Parkinson's disease, will exhibit an artificially elevated threshold. In addition, the value of the threshold is increased considerably when relatively slower conducted sensations, such as thermal sensations, are measured. However, changes are almost insignificant for rapidly conducted sensations (Fruhstorfer et al., 1976; Swerup and Nilsson, 1987; Yarnitsky and Ochoa, 1990). For the healthy individual, one can assume a fairly constant reaction time and relatively constant error, which does not cause any problem in the use of the data.

An alternative methodology that excludes reaction time is the staircase family of tests, including the method of levels and the 4,2,1 paradigm. In these tests, a stimulus of predefined intensity is given and the subject is asked to describe it as painful or not when the stimulus ends. The stimuli given thereafter are either increased or decreased, according to the specific paradigm used, to the point of threshold identification.

Although less commonly used nowadays, the *forced choice* methodology has been used in several research papers. In this method, each stimulation stage includes two successive time epochs, of which only one contains a stimulus. Subjects are requested to indicate which of the two contains a stimulus and the intensity of the stimulus in the next set is determined by this indication in accordance with a certain set of rules (Dyck et al., 1984). This paradigm, being quite lengthy and including a large number of stimuli, is less suitable for pain threshold measurements (see Yarnitsky, 1997, for a more detailed review of the test paradigms). In order to minimize the exposure of the subjects to pain, the psychophysical assessment requires short paradigms. Therefore, the method of limits is most often used in this context.

Due to the low sensitivity of pain thresholds to analgesic manipulations (Chapman et al., 1985; Eisenberg, 2004) and since thresholds change only if there is a neurological lesion, their application in the assessment of non-neuropathic pain conditions is somewhat limited. Thus, a combination of threshold data with additional, more advanced psychophysical data, such as the magnitude estimation of stimuli of suprathreshold intensity as well as measures of pain modulation, may provide a multidimensional view of the clinical pain state of patients.

27.2.3.2. Normative data for thresholds. In order to make meaningful clinical interpretations of QST data, a reference must be made to normative data. Ideally, each laboratory should obtain its own normative data, thereby ensuring that the same instructions, mode of application of the stimulator, ambient conditions, etc., are used and that variability in outcome is minimized. Practically, most laboratories relate to already published normative data. In such cases, great care should be taken to use parameters that are as similar as possible to those under which the set of references was obtained. Several authors have published normative data on pain, including Claus et al. (1987), Meh and Denislic (1994), Yarnitsky et al. (1995), Hilz et al. (1998a,b).

A test-to-test repeatability was assessed by Yarnitsky et al. (1995), who defined an r factor such that there is 95% confidence that two determinations made on the *same subject* under the *same conditions* would differ by less than r. The use of this factor can assist the clinician in evaluating patients on a long-term basis, for both natural history of the disease and for assessing effects of therapy.

27.2.4. Tolerance

Pain tolerance is less commonly used, probably due to ethical reservations, as well as its relatively high dependence on motivational factors and high variability (Chapman et al., 1985). Tolerance is obtained by either increasing stimulus intensity or by increasing its duration at a constant intensity to the point at which the subject can no longer tolerate it. Tolerance for cold pain is often measured by the cold pressor test, whereby subjects are asked to immerse part of a limb in very cold water and hold it for as long as they can. The parameters of cold pain threshold and suprathreshold magnitude estimation can also be obtained from this test. Bisgaard et al. (2001) reported that postoperative pain after cholecystectomy can be predicted by preoperative assessment of cold pain tolerance.

27.2.5. Suprathreshold stimulation

Magnitude estimation of stimuli of suprathreshold intensity is now emerging as a more clinically relevant measure. The latter provides a simple, yet straightforward

way to characterize pain sensitivity, representing the spectrum between threshold and tolerance that reflects the reality of clinical pain conditions (Coghill and Eisenach, 2003). In order to obtain magnitude estimation of stimuli given at suprathreshold intensity, one needs to define the stimulation intensity parameters and the pain scale to be used. For stimulation, two possible modes are possible: either the use of fixed intensities, for example 47ºC for 1 min or the use of intensity that is related to the threshold, for example 2ºC above the threshold. The assessment of pain sensitivity by suprathreshold stimuli can be carried out with either a phasic (short) or a tonic stimulus. Pain rating can be performed on any of the pain scales, that is, VAS, VRS or NRS. In the design of such a stimulation paradigm, consideration should be given to the administration of stimulus intensities that will yield evaluations at the center of the scale used in order to avoid floor or ceiling effects.

In line with our understanding of the transmission of nociceptive data along the different CNS pathways, when relating to the sensory-discriminative and the affective-motivational aspects of pain, it is possible to ask subjects to characterize separately the "algosity" and the "unpleasantness" that they experience in response to the painful stimulus (Fields, 1999).

27.2.6. Summation

The perception of pain depends on summation of incoming data to the brain. The facts that the nociceptive receptor (i.e. primary afferent level) threshold is lower than the psychophysical (i.e. cortical level) threshold and that a single action potential generated in a primary afferent nociceptor and propagated centrally is not sufficient to elicit a painful sensation demonstrate the requirement of the cortex for summation of incoming neural data in order to reach the perception of pain. Characterization of the summation requirements are, therefore, of potential interest in characterization of the pain perception system of an individual in normal as well as abnormal states.

27.2.6.1. Temporal summation

An increase in pain perception is normally expected along a series of noxious stimuli given at high enough frequency and intensity (Price et al., 1977). This normal pattern is considered the psychophysical equivalent of the physiological phenomenon of "wind-up", where repetitive stimulation of small-diameter primary afferent fibers produces a progressive increase in action potential discharge, a prolonged increase in the excitability and enlargement of the receptive fields of wide dynamic range (WDR) second-order neurons in the spinal cord (Price et al., 1971, 1977; Price, 1972; Magerl et al., 1998).

The underlying mechanism is activation of *N*-methyl-D-aspartate (NMDA) receptor-dependent channels (Woolf and Thompson, 1991; Eide, 2000). An intense enough stimulation may lead to sensitization of these neurons, which may be expressed clinically as abnormally increased temporal summation (TS). Further sensitization would be expressed as allodynia and hyperalgesia, with decreased pain thresholds and increased suprathreshold pain magnitudes, respectively (Arendt-Nielsen et al., 1994; Lautenbacher et al., 1995; Kleinbohl et al., 1999; Woolf and Decosterd, 1999; Weissman-Fogel et al., 2003). Further development of this process might lead to chronic pain (Staud et al., 2001, 2003, 2004; Price et al., 2002). It is possible that abnormally increased temporal summation is not accompanied by allodynia, hyperalgesia or spontaneous pain and might be an expression of mild sensitization of nociceptors, which is not sufficient to express the more overt clinical phenomena. We have recently suggested the term suballodynia for this state (Weissman-Fogel et al., 2003).

Temporal summation may be examined at all stimulus modalities: mechanical, electrical and thermal. Several paradigms have been proposed, the most common of which is the administration of repetitive pain stimuli delivered at frequencies higher than 0.3 Hz (Price et al., 1977) and at fixed intensity, which can be "tailored" to pain threshold (Lautenbacher et al., 1995; Vierck et al., 1997; Nielsen and Arendt-Nielsen, 1998; Weissman-Fogel et al., 2003; Staud et al., 2004). The difference between rating of the last and the first stimuli or between the highest and the first stimuli is taken as a measure of TS. A second mode of stimulation is the use of a long-duration (30–120 s) tonic thermal pain stimulus, whereby subjects are asked to rate pain intensity along the stimulation and comparison is done between early and late readings (Kleinbohl et al., 1999; Granot et al., 2002, 2003). The psychophysical tool of TS therefore seems to be a sensitive tool for the identification of mild degrees of changes in the pain perception system, in some cases the very onset of a process leading eventually to chronic pain.

27.2.6.2. Spatial summation

Spatial summation of pain is defined as the ability to integrate nociceptive information from large areas of the body. It has been demonstrated as an important aspect of processing and perception of several cutaneous senses (Stevens and Marks, 1979). This integration is crucial for the detection of noxious events (Van Hees and Gybels, 1981; Torebjörk, et al., 1984), coding of pain intensity (Coghill et al., 1991, 1993) and identification of pain quality (Defrin et al., 2002). Psychophysical studies using noxious stimuli suggest two independent psychophysical processes (that may occur simultaneously) to explain

spatial summation: a lowering of the sensory threshold or an increase in the perceived intensity of suprathreshold stimuli (Price et al., 1989; Defrin and Urca, 1996; Nielsen and Arendt-Nielsen, 1997). Enlarging the stimulus area causes an increase in the subjective sensibility to that stimulus. Spatial summation of thermal pain was reported when stimulus presentations were restricted within a single dermatome. It has been suggested that the integrity of non-noxious thermal systems is essential for the normal perception of thermal pain and that the subjective sensation of pain depends on the integration of information from nociceptive and non-nociceptive channels (Defrin et al., 2002).

27.2.6.3. Clinical application of summation testing

Since enhanced "wind-up" contributes to neural processes that lead to hyperalgesia and persistent pain, TS may serve as an experimental model to assess mechanisms of altered pain processing in cases of chronic pain, such as fibromyalgia (Price et al., 1989, 2002; Woolf and Thompson, 1991; Li et al., 1999; Granot et al., 2003; Staud et al., 2004).

It has been suggested that the dynamic changes in pain perception under tonic stimulation during the early stages of central sensitization may be closely related to the mechanisms eventually leading to increased pain sensitivity over hours and days and, possibly, further long-term plasticity – thus representing a model of central changes in different chronic pain syndromes (Price et al., 1994; Tolle et al., 1996; Kleinbohl et al., 1999; Granot et al., 2003; Flor et al., 2004; Staud et al., 2004). Enhanced temporal summation has been found in both chronic and neuropathic pain patients (Kleinbohl et al., 1999; Price et al., 2002). Therefore, "wind-up" has been suggested as an experimental model for the assessment of hyperalgesia-generating mechanisms in chronic pain syndromes (Price et al., 1989; Woolf and Thompson, 1991; Li et al., 1999).

27.2.7. Endogenous analgesia

Endogenous analgesia (EA) relates to the physiological endogenous inhibition of pain, partially overlapping with the terms "descending inhibition" and "diffuse noxious inhibitory control" (DNIC) (Le Bars, 2002). Upon arrival at the brainstem, pain messages ascending in the spinal cord generate descending inhibitory messages that reach the dorsal horn, using opioidergic, serotonergic and noradrenergic transmissions. Such inhibition is heavily influenced by cerebral regions involved in cognitive and emotional function. This effect can be explored experimentally by the use of two painful stimuli – conditioning and conditioned – given simultaneously or successively (Grill and Coghill, 2002; Lautenbacher et al., 2002; Marchand and Arsenault, 2002; Bouhassira et al., 2003; Edwards et al., 2003; Staud et al., 2003).

A commonly used testing paradigm consists of assessment of pain evoked by a certain stimulus by any of the methods mentioned above (i.e. thresholds, tolerance, suprathreshold or TS). A conditioning stimulus is then given, usually as pain of the same modality at another site in the body and then the first conditioned pain stimulus is repeated simultaneously with the conditioning one or immediately after its conclusion. Endogenous analgesia (EA) is expressed as a decrease in pain magnitude from the first unconditioned situation to the second conditioned one. The term DNIC is usually used in the context of such a testing paradigm.

A somewhat different technique for testing EA was suggested by Marchand and Arsenault (2002), who performed a series of hot water immersions of upper limbs, while gradually increasing the area of immersion and then a reverse series, with a gradual decrease in the area of immersion. Immersions of the same area were less painful in the decreasing series than in the increasing one, due to the analgesic effects of the preceding more intense stimuli.

It must be clarified that such a decrease does not occur under all circumstances, but rather depends on the intensities of stimuli, sites and duration of stimulation and the individual tested, as some individuals seem to have more "efficient" analgesia systems than others.

27.2.8. QST of visceral organs

Clinical evidence suggests that cutaneous and visceral pain differ in sensory, affective and motivational realms; yet, there has been little comparative characterization of these types of pain. The need to better understand pain mechanisms of visceral pain disorders has led to the application of QST in visceral organs, with stimuli applied to the bladder, rectum and esophagus, using pressure, cold, warm or electrical modalities (Ness et al., 1998; Strigo et al., 2002; Drewes et al., 2003; Dunphy et al., 2003; Pedersen et al., 2004). In addition, more unusual approaches have been reported, such as the insertion of a catheter into the ileosigmoidostomy and the application of electrical stimuli, with an assessment of pain threshold and tolerance (Arendt-Nielsen et al., 1997). Visceral pain seems to be more unpleasant, diffuse and variable than cutaneous pain of similar intensity.

27.3. Clinical use of QST

QST is broadly used in the clinical context. In the following section, we will attempt to review all categories

of application and to give a few representative examples for each.

27.3.1. Neurological diagnosis

A major use of QST in clinical neurology is the diagnosis of negative sensory phenomena, that is, sensory deficit, which helps to define the neurological state of the patient. In addition to measuring the negative phenomena of hypoesthesia, positive sensory phenomena, such as allodynia and hyperalgesia, can be measured as well. It must be noted that electrophysiological methods, such as nerve conduction and electromyography, can only measure the negative phenomena and that QST is the only method available to the clinician to measure positive sensory phenomena.

A relatively common diagnostic application of QST is the diagnosis of selective small-fiber neuropathy, to which the standard tests of neuropathy, nerve conduction and electromyography are insensitive, since they reflect changes only in large fibers (Oh et al., 2001). Thus, for example, Hilz and Axelrod (2000) quantified small-fiber related sensory deficits in patients with familial dysautonomia. The relative sensitivity of QST in comparison with other diagnostic methods in the diagnosis of small-fiber neuropathy has recently been reviewed by Lacomis (2002).

Another application is the differentiation between neuropathic and non-neuropathic pain, such as in the case of pain in stroke patients, where the presence of sensory deficit would support the diagnosis of central post-stroke pain (CPSP), while the absence of sensory loss might be relevant for musculoskeletal pain subsequent to the motor changes (Boivie et al., 1989; Vestergaard et al., 1995; Greenspan et al., 2004). The differentiation between complex regional pain syndrome (CRPS) I versus II, depends, by its definition, on the presence of a lesion to a major nerve trunk. QST can document the sensory deficit in that nerve's territory and thus provide support for the diagnosis of CRPS II (Verdugo et al., 2004).

For diabetes, many authors advocate the use of QST for the early detection of diabetic neuropathy. The San Antonio forum, comprising neurologists and dialectologists, suggested the use of QST for the diagnosis of diabetic neuropathy (1988). Reduced vibration detection in diabetic patients, found by QST, was associated with five times more direct medical costs for foot ulcer and amputations and less quality-adjusted life-years (Shearer et al., 2003). Several chemotherapeutic agents, such as vincristine, taxol and platinol, induce painful neuropathies, the detection of which is supported by QST, often to the point of discontinuation of the agent due to the neuropathy (Postma et al., 1999; Dougherty et al., 2004). Orofacial pain is another indication for the use of QST as part of the diagnostic process (Jaaskelainen, 2004).

27.3.2. Patterns of pain responsiveness and the prediction of clinical pain

It is intuitively recognized that people have a certain pattern of response to pain experiences; some are very sensitive, while others present a more stoic response. In most cases, these patterns are consistent along life events. This understanding can be used in order to characterize an individual's pattern of pain response in the laboratory by appropriate QST paradigms and consequently to predict their levels of clinical pain experience. Along these lines, Granot et al. (2003) reported that the level of postoperative pain intensity at the surgical wound of women after cesarean section is predicted by the VAS scores in response to suprathreshold noxious contact heat stimuli applied to the forearm before the operation. Similarly, Werner et al. (2004) applied burn pain to predict postoperative pain intensity. Moreover, Granot et al. (2004) showed the role of the suprathreshold measure in the prediction of treatment efficacy in chronic pelvic pain patients. Future applications of this approach may lead to individual tailoring of the analgesic treatment protocol administered prior to potentially painful procedures in accordance with the patient's needs.

27.3.3. Assessment of pain syndrome severity

Several authors have tried to assess whether the severity of pain syndromes can be faithfully reflected by QST parameters, such as sensory thresholds and suprathreshold magnitude estimations, in line with the direct rating of the clinical pain by the patients. Lowenstein et al. (2004) recently showed a correlation between the severity of vulvar vestibulitis syndrome and quantitative sensory parameters. They applied tactile and pain thresholds for mechanical pressure and thermal pain, as well as magnitude estimation of suprathreshold painful stimuli, which were measured in the vaginal area. Pain thresholds were lower and suprathreshold magnitude estimations were higher in vulvar vestibulitis syndrome (VVS) patients, in agreement with disease severity. In a study on diabetic neuropathy (DN) patients, Kramer et al. (2004) found that the VAS ratings of neuropathic pain were correlated to the impairment of small fiber function, such as cold detection thresholds, thereby suggesting that pain intensity in painful DN seems to depend on small-nerve-fiber damage. These findings emphasize the capability of QST parameters (both threshold and suprathreshold measurements) in discriminating the level of severity of clinical pain syndromes.

27.3.4. QST in understanding of pain mechanisms

QST holds the potential to illuminate the sensory status of patients during various disease conditions by quantifying both positive and negative sensory alterations for different body parts, different stimulation modalities and along different stages of the disease. This understanding can be used to better understand the pathophysiology of changes in the sensory system of these pain disorders. The following examples show how QST has expanded our understating of migraine and central pain.

In a recent series of papers, Burstein et al. (2000a,b, 2004) used pain thresholds as a tool to understand the changes occurring in the sensory system of migraineurs. These authors measured pain thresholds for heat, cold and mechanical pain at the forehead on the side of the headache and contralateral to it, as well as in the upper limbs, during untreated migraine attacks and after the administration of a triptan. A decrease in pain thresholds was found for most patients at the skin ipsilateral to the migraine pain. This was interpreted as reflecting sensitization of the second-order trigeminal nucleus neuron, since the visceral primary afferent involved in the migraine process itself does not have a cutaneous receptive field. Some of the individuals had allodynia in an upper limb, suggesting sensitization of thalamic third-order neurons, whose receptive fields might include both the head and the upper limb. These researchers subsequently found that the absence/presence of allodynia can be used to predict the response to triptans as alleviators of the migraine pain. In a follow-up study, Weissman-Fogel et al. (2003) found increased temporal summation in migraineurs in between attacks, which tended to be correlated to the intensity of their migraine.

CPSP represents a common pain disorder that is difficult to treat. The use of QST with these patients has revealed that individuals with cold hypoesthesia, strictly contralateral to the CVA-affected brain side, are often characterized by the presence of burning, cold and on-going pain and by the absence of cold allodynia. Tactile allodynia has been found to occur in disturbances of thermal/pain pathways that spare the tactile-signaling pathways (Greenspan et al., 2004).

27.3.5. Evaluation of treatment efficacy

A fairly large number of studies have been conducted using QST parameters to assess the effects of pain therapy. These studies can be divided into two main groups – those testing therapies aimed at ameliorating the etiological factor causing the neuropathy and those dealing with symptomatic pain therapy. We will review a few examples from each group.

27.3.5.1. Etiological therapy

The phase II study of nerve growth factor (NGF) in DN (Apfel et al., 1998) was one of the first studies in which QST served as a major end-point for a multicenter-controlled study on a new medication. Although QST supported the effect of NGF in this phase II study, the succeeding phase III results did not concur. In the search for a cure for Fabry's disease, the enzyme replacement with agalsidase beta revealed significantly improved function of C, A-δ and A-β nerve fibers, as shown by the detection thresholds for vibration and cold, heat-pain onset, and intermediate heat-pain assessments on the toe and dorsum of the feet. Lack of recovery in some patients with abnormal cold or heat-pain perception suggested the need for early enzyme replacement therapy prior to irreversible nerve fiber loss (Hilz et al., 2004). Treatment efficacy of growth factors (insulin-like growth factor I) (IGF-I) to encourage axonal growth in painful neuropathy was assessed by QST, change in pain scores and autonomic testing, neuropathy impairment scores, nerve conduction studies and neuropathy symptoms (Windebank et al., 2004).

27.3.5.2. QST in assessing the alleviation of neuropathic pain

Another extensive clinical application of QST in the context of neuropathic pain relates to the measurement of treatment efficacy. Thus far, QST has not yet become a routine method for assessing this effect and is not included in the EFNS recommendations for this purpose. The fact that most studies have failed to detect treatment effects using the measure of mechanical or thermal pain thresholds (see Eide et al., 1995) calls for application of more advanced psychophysical tests in order to evaluate the effects of interventions applied for neuropathic pain as well as for other pain conditions. Suprathreshold pain estimation, such as rating pain induced by brushing the skin for allodynia and hyperalgesia, as well as paradigms that assess temporal summation or mechanisms of endogenous analgesia, may provide a broader spectrum of psychophysical tests and increase the sensitivity of QST in the detection of therapeutic effect.

The pain-reducing effects of ketamine (an antagonist of NMDA receptor) and alfentanil (μ-opioid receptor antagonist) in patients with neuropathic pain, such as postherpetic neuralgia and central dysesthesia pain after spinal cord injury, were demonstrated by an increase in pain thresholds and a reduction in temporal summation (Eide et al., 1994, 1995; Leung et al., 2001). Likewise, the analgesic effect of ketamine and lidocaine in reducing neuropathic pain was assessed by VAS scores, which showed a 50% reduction in the treatment group as compared with the placebo group. QST also showed improved

function in central pain patients receiving lamotrigine (Vestergaard et al., 2001). The role of adenosine infusion in alleviating spontaneous and stimulus evoked pain in patients with neuropathic pain was explored by Belfrage et al. (1995), revealing an increase in mechanical pain thresholds and a decrease in suprathreshold mechanical pain. Wallace et al. (2000) used various sensory parameters to evaluate the efficacy of systemic lidocaine or oral mexiletine in reducing neuropathic pain, including mechanical (von Frey), warm and cold sensory thresholds and heat and cold pain thresholds as well as mechanical hyperalgesia or area of allodynia.

Attal et al. (2000) used the brush technique to demonstrate the effects of lidocaine on allodynia and hyperalgesia in patients with central pain, with no effect on thermal hyperalgesia. In a randomized controlled trial, Attal et al. (2002) assessed the effect of morphine by focusing on sensory measures, including mechanical (dynamic and static) and thermal allodynia/hyperalgesia. An application of suprathreshold thermal stimuli on the nonpainful contralateral side was used in order to explore the contribution of general antinociceptive activity of the drug. They found a correlation between the effect of morphine on spontaneous pain and on the response to suprathreshold thermal stimuli. They concluded that, although the analgesic effects induced by morphine involved general pain perception, only a minority of patients benefited from long-term treatment.

27.4. Conclusions

This chapter reviewed the basic concepts of QST, the methodological issues involved and the clinical applications of this testing method. We believe that the main current applications for QST in the context of pain neurology include support for the neurological diagnostic process, where a need to demonstrate an alteration in sensory function exists; quantification of pain symptomatology; and follow-up of changes in symptoms with time and in response to therapy. We believe that QST methodology holds a great deal of promise for more useful clinical utilization, in so far as the more advanced paradigms of testing involve exploration of the mechanisms of sensory change, rather than being limited to only describing those changes.

In a recent review, Edwards et al. (2005) suggested two additional fields of immediate clinical application of QST that are not the focus of pain in neurology, but rather relate to pain medicine at large and were, therefore, only briefly mentioned in this chapter. The first is the ability to differentiate between groups of healthy subjects and pain patients with fibromyalgia, temporomandibular joint disorders, pelvic pain syndromes and headaches, as such pain patients demonstrate greater pain sensitivity in response to experimental pain tests. Second is the prediction of acute postoperative pain (Nikolajsen et al., 2000; Bisgaard et al., 2001; Granot et al., 2003), as well as the prediction of treatment outcome (Sorensen et al., 1997; Kosek and Ordeberg, 2000; Poitras et al., 2002; Edwards et al., 2003; Granot et al., 2004). QST is anticipated to become an increasingly common pain assessment tool that can advance the understanding and management of pain.

In a recent editorial relating to preoperative pain prediction, Coghill and Eisenbach (2003) provided their vision for the clinical use of QST, saying that at the present time QST offers the possibility "to move toward routine preoperative pain assessment, just as 15 years ago we were at the beginning of a move away from routine preoperative chest radiographs and ECG." We join this line of thinking that the development of sensitive, informative and easy-to-perform test paradigms will make QST a handy and useful instrument for purposes of alleviating pain.

References

American Diabetes Association, American Academy of Neurology (1998). Report and Recommendations of the San Antonio Conference on Diabetic Neuropathy (Consensus Statement). Diabetes Care 11: 592–597.

Apfel SC, Kessler JA, Adornato BT, Litchy WJ, Sanders C, Rask CA (1998). Recombinant human nerve growth factor in the treatment of diabetic polyneuropathy. NGF study group. Neurology 51: 695–702.

Arendt-Nielsen L, Brennum J, Sindrup S, Bak P (1994). Electrophysiological and psychophysical quantification of temporal summation in the human nociceptive system. Eur J Appl Physiol Occup Physiol 68: 266–273.

Arendt-Nielsen L, Graven-Nielsen T, Svensson P, Jensen TS (1997). Temporal summation in muscles and referred pain areas: an experimental human study. Muscle Nerve 20: 1311–1313.

Attal N, Gaude V, Brasseur L, Dupuy M, Guirimand F, Parker F, Bouhassira D (2000). Intravenous lidocaine in central pain: a double-blind, placebo-controlled, psychophysical study. Neurology 54: 564–574.

Attal N, Guirimand F, Brasseur L, Gaude V, Chauvin M, Bouhassira D (2002). Effects of IV morphine in central pain: a randomized placebo-controlled study. Neurology 58: 554–563.

Belfrage M, Sollevi A, Segerdahl M, Sjolund KF, Hansson P (1995). Systemic adenosine infusion alleviates spontaneous and stimulus evoked pain in patients with peripheral neuropathic pain. Anesth Analg 81: 713–717.

Bisgaard T, Klarskov B, Rosenberg J, Kehlet H (2001). Characteristics and prediction of early pain after laparoscopic cholecystectomy. Pain 90: 261–269.

Boivie J, Leijon G, Johansson I (1989). Central post-stroke pain—a study of the mechanisms through analyses of the sensory abnormalities. Pain 37: 173–185.

Bouhassira D, Danziger N, Attal N, Guirimand F (2003). Comparison of the pain suppressive effects of clinical and experimental painful conditioning stimuli. Brain 126: 1068–1078.

Breivik EK, Bjornsson GA, Skovlund EA (2000). Comparison of pain rating scales by sampling from clinical trial data. Clin J Pain 16: 22–28.

Burstein R, Cutrer MF, Yarnitsky D (2000a). The development of cutaneous allodynia during a migraine attack: clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. Brain 123: 1703–1709.

Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH (2000b). An association between migraine and cutaneous allodynia. Ann Neurol 47: 614–624.

Burstein R, Collins B, Jakubowski M (2004). Defeating migraine pain with triptans: a race against the development of cutaneous allodynia. Ann Neurol 55: 19–26.

Chapman AJ, Casey KL, Dubner R, Foley KM, Graceley R, Reading AE (1985). Pain measurement: an overview. Pain 22: 1–33.

Chen AC, Niddam DM, Arendt-Nielsen L (2001). Contact heat evoked potentials as a valid means to study nociceptive pathways in human subjects. Neurosci Lett 316: 79–82.

Chong PS, Cros DP (2004). Technology literature review: quantitative sensory testing. Muscle Nerve 29: 734–747.

Claus D, Hilz MJ, Hummer I, Neundörfer B (1987). Methods of measurement of thermal thresholds. Acta Neurol Scand 76: 288–296.

Coghill RC, Eisenach J (2003). Individual differences in pain sensitivity: implications for treatment decisions. Anesthesiology 98: 1312–1314.

Coghill RC, Price DD, Hayes RL, Mayer DJ (1991). Spatial distribution of nociceptive processing in the rat spinal cord. J Neurophysiol 65: 133–140.

Coghill RC, Mayer DJ, Price DD (1993). The roles of spatial recruitment and discharge frequency in spinal cord coding of pain: a combined electrophysiological and imaging investigation. Pain 53: 295–309.

Coghill RC, Sang CN, Maisog JM, Iadarola MJ (1999). Pain intensity processing within the human brain: a bilateral, distributed mechanism. J Neurophysiol 82: 1934–1943.

Defrin R, Urca G (1996). Spatial summation of heat pain: a reassessment. Pain 66: 23–29.

Defrin R, Ohry A, Blumen N, Urca G (2002). Sensory determinants of thermal pain. Brain 125: 501–510.

Derbyshire SW, Jones AK, Gyulai F, Clark S, Townsend D, Firestone LL (1997). Pain processing during three levels of noxious stimulation produces differential patterns of central activity. Pain 73: 431–445.

Dirks JF, Wunder J, Kinsman R, McElhinny J, Jones NF (1993). A pain rating scale and a pain behavior checklist for clinical use: development, norms and the consistency score. Psychother Psychosom 59: 41–49.

Dougherty PM, Cata JP, Cordella JV, Burton A, Weng HR (2004). Taxol-induced sensory disturbance is characterized by preferential impairment of myelinated fiber function in cancer patients. Pain 109: 132–142.

Drewes AM, Pedersen J, Liu W, Arendt-Nielsen L, Gregersen H (2003). Controlled mechanical distension of the human oesophagus: sensory and biomechanical findings. Scand J Gastroenterol 38: 27–35.

Dunphy RC, Bridgewater L, Price DD, Robinson ME, Zeilman CJ 3rd, Verne GN (2003). Visceral and cutaneous hypersensitivity in Persian Gulf war veterans with chronic gastrointestinal symptoms. Pain 102: 79–85.

Dyck PJ, Karnes J, O'Brien PC, Zimmerman IR (1984). Detection thresholds of cutaneous sensation in humans. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R (Eds.) Peripheral Neuropathy, 2nd edn. W.B. Saunders, Philadelphia, PA, pp. 1103–1138.

Dyck PJ, Dyck PJB, Kennedy WR (1998). Limitations of quantitative sensory testing when patients are biased toward a bad outcome. Neurology 50: 1213–1214.

Edwards RR, Ness TJ, Weigent DA, Fillingim RB (2003). Individual differences in diffuse noxious inhibitory controls (DNIC): association with clinical variables. Pain 106: 427–437.

Edwards RR, Sarlani E, Wesselmann U, Fillingim RB (2005). Quantitative assessment of experimental pain perception: multiple domains of clinical relevance. Pain 114: 315–319.

Eide PK (2000). Wind-up and the NMDA receptor complex from a clinical perspective. Eur J Pain 4: 5–15.

Eide PK, Jorum E, Stubhaug A, Bremnes J, Breivik H (1994). Relief of post-herpetic neuralgia with the *N*-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. Pain 58: 347–354.

Eide PK, Stubhaug A, Stenehjem AE (1995). Central dysesthesia pain after traumatic spinal cord injury is dependent on *N*-methyl-D-aspartate receptor activation. Neurosurgery 37: 1080–1087.

Eisenberg E (2004). Post-surgical neuralgia. Pain 111: 3–7.

Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM (2001). Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 94: 149–158.

Fields HL (1999). Pain: an unpleasant topic. Pain 6 (Suppl.): S61–S69.

Flor H, Diers M, Birbaumer N (2004). Peripheral and electrocortical responses to painful and non-painful stimulation in chronic pain patients, tension headache patients and healthy controls. Neurosci Lett 361: 147–150.

Fruhstorfer H, Lindblom U, Schmidt WC (1976). Method for quantitative estimation of thermal thresholds in patients. J Neurol Neurosurg Psychiatry 39: 1071–1075.

Gibbons C, Freeman R (2004). The evaluation of small fiber function – autonomic and quantitative sensory testing. Neurol Clin 22: 683–702.

Gracely RH (1999). Pain measurement. Acta Anaesthesiol Scand 43: 897–908.

Granot M, Friedman M, Yarnitsky D, Zimmer EZ (2002). Enhancement of the perception of systemic pain in women with vulvar vestibulitis. Br J Obstet Gynaecol 109: 863–866.

Granot M, Sprecher E, Yarnitsky D (2003). Psychophysics of phasic and tonic heat pain stimuli by quantitative sensory testing in healthy subjects. Eur J Pain 7: 139–143.

Granot M, Friedman M, Yarnitsky D, Tamir A, Zimmer EZ (2004). Primary and secondary vulvar vestibulitis syndrome: systemic pain perception and psychophysical characteristics. Am J Obstet Gynecol 191: 138–142.

Granot M, Lowenstein L, Yamitsky D, Tamir A, Zimmer EZ (2003). Postcesarean section pain prediction by preoperative experimental pain assessment. Anesthesiology 98: 1422–1426.

Greenspan JD, Ohara S, Sarlani E, Lenz FA (2004). Allodynia in patients with post-stroke central pain (CPSP) studied by statistical quantitative sensory testing within individuals. Pain 109: 357–366.

Grill JD, Coghill RC (2002). Transient analgesia evoked by noxious stimulus offset. J Neurophysiol 87: 2205–2208.

Hilz MJ, Axelrod FB, Hermann K, Haertl U, Duetsch M, Neundorfer B (1998a). Normative values of vibratory perception in 530 children, juveniles and adults aged 3–79 years. J Neurol Sci 159: 219–225.

Hilz MJ, Stemper B, Schweibold G, Neuner I, Grahmann F, Kolodny EH (1998b). Thermal perception testing in 225 children and juveniles. J Clin Neurophysiol 15: 529–534.

Hilz MJ, Axelrod FB (2000). Quantitative sensory testing of thermal and vibratory perception in familial dysautonomia. Clin Auton Res 10: 177–183.

Hilz MJ, Brys M, Marthol H, Stemper B, Dutsch M (2004). Enzyme replacement therapy improves function of C-, Adelta- and Abeta-nerve fibers in Fabry neuropathy. Neurology 62: 1066–1072.

Jaaskelainen SK (2004). Clinical neurophysiology and quantitative sensory testing in the investigation of orofacial pain and sensory function. J Orofac Pain 18: 85–107.

Johansson RS, Vallbo AB (1979). Detection of tactile stimuli. Thresholds of afferent units related to psychophysical thresholds in the human hand. J Physiol 297: 405–422.

Kleinbohl D, Holzl R, Moltner A, Rommel C, Weber C, Osswald PM (1999). Psychophysical measures of sensitization to tonic heat discriminate chronic pain patients. Pain 81: 35–43.

Kosek E, Ordeberg G (2000). Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. Pain 88: 69–78.

Kramer HH, Rolke R, Bickel A, Birklein F (2004). Thermal thresholds predict painfulness of diabetic neuropathies. Diabetes Care 27: 2386–2391.

Lacomis D (2002). Small-fiber neuropathy. Muscle Nerve 26: 173–188.

Lautenbacher S, Roscher S, Strian F (1995). Tonic pain evoked by pulsating heat: temporal summation mechanisms and perceptual qualities. Somatosens Mot Res 12: 59–70.

Lautenbacher S, Roscher S, Strian F (2002). Inhibitory effects do not depend on the subjective experience of pain during heterotopic noxious conditioning stimulation (HNCS): a contribution to the psychophysics of pain inhibition. Eur J Pain 6: 365–374.

Le Bars D (2002). The whole body receptive field of multireceptive neurones. Prog Brain Res 40: 29–44.

Leung A, Wallace MS, Ridgeway B, Yaksh T (2001). Concentration–effect relationship of intravenous alfentanil and ketamine on peripheral neurosensory thresholds, allodynia and hyperalgesia of neuropathic pain. Pain 91: 177–187.

Li J, Simone DA, Larson AA (1999). Wind-up leads to characteristics of central sensitization. Pain 79: 75–82.

Lowenstein L, Vardi Y, Deutsch M, Friedman M, Gruenwald I, Granot M, Sprecher E, Yarnitsky D (2004). Vulvar vestibulitis severity—assessment by sensory and pain testing modalities. Pain 107: 47–53.

Magerl W, Wilk SH, Treede RD (1998). Secondary hyperalgesia and perceptual wind-up following intradermal injection of capsaicin in humans. Pain 74: 257–268.

Marchand S, Arsenault P (2002). Spatial summation for pain perception: interaction of inhibitory and excitatory mechanisms. Pain 95: 201–206.

Meh D, Denislic M (1994). Quantitative assessment of thermal and pain sensitivity. J Neurol Sci 127: 164–169.

Meier PM, Berde CB, DiCanzio J, Zurakowski D, Sethna NF (2001). Quantitative assessment of cutaneous thermal and vibration sensation and thermal pain detection thresholds in healthy children and adolescents. Muscle Nerve 24: 1339–1345.

Ness TJ, Richter HE, Varner RE, Fillingim RB (1998). A psychophysical study of discomfort produced by repeated filling of the urinary bladder. Pain 76: 61–69.

Nielsen J, Arendt-Nielsen L (1997). Spatial summation of heat induced pain within and between dermatomes. Somatosens Mot Res 14: 119–125.

Nielsen J, Arendt-Nielsen L (1998). The importance of stimulus configuration for temporal summation of first and second pain to repeated heat stimuli. Eur J Pain 2: 329–341.

Nikolajsen L, Ilkjaer S, Jensen TS (2000). Relationship between mechanical sensitivity and postamputation pain: a prospective study. Eur J Pain 4: 327–334.

Ochoa J, Torebjörk E (1983). Sensations evoked by intraneural microstimulation of single mechanoreceptor units innervating the human hand. J Physiol 342: 633–654.

Oh SJ, Melo AC, Lee DK, Cichy SW, Kim DS, Demerci M, Seo JH, Claussen GC (2001). Large-fiber neuropathy in distal sensory neuropathy with normal routine nerve conduction. Neurology 56: 1570–1572.

Pedersen J, Reddy H, Funch-Jensen P, Arendt-Nielsen L, Gregersen H, Drewes AM (2004). Cold and heat pain assessment of the human oesophagus after experimental sensitisation with acid. Pain 110: 393–399.

Poitras P, Riberdy Poitras M, Plourde V, Boivin M, Verrier P (2002). Evolution of visceral sensitivity in patients with irritable bowel syndrome. Dig Dis Sci 47: 914–920.

Porro CA, Cettolo V, Francescato MP, Baraldi P (1998). Temporal and intensity coding of pain in human cortex. J Neurophysiol 80: 3312–3320.

Postma TJ, Hoekman K, van Riel JM, Heimans JJ, Vermorken JB (1999). Peripheral neuropathy due to biweekly paclitaxel, epirubicin and cisplatin in patients with advanced ovarian cancer. Neurooncology 45: 241–246.

Price DD (1972). Characteristics of second pain and flexion reflexes indicative of prolonged central summation. Exp Neurol 37: 371–387.

Price DD, Hull CD, Buchwald NA (1971). Intracellular responses of dorsal horn cells to cutaneous and sural nerve A and C fiber stimuli. Exp Neurol 33: 291–309.

Price DD, Hu JW, Dubner R, Gracely RH (1977). Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. Pain 3: 57–68.

Price DD, McCrath PA, Raffi A, Buckingham B (1983). The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 17: 45–56.

Price DD, Harkins SW, Baker C (1987). Sensory-affective relationships among different types of clinical and experimental pain. Pain 28: 297–307.

Price DD, Bennett GJ, Rafii A (1989). Psychophysical observations on patients with neuropathic pain relieved by a sympathetic block. Pain 36: 273–288.

Price DD, Mao J, Frenk H, Mayer DJ (1994). The *N*-methyl-D-aspartate receptor antagonist dextromethorphan selectively reduces temporal summation of second pain in man. Pain 59: 165–174.

Price DD, Staud R, Robinson ME, Mauderli AP, Cannon R, Vierck CJ (2002). Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients. Pain 99: 49–59.

Proceedings of a consensus development conference on standardized measures in diabetic neuropathy. Quantitative sensory testing. Muscle Nerve 15: 1155–1157.

Shearer A, Scuffham P, Gordois A, Oglesby A (2003). Predicted costs and outcomes from reduced vibration detection in people with diabetes in the U.S. Diabetes Care 26: 2305–2310.

Shy ME, Frohman EM, So YT, Arezzo JC, Cornblath DR, Giuliani MJ, Kincaid JC, Ochoa JL, Parry GJ, Weimer LH (2003). Quantitative sensory testing – report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. Neurology 60: 898–904.

Sorensen J, Bengtsson A, Ahlner J, Henriksson KG, Ekselius L, Bengtsson M (1997). Fibromyalgia – are there different mechanisms in the processing of pain? A double blind crossover comparison of analgesic drugs. J Rheumatol 24: 1615–1621.

Siao P, Cros DP (2003). Quantitative sensory testing. Phys Med Rehabil Clin N Am 14: 261–286.

Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD (2001). Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. Pain 91: 165–175.

Staud R, Robinson ME, Vierck CJ Jr, Price DD (2003). Diffuse noxious inhibitory controls (DNIC) attenuate temporal summation of second pain in normal males but not in normal females or fibromyalgia patients. Pain 101: 167–174.

Staud R, Price DD, Robinson ME, Vierck CJ, Mauderli AP (2004). Maintenance of windup of second pain requires less frequent stimulation in fibromyalgia patients compared to normal controls. Pain 110: 689–696.

Stevens JC, Marks LE (1979). Spatial summation of cold. Physiol Behav 22: 541–547.

Strigo IA, Bushnell MC, Boivin M, Duncan GH (2002). Psychophysical analysis of visceral and cutaneous pain in human subjects. Pain 97: 235–246.

Swerup C, Nilsson BY (1987). Dependence of thermal thresholds in man on the rate of temperature change. Acta Physiol Scand 131: 623–624.

Tolle TR, Berthele A, Schadrack J, Ziegelgänsberger W (1996). Involvement of glutamatergic neurotransmission and protein kinase C in spinal plasticity and the development of chronic pain. Prog Brain Res 110: 193–206.

Torebjörk HE, LaMotte RH, Robinson CJ (1984). Peripheral neural correlates of magnitude of cutaneous pain and hyperalgesia: simultaneous recordings in humans of sensory judgments of pain and evoked responses in nociceptors with C-fibers. J Neurophysiol 51: 325–339.

Van Hees J, Gybels J (1981). C nociceptor activity in human nerve during painful and non painful skin stimulation. J Neurol Neurosurg Psychiatry 44: 600–607.

Verdugo RJ, Bell LA, Campero M, Salvat F, Tripplett B, Sonnad J, Ochoa JL (2004). Spectrum of cutaneous hyperalgesias/allodynias in neuropathic pain patients. Acta Neurol Scand 110: 368–376.

Vestergaard K, Nielsen J, Andersen G, Ingeman-Nielsen M, Arendt-Nielsen L, Jensen TS (1995). Sensory abnormalities in consecutive, unselected patients with central post-stroke pain. Pain 61: 177–186.

Vestergaard K, Andersen G, Gottrup H, Kristensen BT, Jensen TS (2001). Lamotrigine for central poststroke pain: a randomized controlled trial. Neurology 56: 184–190.

Vierck CJ Jr, Cannon RL, Fry G, Maixner W, Whitsel BL (1997). Characteristics of temporal summation of second pain sensations elicited by brief contact of glabrous skin by a preheated thermode. J Europhysiol 78: 992–1002.

Wallace MS, Magnuson S, Ridgeway B (2000). Efficacy of oral mexiletine for neuropathic pain with allodynia: a double-blind, placebo-controlled, crossover study. Reg Anesth Pain Med 25: 459–467.

Werner MU, Duun P, Kehlet H (2004). Prediction of postoperative pain by preoperative nociceptive responses to heat stimulation. Anesthesiology 100: 115–119; discussion 5A.

Weissman-Fogel I, Sprecher E, Granovsky Y, Yarnitsky D (2003). Repeated noxious stimulation of the skin enhances cutaneous pain perception of migraine patients in-between attacks: clinical evidence for continuous sub-threshold increase in membrane excitability of central trigeminovascular neurons. Pain 104: 693–700.

Windebank AJ, Sorenson EJ, Civil R, O'Brien PC (2004). Role of insulin-like growth factor-I in the treatment of

painful small fiber predominant neuropathy. J Periph Nerv Syst 9: 183–189.

Woolf CJ, Decosterd I (1999). Implications of recent advances in the understanding of pain pathophysiology for the assessment of pain in patients. Pain 6 (Suppl.): S141–S147.

Woolf CJ, Thompson SWN (1991). The induction and maintenance of central sensitization is dependent on *N*-methyl-D-aspartic acid receptor activation: implication for the treatment of post-injury pain hypersensitivity states. Pain 158: 347–354.

Yarnitsky D (1997). Quantitative sensory testing. Muscle Nerve 20: 198–204.

Yarnitsky D, Ochoa JL (1990). Study of heat pain sensation in man: perception thresholds, rate of stimulus rise and reaction time. Pain 40: 85–91.

Yarnitsky D, Pud D (2004). Quantitative sensory testing. In: Binnie C, Cooper R, Mauguiere F, Osselton JW, Prior P, Tedman B (Eds.) Clinical Neurophysiology (revised and enlarged edition): EMG, Nerve Conduction and Evoked Potentials, Vol. 1. Elsevier, Amsterdam, pp. 309–336.

Yarnitsky D, Simone DA, Dotson RM, Cline MA, Ochoa JL (1992). Single C nociceptor responses and psychophysical parameters of evoked pain: effect of rate of rise of heat stimuli in humans. J Physiol 450: 581–592.

Yarnitsky D, Sprecher E, Zaslansky R, Hemli JA (1995). Heat pain thresholds: normative data and repeatability. Pain 60: 329–332.

Zaslansky R, Yarnitsky D (1998). Clinical applications of quantitative sensory testing (QST). J Neurol Sci 153: 215–238.