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Research Brief

Methods to measure peripheral and central sensitization using quantitative sensory testing: A focus on individuals with low back pain ☆

Angela R. Starkweather, PhD, FAAN [a,*], Amy Heineman, BS, RN [a], Shannon Storey, BS, RN [a], Gil Rubia, BS, RN [a], Debra E. Lyon, PhD, FAAN [c], Joel Greenspan, PhD [b], Susan G. Dorsey, PhD, RN [b]

[a] Virginia Commonwealth University School of Nursing, Richmond, VA, USA 23298-0567
[b] University of Maryland School of Nursing, Baltimore, MD, USA 21201
[c] University of Florida College of Nursing, Gainesville, FL, USA 32610-0197

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ABSTRACT

Quantitative sensory testing can be used to assess peripheral and central sensitization; important factors that contribute to the individual's experience of pain and disability. Many studies use quantitative sensory testing in patients with low back pain to detect alterations in pain sensitivity, however, because investigators employ different protocols, interpretation of findings across studies can become problematic. The purpose of this article is to propose a standardized method of testing peripheral and central pain sensitization in patients with low back pain. Video clips are provided to demonstrate correct procedures for measuring the response to experimental pain using mechanical, thermal and pressure modalities. As nurse researchers and clinicians increase utilization of quantitative sensory testing to examine pain phenotypes, it is anticipated that more personalized methods for monitoring the trajectory of low back pain and response to treatment will improve outcomes for this patient population.

Quantitative sensory testing (QST) is a non-invasive examination of somatosensory perception using the application of mechanical and thermal stimuli at controlled intensities (Rolke et al., 2006). The battery of tests involved in QST can be used to evaluate the function of large (A-beta) and small (A-delta and C) nerve fibers as well as central pathways of sensory perception (Backonja et al., 2009). QST is a psychophysical examination, and thus, requires a standardized set of instructions, examination settings and procedures in order to achieve valid and reliable results (Rolke et al., 2006). By providing an assessment of the individual's sensory profile, QST can serve as a valuable tool in defining the underlying mechanisms of pain and thereby inform treatment approaches as well as distinguish responders from non-responders to specific treatments (Walk et al., 2009). The purpose of this article is to describe the application of QST in a specific clinical population, individuals with low back pain (LBP), discuss the pain pathways that QST can measure, and provide a protocol summary for using QST in research involving individuals with LBP.

1. Overview of low back pain

As the second most frequently diagnosed pain condition in the United States, LBP sufferers often do not typically receive intensive interventions until after the pain becomes chronic. This may be one reason that even after receiving health care treatment, an estimated 40% of patients will experience persistent LBP (for >24 weeks) (Buchbinder et al., 2013; Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Eduction). Of the $300 billion per year in health care costs for LBP, approximately 95% is spent on the treatment of patients who develop persistent LBP (Burgoyne, 2007; Soni, 2011a). Thus, persistent LBP has become one of the most costly public health issues in the United States (Soni, 2011b). Besides this financial burden, persistent LBP can lead to significant compromises in general health, psychosocial well-being, and quality of life (Burgoyne, 2007). America's young are particularly vulnerable to the repercussions of persistent LBP as it is the leading cause of work disability in people <45 years of age (Soni, 2011a).

Up to 90% of patients with LBP have a nonspecific etiology without an identifiable cause of pain (Chou et al., 2007; Kleinstck, Dvorak, & Mannion, 2006), thus researchers have focused on clinical, psychosocial and environmental risk factors of persistent LBP. Abundant evidence demonstrates that these factors contribute to pain, however, they have not been useful in *predicting* persistent LBP or guiding the delivery of early intensive interventions to reduce the risk of persistent LBP (Hilfiker et al., 2007; Jellema, van der Windt, van der Horst, Stalman, & Bouter, 2007; Kamper et al., 2010). Other studies document functional

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* Corresponding author. Tel.: +1 804 828 3986.
E-mail address: astarkweathe@vcu.edu (A.R. Starkweather).

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alterations that reflect peripheral and central nervous system sensitization in patients with persistent LBP — a phenomenon that may increase the risk of a persistent pain trajectory (Clauw et al., 1999; Giesecke et al., 2004). The sensory alterations, which reflect enhanced pain sensitivity, are measured using QST. Mechanisms of enhanced pain sensitivity include sensitization of nociceptors and neuronal circuits (Gold & Gebhart, 2010), increased pain signaling through membrane excitability and synaptic efficacy, and inadequate descending pain inhibition (Graven-Nielsen & Arendt-Nielsen, 2010; Jankowski & Koerber, 2010); all of which can be measured using QST.

2. Quantitative sensory testing measurements

QST can be used to enhance the traditional clinical exam of LBP to detect somatosensory aberrations that may contribute to the individual's experience of pain and disability. An advantage of QST is that it assesses inadequate function (hypoalgesia) as well as gain of function (hyperalgesia) and results are evaluated using age- and gender-matched reference data or dynamic person-specific measures can be used to provide a more personalized pain profile that can be monitored over time (Krumova, Geber, Westermann, & Maier, 2012). Although there are many different types of nerve fibers (Table 1), the goal of QST is to test the fibers that carry nociceptive signals, the A-delta and C-fibers.

Somatosensory aberrations occur through peripheral and central mechanisms. Peripheral sensitization is an increase in the excitability of nociceptors, the sensory receptors that transfer input from innervated tissues (skin, muscles, joints and viscera) through peripheral nerves to the central nervous system (Krumova et al., 2012). Peripheral sensitization occurs when primary sensory neurons are exposed to inflammatory mediators released by damaged tissue, which leads to neuroinflammation. This results in a reduced threshold to activate a nociceptor (i.e., a less intense stimulus will evoke an action potential), and a greater response (i.e., greater number of action potentials generated) for a given level of stimulation. This produces an enhanced pain referred to as hyperalgesia, however, the hyperalgesia is restricted to the site of tissue injury. Using QST, peripheral sensitization is reflected by altered thermal sensitivity, a lower pain threshold to heat stimuli, but not necessarily mechanical sensitivity (Granovsky & Yarnitsky, 2013).

Central sensitization is an increase in the excitability of neurons within the central nervous system (CNS), typically those receiving synaptic input from sensitized nociceptors. This central sensitization leads to mechanical hyperalgesia (in which a painful mechanical stimulus feels more painful than normal) and mechanical allodynia (in which normally non-painful stimuli are perceived as painful). In contrast to peripheral sensitization, central mechanisms include recruitment of large (Aβ), low-threshold myelinated mechanoreceptor fibers into the response of CNS neurons that contribute to pain and expansion of sensory alterations to other regions of the body (Granovsky & Yarnitsky, 2013). In some cases, the sensitized nociceptive and CNS neurons can become activated even in the absence of obvious stimulation, leading to spontaneous pain.

Temporal summation (TS) of pain is a c-fiber mediated alteration in CNS nociceptive processing that leads to enhanced pain under conditions of repetitive stimulation. It can be evoked using mechanical, chemical or thermal modalities, however, thermal stimuli are most commonly employed. TS is related to "wind-up" of CNS neurons receiving repetitive nociceptive input, in which the neuron's response increases with successive stimuli, despite receiving the same peripheral input each time. This wind-up is caused by excessive activation of N-methyl-D-aspartate (NMDA) receptors of the CNS neurons in response to intensive nociceptive input and its expression depends on the flow of calcium ions into the neuronal cytoplasm. Thus, neuronal windup subsequent to the enhanced calcium influx-dependent release of glutamate, norepinephrine, and substance P may serve as a target for the agents that are expected to diminish this central neuronal hyperexcitability. TS is tested using a series of identical stimuli while acquiring numerical pain scale ratings along the series. An increase in pain ratings along the series reflecting the physiological phenomenon of wind-up occurs normally under the appropriate stimulus conditions. In the presence of central sensitization, TS is exaggerated in amplitude and extended in duration. Thus, enhanced TS is considered a marker of upregulated CNS processing of nociceptive signal.

In recent years, there has been an increasing focus on the value of conditioned pain modulation (CPM; aka. diffuse noxious inhibitory controls (DNIC)-like effect) as a measure of the function of the descending tracts that control and modulate pain perception. With normal functioning of the descending endogenous inhibitory system, painful stimuli exert inhibitory effects over other painful stimuli. This system includes brainstem regions receiving nociceptive signals (such as periaqueductal gray - PAG, and rostral ventral medulla - RVM) and is also influenced by higher cerebral brain regions (such as the anterior cingulate cortex - ACC). This system can exert either inhibition or facilitation on the spinal neurons receiving nociceptive input. Descending pain inhibition that underlies the CPM response is based on a spino-bulbar-spinal loop that involves serotonergic and noradrenergic neurotransmission. Since pain thresholds and tolerance can be influenced by many factors, CPM provides a more precise way to measure the functional status of the patient's pain modulatory system and identify the risk of a chronic pain trajectory.

To measure CPM, a test stimulus and a conditioned stimulus is employed (Granovsky & Yarnitsky, 2013). The test stimulus is a painful but tolerable stimulus that is administered for a short time period (seconds). The conditioning stimulus is a different type of painful stimulus that is applied to another body region for a longer time period (tens of seconds). The subject is asked to rate the pain of the test stimulus on a numerical pain scale as it is applied before and then during the application of the conditioning stimulus. To calculate the CPM score, the first numerical score rating (acquired before the conditioning stimulus) is subtracted from the subsequent numerical score rating (acquired during exposure to the conditioning stimulus). This change score is an indication of the functioning of the endogenous analgesic system that can be evoked by a painful event.

3. Quantitative sensory testing in individuals with low back pain

Several publications have reported finding altered pain sensitivity in people with chronic low back pain. However, these studies reported limited assessment of somatosensory function at one or two sites such as the thumb (Giesecke et al., 2004); forehead and thumbnail (Clauw et al., 1999); and forearm (O'Neill, Manniche, Graven-Nielsen, & Arendt-Nielsen, 2007). While these studies provide evidence of enhanced pain sensitivity in patients with persistent LBP, these studies

Table 1
Types of myelinated and unmyelinated nerve fibers.

Large myelinated fibers	
A-alpha	afferent/efferent — transfer non-noxious information pertaining to muscle contraction
A-beta	afferent/efferent — transfer non-noxious information pertaining to touch and muscle movement
A-delta	afferent — transfer noxious information pertaining to touch, temperature (thermal), pressure, transmits sensation of localized "sharp" pain
A-gamma	efferent — transfer non-noxious information pertaining to touch and pressure
B fibers	efferent preganglionic — carry non-noxious messages related to automatic involuntary functions such as digestion and breathing
Small unmyelinated fibers	
C fibers	afferent/efferent, postganglionic — transfer noxious mechanical (including touch), chemical and temperature (thermal) information, transmits sensation of dull, diffuse, "burning" pain