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SPECIAL ISSUE ON CENTRAL SENSITIZATION

Central Sensitization: A Brief Overview

Robert J. Gatchel[1] | **Randy Neblett**[2]

[1]Department of Psychology, College of Science, The University of Texas at Arlington, Arlington, Texas

[2]Productive Rehabilitation Institute of Dallas for Ergonomics, Dallas, Texas

Correspondence
Robert J. Gatchel, Department of Psychology, College of Science, The University of Texas at Arlington, Arlington, TX.
Email: gatchel@uta.edu

This article introduces a SPECIAL ISSUE of the *Journal of Applied Biobehavioral Research* on Central Sensitization (CS). First, a general overview of CS is provided, including some historical perspective, the prevalence of CS in various chronic pain disorders, and common ways of measuring CS and related symptoms. Then a brief summary of each contributing article to this SPECIAL ISSUE is provided. Article topics include: CS-related neurobiology; diagnostic phenotyping; a biopsychosocial perspective of CS-related disorders; use of the Central Sensitization Inventory (CSI); evaluation of CS and related symptoms in some specific disorders (including general chronic pain, fibromyalgia, and breast cancer survivors); and how the concept of CS has changed our current view of chronic pain.

1 | OVERVIEW

Clifford Woolf, who can be considered as the "grandfather" of central sensitization (CS), first introduced the concept in 1983 (Woolf, 1983). He suggested that neuroplasticity and abnormal changes in the central nervous system could result in an intense enhancement of pain. Since that time, CS mechanisms have been demonstrated in many animal and human studies (Latremoliere & Woolf, 2009; Woolf, 2011). Our evolving understanding of CS has fundamentally changed our view of pain and is now recognized as a major underpinning of many chronic pain disorders (Harte, Harris & Clauw, this Issue; Woolf, 2011). Woolf (this Issue) has contributed the first article to this present SPECIAL ISSUE.

Central sensitization has been proposed as the root cause of many pain-related conditions, with no obvious tissue pathology that, in the past, have been considered psychiatrically-based, "functional," or "medically unexplained" (Kindler, Bennett & Jones, 2011; Schur et al., 2007; Yunus, 2007a). Yunus first proposed the term "central sensitivity syndrome" (CSS) to characterize "nonorganic disorders" that are presumed to share a common etiology of CS (Yunus, 2000, 2007b), including fibromyalgia, irritable bowel syndrome, and temporomandibular joint disorder. Indeed, a number of studies have demonstrated strong evidence that these varied disorders: share a

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strong comorbidity with each other; have similar comorbid symptoms (including sleep problems, fatigue, cognitive slowing); and are associated with objective markers of CS (Harte et al., this Issue; Kindler et al., 2011; Phillips & Clauw, 2011; Yunus, 2007b, 2008). More recently, the National Institute of Health has coined the term *Chronic Overlapping Pain Conditions (COPCs)*, to categorize these same related disorders (Levitt et al., 2017; Maixner, Fillingim, Williams, Smith, & Slade, 2016a). It should also be noted that the "*Gate Control Theory of Pain*," first proposed by Melzack and Wall (1965), was subsequently extended by Melzack (2005) in proposing the "*Neuromatrix Theory of Pain*." His theory proposed that the experience of pain is a multidimensional process, and is produced by patterns of new impulses generated by a widely-distributed neural network comprising what he labelled the "body-self neuromatrix." This neuromatrix can be modified by sensory experiences and learning, and patterns of nerve impulses can be triggered either by sensory inputs or centrally. This theory can be viewed as complementary to current work on CS.

Subsequently, we published an article suggesting that CS may be the common etiology of the earlier DSM-IV (American Psychiatric Association, 2004) diagnosis of "Somatoform Disorders" (Roberts, Lorduy & Gatchel, 2013). The Editor's Note of that article highlighted that "The understanding of centralization of pain from a peripheral pain site is a major scientific discovery of recent times that enhances clinical understanding and therapeutics… One of the mysteries of pain is what appears to be the 'de novo' occurrence in the central nervous system…of some painful conditions, such as fibromyalgia…intestinal cystitis, temporomandibular joint…disorders, and irritable bowel syndrome…the authors attempt to categorize these disorders into one group called 'somatoform', purporting that 'central sensitization' is a common thread among these disorders" (p. 46). The original DSM-IV (American Psychiatric Association, 2004) category of "Somatoform Disorders" has now been changed to "Somatic Symptoms and Related Disorders" in the newer DSM-5 because of the controversy surrounding the former term. The new classification now refers to it as a maladaptive reaction to a somatic disorder, rather than the earlier version which attempted to delineate whether the somatic symptoms were "medically unexplained." This earlier version of the DSM-IV created problems in defining what "medically unexplained" events actually were, and how to assess them.

In this SPECIAL ISSUE, Harte et al. (this Issue) provide a comprehensive review of the "Neurobiology of Central Sensitization," including an in-depth discussion of how both spinal cord and supraspinal mechanisms play a significant role in CS. From recent investigations that used "state-of-the-art" technology, they have now proposed two major sub-types of central sensitization: a *bottom-up* type, which is driven by ongoing nociceptive input; and a *top-down* type, for which the primary problem may originate in supraspinal structures, and not require ongoing nociceptive input to maintain the process. This is exciting new research which requires additional investigation.

2 | ASSESSMENT METHODS FOR CENTRAL SENSITIZATION

Evidence of CS can be identified in a number of ways. Quantitative sensory testing (QST) involves protocolized procedures that assess perceptual responses to systematically applied and quantifiable sensory stimuli, in order to evaluate somatosensory function or dysfunction (Cruz-Almeida & Fillingim, 2014). QST can identify CS-related symptomology, including increased sensitivity to nonpainful stimuli (e.g., allodynia), enhanced pain response to painful stimuli (e.g., hyperalgesia), facilitation of centrally-mediated pain (e.g., temporal summation), and centrally-mediated pathology in pain inhibitory mechanisms (e.g., conditioned pain modulation; Williams, this Issue). Objective biological markers of CS can also be measured. "Evoked pain" paradigms, in which brain responses to stimuli are measured with functional magnetic resonance imaging (fMRI), have consistently found that subjects with CS-related disorders (e.g., CSS) show increases in activation of pain-related networks that correspond with increases in pain-reporting (Walitt, Ceko, Gracely & Gracely, 2016). CS is also associated with increased production of pain-facilitating neurotransmitters and inflammatory cytokines, and decreased production of pain-inhibiting neurotransmitters, including brain-derived neurotrophic factor (BDNF) and tumor

necrosis factor, all of which can be measured with blood testing (Caumo et al., 2016; Deitos et al., 2015; Nijs et al., 2015).

The use of many of the above assessments, however, is not viable for most healthcare providers in clinical practice. Therefore, there have been some recent attempts to provide clinical guidance on a clinical methodology for identifying when a patient's symptom-presentation may be related to CS, or to indicate the presence of CSS. Smart, Blake, Staines, Thacker and Doody (2012) have proposed a "mechanisms-based" classification system based on a standardized assessment protocol and clinical judgement of pain patterns. Specific symptomology is used, including disproportionate, nonmechanical, and unpredictable pain patterns, relative to the nature and extent of injury or pathology; diffuse/nonanatomic areas of pain/tenderness upon palpation; and associated maladaptive psychosocial factors (e.g., negative emotions, poor self-efficacy, maladaptive beliefs, and pain behaviors). These factors were found to have considerable accuracy in identifying CS in a group of low back pain subjects (sensitivity = 91.8%, and specificity = 97.7%). Subsequently, Nijs et al. (2014) proposed an alternative classification system for identifying CS-related pain. The first step was to exclude neuropathic pain, defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" (Treede et al., 2008). The second step involves differential classification of nociceptive vs. CS-related pain. Similar to Smart et al. (2012), a diffuse pain distribution involving allodynia and/or hyperalgesia, and pain that is disproportionate to the extent of injury, corresponded to a CS classification. Nijs' et al. (2014) methodology also involves the assessment of hypersensitivity of senses unrelated to the musculoskeletal system. To do that, they recommend the use of a self-report measure—the *Central Sensitization Inventory* (CSI; Mayer et al., 2012).

The CSI is a psychometrically-sound instrument designed to screen for CS-related symptomology (Cuesta-Vargas et al., 2018). It includes 25-items, with a total score range from "0" to "100." A 40-point cut-off score (also used with the Nijs et al., 2014 classification system) has successfully discriminated between CSS and nonpatient subjects, with adequate sensitivity (81%) and specificity (75%; Neblett et al., 2013). A recent systematic review of 14 CSI studies (all of which were determined to have good-to-excellent quality of evidence) concluded that the CSI is a reliable and valid instrument for quantifying the severity of CS-related symptoms (Scerbo et al., 2017). Indeed, as will be reviewed in this present SPECIAL ISSUE, many studies are now using the CSI, as well as cross-validating it in different languages around the world. Multiple language versions are available at: www.pridedallas.com/questionnaires. Neblett (this Issue) has provided a "User's Manual" for the CSI in this SPECIAL ISSUE.

3 | OTHER ARTICLES IN THIS SPECIAL ISSUE

As noted earlier, the first article in this SPECIAL ISSUE is by Clifford Woolf, who provides an excellent overview of the important need of the construct of CS for a full understanding of peripheral and central pain states. Such a comprehensive understanding will lead to the most effective pain management approaches for patients. Woolf's article is then followed by a review by Adams and Turk (this Issue), which highlights the need for a comprehensive biopsychosocial perspective to address all the important components (biological, psychological, social, and contextual factors) that influence the experience and countenance of pain. They present this biopsychosocial perspective in the context of treating central sensitivity syndromes (CSSs), such as fibromyalgia and irritable bowel syndrome.

The next series of studies discuss the role of both objective and patient-reported CS-related symptoms in different medical disorders, such as breast-cancer survivors (Cuesta-Vargas et al.), fibromyalgia (Feliu-Soler et al.), and general chronic pain patients (van der Nood et al.). These are examples of the importance of self-report measures in pain evaluation. It is also a great demonstration of the growing need for translation research across different languages and cultures for evaluation and treatment of major clinical disorders.

At last, David Williams (this Issue) reviews the growing literature on diagnostic phenotyping of CS, including the use of endophenotypes, biomarkers, quantitative sensory testing, and symptom clusters (e.g., sleep difficulties, pain, affect, cognitive difficulties, and low energy [S.P.A.C.E.]) to evaluate CS-related symptomology.

4 | SUMMARY

Our evolving understanding of CS has fundamentally changed our view of pain and is now recognized as a major underpinning of many chronic pain disorders (Woolf, 2011). With our new understanding of CS pain mechanisms, patients with chronic pain, but without objective tissue damage, no longer need to be stigmatized with "psychosomatic"-type labels.

> *The lack of a definitive clinical test for persistent pain does not mean that the condition, has no biological basis.* – *Mark R. Hutchinson, 2018.*

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