HHS Public Access

Author manuscript

J Appl Biobehav Res. Author manuscript; available in PMC 2019 June 01.

Published in final edited form as:

J Appl Biobehav Res. 2018 June ; 23(2): . doi:10.1111/jabr.12135.

Phenotypic Features of Central Sensitization

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Abstract

Purpose—The current manuscript reviews approaches for phenotyping central sensitization (CS).

Methods—The manuscript covers the concept of diagnostic phenotyping, use of endophenotypes, biomarkers, and symptom clusters. Specifically, the components of CS that include general sensory sensitivity (assessed by quantitative sensory testing) and a symptom cluster denoting sleep difficulties, pain, affect, cognitive difficulties, and low energy (S.P.A.C.E.).

Results—Each of the assessment domains are described with reference to CS and their presence in chronic overlapping pain conditions (COPCs) - conditions likely influenced by CS.

Conclusions—COPCs likely represent clinical diagnostic phenotypes of CS. Components of CS can also be assessed using QST or self-report instruments designed to assess single elements of CS or more general composite indices.

Keywords

Central Sensitization; Chronic Overlapping Pain Conditions (COPCs); Phenotyping; Sensory Hypersensitivity; Unwellness; Mental Load

Introduction

Central Sensitization (CS) is a multifaceted spinal and cortical process by which the central nervous system (CNS) amplifies nociceptive sensory stimuli, which may then be perceived as experiences of unpleasantness, threat or pain. This special issue has combined decades of research to shed light on the mechanisms of this process. While CS requires multiple processes to occur, the clinical phenotype is an individual who presents with unpleasant sensory experiences disproportionate to any observable peripheral cause. The International Association for the Study of Pain (I.A.S.P.) defines CS as “Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent

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For inclusion in the JABR special issue on Central Sensitization
Edited by Robert Gatchel and Randy Neblett

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CONFLICT OF INTEREST

Dr. Williams serves as a consultant to Community Health Focus Inc. He is currently the Immediate Past President of the American Pain Society. There is no conflict associated with the content or preparation of this manuscript.

input" (IASP, 2015). CS can be inferred clinically from the presence of allodynia and hyperalgesia. In addition to these markers derived from quantitative sensory testing (QST), there may be other indices suggestive of CS (Nijs et al., 2014). This article provides additional insights into the clinical characteristics of individuals suspected of experiencing CS.

Clinical Characterization: Phenotyping, Biomarkers, and Symptoms

A phenotype refers to the composite of one's observable traits or characteristics resulting from an interaction between an individual's genetic code, in combination with influences from the environment. In practice, clinical phenotypes are often just the diagnostic label for a given disease [e.g., Diagnositic and Statistical Manual for Mental Disorders (DSM) or International Classification of Diseases (ICD) code]. Such clinical phenotypes tend to be defined by expert consensus and often incorporate multiple symptoms rather than reflecting discrete or unique pathology. Due to their breadth, diagnostic labels are often less than optimal phenotypes for genetic studies (Hall & Smoller, 2010; Tsuang, 2001).

An alternative to using diagnostic labels as phenotypes is the use of more genetically informative alternative phenotypes, of which there are three types: (a) component phenotypes, (b) intermediate phenotypes, and (c) covariates (Szatmari et al., 2007). The component phenotype refers to a cardinal symptom or dimension of a disorder [e.g., hallucinations in schizophrenia,(Szatmari et al., 2007) widespread pain in fibromyalgia (Wolfe et al., 2010)]. To be genetically informative, the component symptom should only be found in affected individuals. Intermediate phenotypes occur with greater intensity in affected family members than unaffected family members, but family members (affected or unaffected) should exhibit the trait more than in the general population. Of note, given that the trait occurs in both affected and unaffected family members, it cannot be a defining feature of the disorder, like the component phenotype. An intermediate phenotype is analogous to the concept of an "endophenotype" and can include biochemical, physiological, behavioral, cognitive, and self-reported forms of data. Examples of intermediate phenotypes include oculomotor function in schizophrenia (Gottesman & Gould, 2003) and affective vulnerability in Temporomandibular Joint Disorders (Diatchenko, Nackley, Slade, Fillingim, & Maixner, 2006). Finally, covariates act as moderators defining sub-groups in which the linkage between genetics and the disorder may be stronger or weaker depending upon the covariate (e.g., groups with early life exposure to pain may be more vulnerable to developing fibromyalgia; (Low & Schweinhardt, 2012)).

While the intent of identifying phenotypes is to help link observable characteristics to genetic markers, much of what has been called phenotyping has never actually been validated as having clear links to genetics (e.g., the literature on initial smoking risk factors; (Audrain-McGovern, Nigg, & Perkins, 2009). Thus, using the term "phenotyping" may simply reflect a clinical feature that appears to be related to a condition but fails to demonstrate genetic linkage. Such clinical features may simply be medical symptoms associated with a diagnostic label or mechanism.

Often confused with phenotypes is the concept of a biomarker. Biomarkers can also be used to characterize a disorder and can be defined broadly as any interaction between a biological system and potential hazard that can be reproducibly measured (Strimbu & Tavel, 2010). Biomarkers can be functional, physiological, biochemical or molecular, but unlike phenotypes, may or may not have genetic influences and can tend to be state-dependent phenomena (Beauchaine & Constantino, 2017). Blood pressure is a good example of a biomarker associated with the clinical phenomena of hypertension.

Central sensitization, as defined by Woolf (Latremoliere & Woolf, 2009; Woolf, 2011), has been translated into clinical diagnostic criteria by Nijs and colleagues (Nijs et al., 2014). Summarizing this approach for identifying CS, the pain complaint cannot be due to neuropathic pain (e.g., lesions, neuropathy, diseases of the nervous system) or described as such (e.g., shooting, burning pricking pain) and not due to nociceptive or inflammatory processes (e.g., pain proportional to injury or identifiable inflammatory processes). In addition, there needs to be evidence of widespread pain (i.e., not just the localized complaint), hypersensitivity to sensory processes in general (e.g., sensitivity to light, sound, touch, odors etc.), and symptoms that are both products and contributors to the construct of "mental load" (e.g., sleep problems, pain intensity, affective lability, cognitive difficulties, and lack of energy/fatigue). See Table 1 for a summary of Nils et al.'s approach to clinically identifying patients experiencing CS. Based upon this conceptualization, the clinical characterization of CS appears to involve a combination of candidate phenotypes, biomarkers, and medical symptoms.

Chronic Overlapping Pain Conditions (C.O.P.C.s): The Diagnostic Phenotypes of CS

Of the 100 million individuals who suffer with chronic pain, a sizable percentage, mostly women, will suffer from multiple chronic pain conditions simultaneously [i.e., COPCs; (Committee on Advancing Pain Research, Education, & Institute of, 2011; Maixner, Fillingim, Williams, Smith, & Slade, 2016; Veasley et al., 2015)]. The concept of coexisting pain conditions has been recognized by the National Institutes of Health (NIH) as a set of disorders that may share a common mechanism (e.g., CS) and includes, but should not be limited to, temporomandibular disorders (TMD), fibromyalgia (FM), irritable bowel syndrome (IBS), vulvodynia (VVD), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), interstitial cystitis/painful bladder syndrome (IC/PBS), endometriosis (ENDO), chronic tension-type headache (CTTH), migraine headache (MI), and chronic lower back pain (CLBP). Thus, despite being diagnosed with each condition separately, the problem may not be with the specific presenting complaint but with a common mechanism that amplifies peripheral input from multiple bodily locations so as to produce centrally augmented pain [i.e., CS; (Clauw, 2014; Maixner et al., 2016)]. For example, a patient with both IBS and TMD would likely be seen by a Gastroenterologist focused upon identifying pathology in the gut as well as a Dentist focused upon identifying pathology in the jaw. In practice, neither practitioner would be likely to suspect a common underlying mechanism such as aberrant central pain processing. Instead, treatment would likely focus on "correcting" the peripheral or anatomical source of each pain complaint - an approach which

is not likely to address the common underlying etiology of the conditions (Maixner et al., 2016; Williams & Clauw, 2009). Given, the COPCs are suspected of being diagnostic manifestations of CS, comparisons of COPCs with other forms of chronic pain may provide valuable insights into pragmatic clinical indices of CS.

Generalized Sensory Hypersensitivity

One feature of CS that has been explored in the context of COPCs is the concept of generalized sensory hypersensitivity. For example, in FM, the cardinal symptom is widespread pain and tenderness upon touch. Upon further assessment however, such individuals also tend to report hypersensitivity to other sensory modalities including auditory, olfactory, and visual stimuli (Geisser et al., 2008; Wilbarger & Cook, 2011). This generalized sensory hypersensitivity has been documented in other COPCs such as migraine (Friedman & De ver Dye, 2009; Goadsby et al., 2017; Main, Dowson, & Gross, 1997), IBS (Berman et al., 2002; Blomhoff, Jacobsen, Spetalen, Dahm, & Malt, 2000), and TMD (Hollins et al., 2009). Generalized sensory hypersensitivity has been associated with activation of a cortical network composed of the anterior cingulate, the insula, and the prefrontal cortex (Pujol et al., 2014). The function of this network is not unique to pain but appears to have the more general function of extracting salient sensory stimuli for subsequent higher-order neural processing (Iannetti & Mouraux, 2010; Schmidt-Wilcke et al., 2014). The means by which this network determines salience appears to be based upon the following factors: (1) stimulus novelty, (2) sharpness of the stimulus onset, (3) stimulus deviance, and (4) stimulus intensity in contrast to less relevant background stimuli (Legrain, Iannetti, Plaghki, & Mouraux, 2011).

While clinically it would be difficult to assess and document these cortical events using imaging techniques, there are methods from quantitative sensory testing (QST) and self-report inventories that can assist in documenting the presence of generalized sensory hypersensitivity in clinical settings.

Quantitative Sensory Testing (QST) assesses psychophysiological mechanisms thought to be associated with CS. Such mechanisms include sensitivity to non-painful stimuli (e.g., allodynia), generalized increased pain in response to previously painful stimuli (e.g., hyperalgesia), indices of centrally-mediated pain facilitation (e.g., temporal summation), and indices of centrally-mediated pathology in pain inhibitory mechanisms (e.g., conditioned pain modulation).

Allodynia refers to the experience of pain resulting from traditionally non-painful stimuli. For example, someone with CS might experience pain in response to a light stroke of a feather or brush. Often the standardized assessment of allodynia utilizes monofilaments or exposure to light brush strokes (Maracle et al., 2017). Many of the COPCs exhibit allodynia including fibromyalgia (Eken et al., 2017), TMD (Ernberg, Hedenberg-Magnusson, Alstergren, Lundeberg, & Kopp, 1999), migraine (Tietjen et al., 2009), and chronic fatigue (Yasui et al., 2014). In general, allodynia may be a by-product of the CS concept of “mental load” (Crettaz et al., 2013).

Hyperalgesia is typically assessed by identifying pain thresholds in individuals using standardized stimuli facilitated by pressure devices such as algometers, ischemic cuff algometry, or computerized mechanical testing devices such as the Multimodal Automated Sensory Testing (MAST) System [AMI, Ann Arbor, MI https://www.arbormedicalinnovations.com/] (Harte et al.; Harte et al.; Henry et al.; Schrepf et al.; Wasserman et al., 2015) - an automated QST platform. In patients presenting with a localized pain complaint, increased pain sensitivity at remote or unaffected body areas is strongly suggestive of central pain mechanisms and is a common feature of the COPCs (Berkley, Cason, Jacobs, Bradshaw, & Wood, 2001; Chaves et al., 2016; Janig, 2015; Jayaram et al., 2015; McAllister, McGinty, Resuehr, & Berkley, 2009; Scheich et al., 2017; Toriyama, Horiuchi, & Hongo, 2017).

Temporal Summation and its associated metric of windup, is a marker of CNS facilitation of pain perception. Technically, it is an increase in pain perception following repeated painful stimulation at a constant stimulus intensity. For example, a 256 mN pinprick stimulus can be applied once to the forearm or hand, followed by a train of 10 identical stimuli (1 Hz). Comparison of the original single pinprick stimuli with the ratings after repeated stimulation is used to calculate a wind-up ratio (WUR). A WUR >1 indicates temporal summation (Rolke et al., 2006). The presence of windup has long been proposed as a feature of central sensitization (Nijs et al., 2014; Woolf, 2011) and has been identified in many COPCs [e.g., FM (Price et al., 2002), including TMD (Maixner, Fillingim, Sigurdsson, Kincaid, & Silva, 1998), LBP (Tesarz, Eich, Treede, & Gerhardt, 2016), endometriosis (Napadow et al., 2012), and IBS (Zhou, Price, Callam, Woodruff, & Verne, 2011)].

QST may not be feasible in all clinical settings, so self-reported sensory hypersensitivity may also be used to document this phenomena. One such measure is the Sensory Hypersensitivity Scale (SHS)(Dixon et al., 2016). The SHS is a 25-item measure that assesses both general hypersensitivity as well as modality-specific sensitivity (e.g., touch taste, auditory). This instrument demonstrated modest associations with three modalities of QST (i.e., heat threshold and tolerance, and cold tolerance), and weaker relationships with psychiatric constructs such as depressive symptoms and anxiety in a mixed chronic pain and healthy sample. Individuals with FM scored higher on this measure than did individuals with low back pain, osteoarthritis or healthy controls, thus supporting its construct validity as a measure of sensory hypersensitivity (a component of CS).

Symptom Clusters

Patients and clinicians may perceive symptoms as arising independently when in fact, they may be interacting synergistically (Aktas, Walsh, & Rybicki, 2010). Such an observation has given rise to the study of symptom clusters (Miaskowski, Dodd, & Lee, 2004) A common symptom cluster observed within the context of primary care is composed of sleep disturbance, pain, anxiety, depression, and low energy/fatigue (SPADE) (Davis, Kroenke, Monahan, Kean, & Stump, 2016). In this study of 250 patients with musculoskeletal pain, only 9.6% were monosymptomatic while 20% of the sample had all 5 symptoms in the SPADE cluster. Clearly most of the sample was polysymptomatic. The study went on to demonstrate significant associations between the number of symptoms and greater

functional impairment within the domains of general health, physical and mental functioning, social functioning, and health-related disability.

A similar symptom cluster has attracted attention within the oncology literature. This cluster, composed of 3 of the SPADE elements, includes pain, sleep insufficiency, and fatigue. Being one of the most common combined symptom presentations, this cluster is similarly associated with poorer outcomes and poorer functional status in oncology patients (Dodd, Miaskowski, & Paul, 2001) and is thought to be associated with an underlying inflammatory mechanism (C. S. Cleeland et al., 2003).

Potentially related to the symptom cluster seen in oncology, “Sickness Behavior” is a construct translated from the animal literature describing a coordinated set of symptoms elicited by pro-inflammatory cytokines, tumor necrosis factor alpha, interleukin-6, and interleukin 1-beta (Shattuck & Muehlenbein, 2016). The effect in animals of such activation is to alter the normal homeostatic condition, so as to cause fever, lose appetite, and lose weight. It also causes symptoms similar to those defined above, including sleep disturbance, fatigue, altered affect, and increased pain sensitivity (Tizard, 2008). Early on, it was observed that sick animals tended to exhibit these symptoms, and as such, it was thought to represent weakness or illness. Later studies suggested that rather than being a by-product of illness, these symptoms might represent an adaptive physiological response designed to enhance the animal’s chances of recovery and survival. For example, increased pain sensitivity and fatigue could limit hunting and mating, thus conserving energy to fight infection or recover from injury. Studies in humans have identified the same sickness behavior symptom cluster with the addition of cognitive disturbances (e.g., memory) (Shattuck & Muehlenbein, 2016), again with the potential role of adaptive functioning to conserve resources.

Whether inflammation is required (as in the sickness behavior model) or not (as in the SPADE and some cancer examples), there is remarkable similarity in these symptom clusters suggestive of a common mechanism representing a state of “general unwellness.” A symptom cluster commonly identified in COPCs includes Sleep disturbance, Pain of a widespread distribution, Affective perturbation, Cognitive disturbance, and Energy deficit (fatigue). The acronym S.P.A.C.E. can be used to remember the elements of this cluster. S.P.A.C.E. is very similar to SPADE except that it adds the construct of cognitive difficulties given the importance of this symptom to human sickness behavior model. In a recent longitudinal study using environmental momentary assessment of dyscognition, pain, mood, and fatigue, a lagged relationship was identified amongst symptoms, suggesting that dyscognition may actually precede or trigger the rest of the symptom cluster (Kratz, Murphy, & Braley, 2017). These results underscore the importance of including cognitive problems in a symptom cluster for CS. Thus, the presence of S.P.A.C.E. may reflect a state of general unwellness. Perhaps this perturbed state is perceived as threatening and gives rise to the sensory hypervigilance described above. Clinically, S.P.A.C.E. can be assessed using a number of instruments which will be reviewed next.

Sleep—Disturbances in sleep are common in the context of chronic pain and can manifest as problems with falling asleep, staying asleep and early morning awakening. Brief

instruments for assessing sleep quality and disturbances can be obtained through the Patient Reported Outcomes Measurement Information System (PROMIS) administration and information website, AssessmentCenterTM. (Cella et al., 2010). Other measures of sleep disturbances that have been used in the assessment of COPCs include the Medical Outcomes Study (MOS) sleep scale (Allen, Kosinski, Hill-Zabala, & Calloway, 2009) and the Pittsburg Sleep Quality Index [PSQI; (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989)]. Sleep duration may not have to be disturbed to impact wellness. It is not uncommon for some patients to report getting a sufficient quantity of sleep only to experience that sleep as unrefreshing or non-restorative. Non-restorative sleep has been associated with reduced short-wave sleep and abnormal ?-rhythms, suggestive of wakefulness during non-REM (rapid eye movement) sleep (Choy, 2015). This latter from of sleep problem may be the more relevant in the context of COPCs and CS (Calhoun, Ford, Finkel, Kahn, & Mann, 2006; Choy, 2015; Tu, Heitkemper, Jarrett, & Buchanan, 2017). A measure that captures some of these non-restorative features of sleep is the PROMIS measure of sleep-related impairment (Yu et al., 2011).

Clinical Pain—The most common approach to assessing pain is through the use of visual analogue scales (VAS), numeric rating scales (NRS) or a “faces” approach (by choosing from a range of smiling and frowning faces) (Jensen & Karoly, 2011a). Pain intensity, however, is not unique to CS, and pain intensity alone may not differentiate individuals with COPCs from individuals with other forms of chronic pain. For example, in a study comparing pain characteristics of patients with fibromyalgia versus rheumatoid arthritis, pain intensity did not differ on a 0-100 VAS (i.e., 61 vs 59 respectively) (Leavitt, Katz, Golden, Glickman, & Layfer, 1986). Despite pain intensity failing to distinguish these conditions, other aspects of pain did appear distinguishing, such as the quality of pain, its distribution (e.g., how wide-spread it was), and its temporality (e.g., constant vs. intermittent). Thus in the context COPCs and CS, assessing these other aspects may be important (Spiegel et al., 2010). Perhaps most important for CS is the concept of widespread pain distribution, which is often captured using a body map. Many of the standardized pain assessment tools include a body map, along with measures of pain intensity, such as the Brief Pain Inventory [BPI; (C. Cleeland, 2009)] or qualitative descriptors such as the McGill Pain Questionnaire [MPQ; (Melzack, 1975)] and the painDETECT.(Freynhagen, Baron, Gockel, & Tolle, 2006a) In a study of over 400 individuals with urologic chronic pelvic pain syndrome (UCPPS), only 25% indicated pain on a body map as being localized to the pelvic region. In this study, 75% reported pain beyond the pelvic region, with 38% reporting pain in more than 3 sites simultaneously. Those with broader pain distributions demonstrated significantly poorer scores on the other elements of the SPACE symptom cluster (Lai et al., 2017). Similar findings have been reported in the context of TMD (Slade et al., 2013) and FM (Cassisi et al., 2014).

Affect—By definition, pain of all types is both a sensory phenomenon as well as an emotional one (IASP, 2015). This has been supported empirically using neuroimaging techniques, which show that chronic pain in particular is represented by cortical activations within emotional regions more so than in sensory regions (Apkarian, Bushnell, Treede, & Zubieta, 2005). The three emotions that are most commonly associated with chronic pain are

depressed mood, anxiety, and anger. These emotions are in turn associated with reduced pain thresholds, reduced pain tolerances, and increased reported pain intensity (Tang et al., 2008; van Middendorp, Lumley, Jacobs, Bijlsma, & Geenen, 2010; Wagner, Koschke, Leuf, Schlosser, & Bar, 2009). Depressed affect can be assessed using a variety of instruments including the Beck Depression Inventory-II (BDI-II; (Beck, Steer, Ball, & Ranieri, 1996; Beck, Steer, & Garbin, 1988), the Center for Epidemiological Studies Depression Scale [CESD, CESD-R; (Eaton, Muntaner, Smith, Tien, & Ybarra, 2004; Radloff, 1977)] or the Patient Health Questionnaire 9 (PHQ-9) (Kroenke, Spitzer, & Williams, 2001)). Two measures of anxiety include the State-Trait Anxiety Inventory [STAI; (Spielberger, Gorsuch, Lushene, & Vagg, 1983)] or the General Anxiety Disorder-7 [GAD-7; (Spitzer, Kroenke, Williams, & Lowe, 2006)]. Some measures, such as the Hospital Anxiety and Depression Scale [HADS; (Snaith, 2003)] assess both constructs. Scoring of these instruments can reveal either a probable diagnosis of an affective disorder or a continuous measure of negative affect. Other measures of negative affect (i.e., not diagnostic of disorders) include the PROMIS negative emotions scales (e.g., depressed affect, anxious affect, and anger) (Cella et al., 2010) and the Positive and Negative Affect Scale [PANAS; (Watson, Clark, & Tellegen, 1988)]. Currently more studies are needed to identify if there are unique affective characteristics that differentiate COPCs (and by implication CS) from other forms of chronic pain. As mentioned previously, the study of UCPPS patients demonstrated that greater wide-spreadedness of pain was associated with worse depressive and anxiety symptoms (as measured by the HADS) and worse mental health overall (as measured by the SF12) for both males and females (Lai et al., 2017).

Cognition—Perhaps one of the most under-assessed symptoms in the S.P.A.C.E. cluster is cognition. In an exercise to identify relevant assessment domains for fibromyalgia, the Outcome Measures in Rheumatology clinical Trials network (OMERACT) conducted two Delphi studies; one with providers and one with patients. While there was agreement between the groups as to the importance of including symptoms such as pain, fatigue, and sleep, the patients rated cognitive problems as being far more important than did clinicians (Arnold et al., 2008; Mease et al., 2008; Mease et al., 2005).

To assess perceived cognitive difficulties across several dimensions, the Multiple Ability Self-Report Questionnaire [MASQ; (Seidenberg, Haltiner, Taylor, Hermann, & Wyler, 1994)] has been used with FM samples (Williams & Arnold, 2011; Williams, Clauw, & Glass, 2011) and is able to capture perceived cognitive difficulties across language ability, visual-perceptual ability, verbal memory, visual memory, and attention/concentration. A second shorter measure, using items from the NIH PROMIS item banks is called the Multidimensional Inventory of Subjective Cognitive Impairment [MISCI; (Kratz, Schilling, Goesling, & Williams, 2015)]. This 10-item inventory, which provides indices for cognitive concerns in the areas of mental clarity, memory, attention/concentration, executive functioning, and language, is highly correlated ($r = 0.82$) with the lengthier MASQ, and was validated on a sample of FM patients.

Energy—Fatigue may be as concerning to patients as pain and has become a research priority in painful conditions, including IBS (Lackner, Gudleski, Dimuro, Keefer, &

Brenner, 2013), TMS (Robinson, Durham, & Newton, 2016), FM (Dailey, Keffala, & Sluka, 2015), and migraine (Lau, Lin, Chen, Wang, & Kao, 2015). The assessment of fatigue is challenging, given the need to distinguish qualitative aspects of the experience of fatigue; that is, to differentiate normal tiredness that might follow energy exertion from the more profound existential weariness that is described by individuals with COPCs (Humphrey et al., 2010). It can also be important to differentiate the experience of fatigue from the impact of fatigue (e.g., too fatigued to work, too fatigued to participate in activities of daily living etc.). One measure that nicely differentiates the experience of fatigue from its impact is the Multidimensional Fatigue Inventory (MFI; (Smets, Garssen, Bonke, & De Haes, 1995)). The latter instrument allows for the assessment of general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. PROMIS also offers brief assessments of fatigue experience and interference/impact (Cella et al., 2010). Based upon the PROMIS item-banks, a Fatigue Profile has been developed that was specifically validated with a group of individuals with FM (Kratz, Schilling, Goesling, & Williams, 2016).

Associated Domains of Assessment

Two additional domains of assessment that may have relevance to CS are perceived stress and early life trauma. Nijs et al. highlighted the importance of hypersensitivity of senses that are unrelated to the musculoskeletal system. Included in the list of drivers of hypersensitivity are stress and the concept of mental load (Nijs et al., 2014). When sensory stimuli ascend from the periphery, they must be evaluated by the current state of the CNS, which can include stress and negative aspects of mental load. Stress is a state-like phenomena with influences on pain perception and other elements of CS and can be assessed with measures such as the Perceived Stress Scale [PSS; (Cohen, Kamarck, & Mermelstein, 1983)]. More enduring stressful events, such as early life trauma, can influence affect and mental load in a trait-like manner. A variety of early life traumas (e.g., prolonged medical illness, loss of a parent, abuse etc.), and whether or not such traumatic events were disclosed to anyone, can be assessed using the Childhood and Recent Traumatic Events Scales [CTES/RTES; (Pennebaker & Susman, 1988)] as a contributor to mental load.

Existing and Future Measures of CS and COPCs

The Central Sensitization Inventory (CSI) (Neblett et al., 2013) was developed for the expressed purpose of assessing CS-related symptoms and has been mentioned frequently throughout this special issue. The CSI efficiently captures many of the domains covered in this article that are conceptually related to CS. For example, the CSI includes items associated with medical symptoms such as sleep problems, stress (mental load), pain, emotionality, concentration/memory, fatigue, and limited physical functioning. The CSI also includes items associated with general sensory hypersensitivity (e.g. sensitivity to bright lights and olfactory stimuli). The CSI is one assessment component of the clinical diagnostic algorithm by Nijs and colleagues, mentioned earlier in this article, for identifying CS-related pain (Nijs et al., 2014). While conceptually strong, future instruments may want to demonstrate stronger empirical relationships between self-reported items and QST, neuroimaging markers of CS, and S.P.A.C.E. Such a prospective measure [i.e., the Central Pain Index (CPI)] is currently in development [NIH/NIAMS funding (AR070600)].

The modified ACR 2010 diagnostic criteria for FM can also be used as a proxy for assessing CS or centrally augmented pain (Wolfe et al., 2016). When scored as a continuous measure rather than a dichotomous diagnosis, the Poly-Symptomatic Distress score (PSD) appears to capture important elements of CS. The PSD is composed of an index of wide-spread pain, and each of the other elements of the S.P.A.C.E. symptom cluster. One might predict that peripherally driven interventions (e.g., surgery) would be less successful in individuals where CS is driving the pain experience. Such a hypothesis is supported by several studies, were higher scores on the PSD scale were associated with greater need for opioids and poorer outcomes following knee and hip arthroplasty and hysterectomy (As-Sanie et al., 2017; Brummett et al., 2015; Janda et al., 2015).

Another way of assessing CS indirectly is by identifying the presence of COPCs. Until recently, there were no diagnostic tools that could capture the presence of all 10 COPCs using established diagnostic criteria. The NIH Pain Consortium has recently championed the development of such a tool using funding with the Office of Research on Women's Health, the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) and the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) research networks. This new instrument, the "COPC Screener", will be made publically available and will be able to serve as a standardized way of assessing individuals suspected of having conditions where CS is the suspected pathophysiologic mechanism.

Conclusion

Central Sensitization likely underlies how normal sensory or mild nociceptive stimuli can be amplified by the CNS to produce a profound and prolonged pain experience. Clinically COPCs are the best representations of conditions having CS as a primary mechanism. To comprehensively phenotype the facets of CS in a clinical sample, a combination of QST, to identify multi-sensory hypersensitivity, and patient-reported outcomes of the S.P.A.C.E. symptom cluster (i.e., "unwellness") can be used. (see Table 2) In addition, multi-component self-report instruments such as the CSI or FM diagnostic criteria are efficient clinical tools for indexing CS comprehensively.

Acknowledgments

AR070600 University of Michigan CORT (NIH/NIAMS)

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Table 1

Criteria for the Clinical Classification of Central Sensitization Pain (Nijs et al., 2014)

Step 1	Rule out Neuropathic Pain	• No history or identification of lesion or disease of the nervous system • Pain is not neuroanatomically logical • Pain is not described as burning, shooting or pricking.
Step 2	Rule out Nociceptive Pain	Pain will be disproportionate to the extent of injury or pathology
Step 3	At least one of the following *(if Steps 1-3 are positive then CSpresent)*	• Bilateral symmetrical pain pattern • Pain varying in anatomical location (i.e., traveling) or large neuroanatomically illogical distributions • Widespread pain in all four quadrants of the body • Allodynia/hyperalgesia outside the reported primary site of pain
Step 4	General hypersensitivity to sensory stimuli *(If Steps 1-2, & 4 are positive then CSpresent)*	Can include: mechanical pressure, odors, chemicals, cold, heat, electrical stimulation, light, sounds, weather, food, stress, emotions, mental load. Can be assessed as a score of >= 40 on the CSI.

Table 2

CS Domains and Sample Self-Reported Assessment Tools

Domain and Instruments	Purpose	Reference
Chronic Overlapping Pain Conditions	Diagnostic entities with CS being the suspected pathophysiological mechanism	
CMSI	Assesses a subset of the 10 COPCs	(Williams & Schilling, 2009)
COPCS	Assesses all 10 COPCS	(still in beta version as of this publication)
General Hypersensitivity		
SHS	Assesses general and specific sensory hypersensitivity	(Dixon et al., 2016)
S.P.A.C.E. Symptom Cluster		
MOS Sleep Scale	Sleep Problems	(Allen et al., 2009)
PSQI	Sleep Problems	(Buysse et al., 1989)
PROMIS Sleep Disturbance	Sleep Problems	(Yu et al., 2011)
PROMIS Sleep-related Impairment	Non-restorative sleep	(Yu et al., 2011)
VAS, NRS	Pain intensity	(Jensen & Karoly, 2011b)
MPQ	Pain Quality and intensity	(Melzack, 1987)
BPI	Pain distribution and intensity	(C. Cleeland, 2009)
PainDetect	Pain distribution, intensity quality: differentiate nociceptive from neuropathic	(Freynhagen, Baron, Gockel, & Tolle, 2006b)
BDI-II	Depressive symptomatology	(Beck et al., 1996)
CESD-R	Depressive symptomatology	(Eaton et al., 2004)
PHQ-9	Depressive symptomatology	(Kroenke et al., 2001)
STAI	Anxiety symptoms	(Spielberger et al., 1983)
GAD-7	Anxiety symptoms	(Spitzer et al., 2006)
HADS	Both anxiety and depressive symptoms	(Snaith, 2003)
PANAS	Positive and negative affect	(Watson et al., 1988)
PROMIS Negative Emotions	Negative emotions	(Cella et al., 2010)
MASQ	Perceived cognitive difficulties	(Seidenberg et al., 1994)
MISCI	Perceived cognitive difficulties	(Kratz et al., 2015)
MFI	Fatigue experience	(Smets et al., 1995)
PROMIS Fatigue	Fatigue experience and impact	(Cella et al., 2010)
Fatigue Profile	Fatigue experience and impact	(Kratz et al., 2016)
Supplemental Domains		
PSS	Perceived stress	(Cohen et al., 1983)
CTES/RTES	Early and recent trauma	(Pennebaker & Susman, 1988)
Comprehensive CS Instruments		
CSI	Multiple components of CS	(Neblett et al., 2013)
Modified FM Criteria	Multiple components of central pain	(Wolfe et al., 2016)

Note. Complex Medical Symptom Inventory (CMSI); Chronic Overlapping Pain Conditions Screener (COPCS); Sensory Hypersensitivity Scale (SHS); Medical Outcomes Survey Sleep Scale (MOS sleep Scale); Pittsburgh Sleep Quality Index (PSQI); PROMIS Sleep Disturbance Scale; PROMIS Sleep-related impairment scale; Visual Analogue Scale (VAS), Numeric Rating Scale (NRS); McGill Pain Questionnaire (MPQ); Brief

Pain Inventory (BPI); PainDetect; Beck Depression Scale-II (BDI-II); Center for Epidemiologic Studies Depression Scale (CESD-R); Patient Health Questionnaire 9-item Scale (PHQ-9); State Trait Anxiety Inventory (STAI); General Anxiety Disorder 7-item Scale (GAD-7); Hospital Anxiety and Depression Scale (HADS); Positive and Negative Affect Scale (PANAS); PROMIS Negative Emotions Scale; Multiple Abilities Symptom Questionnaire (MASQ); Multidimensional Inventory of Subjective Cognitive Impairment (MISCI); Multidimensional Fatigue Inventory (MFI); PROMIS Fatigue Scale; Fatigue Profile; Perceived Stress Scale (PSS); Childhood/Recent Traumatic Events Scale (CTES/RTES); Central Sensitization Index (CSI); Modified ACR2010 FM diagnostic Criteria.