THE CENTRAL SENSITIZATION INVENTORY (CSI): A USERS MANUAL

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ABSTRACT

The Central Sensitization Inventory was introduced in 2012. It was initially intended as a

screener to help identify when presenting symptoms may be related to central sensitization or

indicate the presence of a central sensitivity syndrome. It has now been translated and validated

in a number of European, Asian, and South American languages. This article provides an

overview of CSI rationale, development, recommended uses, and research results, including

evidence of validity and reliability, in clinical and non-clinical subject samples.

Central Sensitization

Central Sensitization (CS) refers to an amplification of neural signaling within the central nervous system, resulting in pain hypersensitivity (Woolf, 2011). Symptoms of CS include allodynia, hyperalgesia, expansion of the receptive field beyond the area of peripheral nerve supply, and prolonged pain after a stimulus has been removed (Latremoliere & Woolf 2009). A number of CS-related biological mechanisms have been identified, including dysregulation of ascending and descending tracks in the central nervous system (Ren & Dubmer, 2002; Yunus, 2007; Heinricher et al, 2009; van Wijk & Veldhuijzen, 2010; Kindler, et al 2011); over-activation of glial cells, resulting in the release of pro-inflammatory cytokines (Ji et al 2013; Loggia et al 2015; Nijs et al 2017); dysfunction of the stress system, including the hypothalamic-pituitary-adrenal axis (Van Houdenhove & Luyten 2009); decreased production of pain-inhibiting neurotransmitters, and increased production of pain-augmenting neurotransmitters, including excess production of brain-derived neurotropic factor (BDNF) (Phillips & Clauw 2011; Trang et al 2011; Deitos et al 2015; Nijs et al 2015-A; Caumo et al 2016).

CS has been most often identified with fibromyalgia, and associated chronic widespread pain and sensitivity, which often have no observable pathology or nocioceptive etiology. However, CS has also been identified in subsets of patients with clear evidence of tissue trauma, pathology, and/or nocioceptive component, including multiple sclerosis (Fernández-de-las-Peñas et al 2015), osteoarthritis (Lluch et al 2014; Akinci et al 2016), rheumatoid arthritis (Meeus et al 2012), and post-surgical breast cancer (Fernández-Lao et al 2011). Interestingly CS has also been tied to various other conditions in which pain is not a primary symptom, including post-traumatic stress disorder, multiple chemical sensitivity, restless leg syndrome, (Yunus, 2007; Yunus, 2015) over-active bladder (Reynolds et al 2016), and chronic hives (Torresani et al 2009), suggesting

that CS may not only be associated with pain hypersensitivity but could also involve hypersensitivity to other stimuli, including lights, sounds, fragrances, skin irritants, bodily sensations, and stress-evoking life events (Yunus 2007; Yunus, 2015; Nijs et al 2016).

Many studies have demonstrated that CS can be induced in human volunteers by activating nociceptors in a variety of ways, including electrical stimulation, capsaicin injections, mustard oil injections, acid, heat burn, UV burn, and hypertonic saline (Woolf, 2011). Subjective evidence for central-related pain hypersensitivity has been demonstrated by differences in self-reported pain severity ratings to heat, cold, electrical, and pressure stimuli between subjects with and without pain disorders (Yunus, 2007). Objective measures of CS, including brain imaging (Robinson et al 2011; Walitt et al, 2016), cortical excitability parameters assessed by transcranial magnetic stimulation (TMS), and levels of brain-derived neurotrophic factor (BDNF) (Deitos et al 2015; Caumo et al 2016) have demonstrated biological differences between control subjects and those with CS-related pain disorders.

The development of CS, and associated symptoms, is often related to trauma. CS is most often associated with physical trauma/injury (McBeth et al, 2003; Wenzel et al 2009; Myrtveit, et al, 2012), but can it also result from other types of trauma, such as certain infections (e.g. Hepatitius C, Epstien Barr, Lime Disease) and emotional trauma, including childhood abuse ((Yunus, 2008; Kindler et al 2010; Wilson, 2010; Häuser, et al 2011; Phillips & Clauw 2011; Spiegel et al 2015). Spinal injuries to the low back (Sanzarello et al, 2016; Bid et al, 2016-A) and neck (Van Oosterwijcket al 2013) appear to be especially susceptible to developing CS symptoms, including chronic widespread pain (McBeth et al 2003; Wenzel et al 2009; Kindler et al 2010; Myrtveit et al 2012) and fibromyalgia (Buskila et al 2011; Waylonis & Perkins 1994; Buskila et al 1997).

After CS develops, little or no nociceptive stimulus is necessary to perpetuate and sustain a state of hyperalgesia or allodynia. Painful sensations can occur in the absence of either peripheral pathology or noxious stimuli (Latremoliere & Woolf 2009). Because no apparent cause for pain can be identified (pain is no longer nociceptive in nature) physicians and other health care providers may have a tendency to interpret these patients as neurotics, malingerers, or somatizers (Yunus, 2012; Yunus, 2015).

Historical Background of the CSI

The development of the Central Sensitization Inventory (CSI) was initially inspired by articles from Muhammad Yunus (Yunus, 2007; Yunus, 2000) and then a later article from Lindsay Kinder (Kindler et al 2011). A very compelling argument was made that many pain-related syndromes, previously viewed as separate disorders, and often termed as "functional" or "medically unexplained," have a common etiology of central sensitization (CS). Yunus introduced the term Central Sensitivity Syndromes (CSSs) to describe these disorders (Yunus, 2000). Proposed members of the CSS family include fibromyalgia, irritable bowel syndrome, temporomandibular joint disorder, migraine and tension headache, myofacial pain syndrome, and some chronic pelvic pain disorders (e.g. interstitial cystitis, primary dysmenorrhea) (Yunus, 2007; Yunus, 2015; Kindler et al 2011; Phillips & Clauw 2011). Other types of disorders have also been in the CSS family, which all related to hypersensitivity, but which pain is not a primary component, including post-traumatic stress disorder, multiple chemical sensitivity, and restless leg syndrome (Yunus, 2007; Phillips & Clauw 2011). Though many of these conditions may appear unrelated, they all share a common theme of sensitivity to stimuli.

When investigating the supporting literature, one finds a striking over-lap in diagnoses among the CSS family, especially regarding fibromyalgia (Yunus, 2007; Woolf 2011; Phillips and

Clauw 2011). For instance, in a review of previous studies, Yunus (2012) reported that 13% to 52% of TMD patients, 10% to 40% of headache patients, and 20% to 65% of IBS patients also met criteria for fibromyalgia. A relatively large amount of co-morbid symptomology is also evident among various CSSs, including insomnia, feeling "unrefreshed" after sleeping, difficulty concentrating, bowel and bladder problems, and fatigue (Yunus, 2007; Yunus 2015). It was also clear that psychiatric disorders, emotional symptoms (including anxiety and depression), and trauma (including childhood abuse) are often associated with CSSs (Henningsen et al, 2003; Arnold et al, 2006; Phillips & Clauw 2011). It was within this framework that the Central Sensitization Inventory (CSI) was developed.

Development and Growth of the CSI

The CSI was originally designed as an instrument for screening patient symptomology, to help identify if symptoms may be related to CS or may indicate the presence of a CSS (Mayer et al 2012). It was recognized by our group that patient symptom presentations are often complex and distressing. When no clear pathology can be identified to explain symptoms, physicians and other health care workers may be inclined to either 1. dismiss the symptoms as a sign of mental illness/stress/somatization or 2. order expensive and invasive assessment procedures (e.g. imaging, colonoscopy, etc.) in an attempt to find a medical cause and eventual invasive treatments (e.g. surgery) in attempt to alleviate the symptoms. However, when symptoms are related to CS, or represent a CSS, the primary target for treatment should be the central nervous system, not the periphery (Latremoliere & Woolf 2009). For patients with a CS-related disorder, medical interventions targeted in the periphery are often unnecessary, unhelpful, and potentially harmful. The CSI was an attempt to provide a relatively quick means of identifying when

symptoms may be associated with CS/CSS so that additional diagnostic evaluation can be performed (to assess for CSS), and appropriate treatment can be initiated.

The items were developed based on an extensive literature search of overlapping somatic and emotional health-related symptom dimensions that have been found in previous studies to be associated with CS/CSSs. As a result, the CSI contains a very heterogeneous list of 25 items (widespread pain, sleep disturbance, cognitive slowing, digestive and urological problems, sensitivity to environmental stimuli, etc.). In Part A, one is asked how often he/she experiences each symptom ("never, rarely, sometimes, often, or always"). Individual items are scored from "0" (never) to "4" (always), resulting in a total score range for all 25 items from "0" to "100." It was recognized that it may be important to know if subjects were aware of previous CSS or related diagnoses, so a second section was developed. Part B asked if one has been previously diagnosed with seven common CSS diagnoses (tension headaches/migraines, fibromyalgia, irritable bowel syndrome, restless leg syndrome, temporomandibular joint disorder, chronic fatigue syndrome, and multiple chemical sensitivities) and three CS-related diagnoses (depression, anxiety/panic attacks, and neck injury). CSI B is for information only and is not scored.

At the time of this writing, the CSI had been translated, validated, and published in Dutch (Kregel et al, 2016), French (Pittance et al, 2016), Spanish (Cuesta-Vargas et al, 2016), Gujarati (Bid et al, 2016-B), Brazilian Portuguese (Caumo et al, 2016), Serbian (Knezevic et al 2017), and Japanese (Tanaka et al 2017). The author of the present article has also been in communication with other groups who are in the process of translating and validating the CSI in Italian, Turkish, German, Korean, Nepali, Russian, and Tatar (personal communications). The

English version of the CSI can be found in the appendix. Multiple-language versions of the CSI, with supporting references, can be found at www.pridedallas.com/questionnaires.

Psychometric Reliability of the CSI

The CSI has been found to be psychometrically sound in all published studies to the present. The original English version of the CSI demonstrated good test-retest reliability and internal consistency (Pearson's r = .82; Cronbach's alpha= .88, respectively) (Mayer et al 2012). Similar results have been found in the other published translated versions, (Tanaka et al 2017; Knezevic et al 2017; Kregel et al, 2016; Pittance et al, 2016; Cuesta-Vargas et al, 2016; Bid et al, 2016-B; Caumo et al, 2017), with test-retest from .85 to 0.971 and Cronbach's alpha from 0.88 to 0.914.

Factor Structure of the CSI

Factor analyses from individual different published versions of the CSI have produced some similar but conflicting results. The original English CSI (Mayer et al 2012) determined a 4-factor structure: 1. *Physical Symptoms*, 2. *Emotional Distress*, 3. *Headache/Jaw Symptoms*, and 4. *Urological Symptoms*. Three items that did not load on any of the factors. A confirmatory factor analysis (CFA) of the French version confirmed the same 4-factor structure, with the same 3 items that did not load on any of the factors (Pitance et al 2016). A CFA of the Dutch version resulted in a similar 4-factor structure, but the item pool for each factor was somewhat different than the English version, and 5 items did not load on any of the factors (Kruegel et al 2016). CFA of the Brazilian Portuguese version also determined a 4-factor solution, but with a somewhat different item pool and 1 item that did not load on any of the factors (Caumo et al 2017). CFA of the Serbian version confirmed the 4-factor solution, with all items retained, and determined the presence of a single second-order general factor (Knezevic et al 2017).

Exploratory analysis of the Japanese version determined a 5-factor model (Tanaka et al 2017). A principal component analysis with Maximum Likelihood Extraction (MLE) determined a 1-factor solution in the Spanish version (Cuesta-Vargas et al 2016). To help resolve these factor structure discrepancies, a large multi-country study was performed with a coalition of research groups from The Netherlands, Spain, France, Italy, Serbia, Brazil, and the U.S (Cuesta-Vargas et al 2017). CSI data from approximately 1,987 subjects were pooled into a single database for analysis. A bi-factor solution was determined Rodriguez et al 2016). The results confirmed the same four orthogonal factors found in previous studies but found that the reliability of the four factors was too low to be recommended for subscales. CSI items in each of the 4 factors were: Physical Symptoms (1, 2, 5, 6, 8, 9, 12, 14, 17, 18, 22), Emotional Distress (3, 13, 15, 16, 23, 24), Headache/Jaw Symptoms (4, 7, 10, 19, 20), and Urological Symptoms (11, 21, 25). One general factor, representing "*CS-Related Symptoms*," showed substantial reliability [i.e. Cronbach $\alpha= 0.92$; Omega $\omega= 0.95$; and omega hierarchical $\omega\text{-h}= 0.89$]. The results of this study suggest that only total CSI scores should be used and reported. However, for individual clinical purposes, a review of individual item scores may be beneficial for better understanding the patient's symptom presentation.

Interpreting CSI Scores

A score of 40 or higher has been recommended as a reasonable cutoff to alert health care professionals that a patient's symptom presentation may indicate the presence of CS/CSS. This 40-point cut-off was determined based on its ability to discriminate between CSS and non-patient subjects. Sensitivity (81%) was good in correctly identifying CSS patients, and specificity (75%) was adequate in correctly identifying non-patient comparison subjects (Neblett et al, 2013). A separate study with the French CSI found even better sensitivity (95%) and specificity

(90%) with distinguishing between fibromyalgia subjects and acute ankle pain and control subjects. This 40-point cut-off score has been recommended as one component of an algorithm for helping to identify CS-related pain (vs. neuropathic and nocioceptive pain) in generalized chronic pain (Nijs et al, 2014-A; Nijs et al, 2014-B) and low back pain subjects (Nijs et al, 2015), and for classifying of temporomandibular joint disorder subtypes (Monaco et al 2017). Most recently, five severity levels have been developed to help aid in the clinical interpretation of the CSI [subclinical = 0-29; mild = 30-39; moderate = 40-49; severe = 50-59; and extreme = 60-100] (Neblett et al, 2017).

The 40-point cut-off has shown promise in some studies with other clinical populations (Kim et al, 2015; Bennett et al 2017). Some groups, however, have found different cutoff scores to more accurately identify significant levels of CS-related symptomology for specific populations, such as migraine subjects (Aguila, et al, 2016). Further validation of severity level scores in different subject populations are needed to verify their clinical usefulness. Preliminary analyses of the 5 severity levels, however, has been positive. In 3 separate studies, different chronic pain populations were placed in severity groups based on CSI scores. Mean scores for each severity group were significantly different than all the other severity groups, demonstrated good score discrimination (Knesvic et al 2016; Neblett et al 2017-A; Neblett et al 2017-B). Perhaps these severity cutoffs can be a useful guide for clinicians and researchers in the clinical interpretation of CSI scores for other clinical populations. It is possible, however that alternative severity level cutoffs may be found to be more useful in different language versions of the CSI or with different subject populations (van Wilgen et al 2018)

Validity of the CSI

Despite its name, the CSI does not measure CS. No self-report instrument can do that. But there is growing evidence that CSI scores are associated with CS-related symptoms and diagnoses. A recent systematic review identified 14 CSI studies, which were determined to have good-to-excellent quality of evidence. The authors concluded that the CSI generates reliable and valid data to quantify the severity of CS-related symptoms (Scerbo et al 2017).

Evidence of Convergent Validity

Strong correlations have been found among total CSI scores and other validated self-report measures of pain intensity, depressive symptoms, anxiety symptoms, sleep disturbance, pain catastrophizing, and perceived disability/pain interference/quality of life, all of which have been associated with CS/CSS (Huysmans et al 2018; Kregel et al 2017: Caumo et al 2017; Tanaka et al 2017; Knezevic et al 2017; Neblett et al, 2017-A; Neblett et al, 2017-B; Neblett et al, 2013).

CSI scores have been shown to be associated with CS-related pain symptoms. Higher CSI scores were associated with wider body area distribution of self-reported pain, and lower pain thresholds in the knee, in a group of osteoarthritis patients who were scheduled to undergo primary total knee arthroplasty (Lluch Girbés, et al, 2016); increased widespread pain sensitivity in a group of shoulder patients who were undergoing quantitative sensory testing (QST) (Coronado et al 2016); longer pain duration, higher pain intensity, and more widespread pain pattern in a general chronic pain population (Van Wilgen et al 2017); and higher pain intensity and pain behavior (as assessed with a 1-minute stair-climbing test) in a group of subjects with chronic nonspecific low back pain (Huysmans et al 2018).

Additional evidence has been demonstrated by associations among CSI scores and known risk factors of CS. Higher CSI scores were associated with longer length of pre-admission disability, more pre-admission surgeries, greater number of injured body parts, childhood abuse history, and a major depressive disorder diagnosis in a group of chronic spinal disorder patients in functional restoration treatment (Neblett et al 2017-B).

Finally, positive correlations have been found among CSI scores and objective biological markers of CS. CSI scores were associated with higher levels of serum brain-derived neurotrophic factor (BDNF) in fibromyalgia, myofascial pain, and osteoarthritis knee patients, compared to pain-free control subjects (Caumo et al 2017). The same study also identified that higher CSI scores were associated with dysfunction of the descending pain-modulatory system, as measured quantitative sensory testing (QST). CSI scores were associated with brain gammaaminobutyric acid (GABA) levels in migraine subjects (Aguila, et al, 2016). Further analysis, using a Receive Operator Curve (ROC) analysis, indicated that subjects with CSI scores $\geq$ 22.5 were nearly 5 times more likely to have migraine than those with lower scores. However, a separate study with chronic spinal pain subjects found a significant, but weak correlation between the CSI and pain pressure thresholds, and no significant correlation with a conditioned pain modulation test (Kregel et al 2017).

Evidence of Discriminant Validity

Total CSI scores have been shown to discriminate between subjects with general chronic musculoskeletal pain and pain-free controls (Kregel, 2016); between subjects with fibromyalgia and both acute ankle sprain and pain-free controls (Pittance, 2016); among patients with fibromyalgia/chronic widespread pain subjects, regional chronic low back pain, and non-patient university students and faculty (Mayer et al 2012); between subjects with interstitial cystitis, overactive bladder, and healthy controls (McKernan et al 2017); and between subjects with, and without, a diagnosed CSS (Knezevic et al 2017; Caumo et al 2017; Neblett et al, 2017-A; Neblett et al, 2013).

Self-reported CSS diagnoses on CSI part B have also been found to correlate with physician-diagnosed CSSs and total CSI scores. Several studies have shown that CSI scores rise as the number of self-reported CSS diagnoses increases (Neblett et al 2013; Neblett et al 2015; Neblett et al 2017-A; Caumo et al 2017). In one study, the percentage of chronic spinal pain disorder

patients who reported a comorbid CSS diagnosis increased in a stair-step pattern, from 11% in a subclinical CSI severity group to 56% in an extreme CSI severity group. Agreement between physician-diagnosed CSSs and self-reported CSS, in a group of general chronic pain subjects, was relatively high with fibromyalgia, headache, irritable bowel syndrome and moderate with restless leg syndrome and temporomandibular joint disorder (Neblett et al 2013).

Evidence of Predictive Validity

Higher CSI scores (above the proposed 40-point cutoff), obtained before participating in knee arthroplasty, predicted higher dosages of post-surgical analgesics and more severe post-surgical pain intensity ratings (Kim et al, 2015). CSI scores above 40 were the strongest predictive variable, of all those studied, for persistent pain 3 months after surgery, with an odds ratio of 5.091. In a separate study of spinal fusion surgery subjects, higher pre-surgical CSI scores (above 40) predicted worse post-surgical self-reported disability, depressive symptoms, and quality of life, and a longer post-surgical hospital stay (Bennett et al 2017). In fact, for each 10-point score increase above 40, the average length of stay increased by 6.4%.

Treatment Responsiveness of the CSI

Though it was originally designed as a symptom screener, there is some recent evidence that the CSI may be an effective treatment outcome measure. CSI scores decreased following five sessions (over two months) of a conventional physiotherapy program and a McKenzie exercise program in two groups of chronic non-specific low back pain subjects (Bid et al 2017). Results were significantly better in the McKenzie program. CSI scores, and other associated self-reported symptoms (pain intensity, pain-related anxiety, sleep disturbance, perceived disability depressive symptoms, and somatization symptoms) improved in a group of chronic spinal

disorder patients who completed a functional restoration treatment program (Neblett et al 2017-B). An as-yet unpublished report found similar decreases in CSI scores, and other associated symptoms, in a group general chronic pain subjects who completed a separate functional restoration program (Jimenez et al 2017).

Clinical Use of the CSI

As stated previously, the CSI was originally intended as a screener. It can be included in an initial patient evaluation, along with a review of symptoms, medical evaluation, medical history, mental health evaluation, and other relevant self-report questionnaires. It may be especially useful for patients who present with pain, or other physical symptoms, of unknown origin.

Some clinical indications of CS include pain levels that are disproportionate to the extent of injury, a neuroanotomically illogical pain pattern, and hypersensitivity of senses unrelated to the musculoskeletal system (Nijs et al 2016). So, low CSI scores (along with no clinical evidence of CS) suggest that additional medical tests may be warranted to evaluate the cause of the symptoms. High CSI scores, and clinical evidence of CS, suggest that the patient should be first evaluated for a CSS and/or CS involvement before additional medical tests are ordered. Detailed guidelines are available (with CSI scores as one component) for identifying when pain is likely related to CS (Nijs et al 2016; Nijs et al 2014-A). Also, established criteria for diagnosing individual CSSs, such as fibromyalgia (Wolfe & Häuser 2011; Wolfe et al 2016), are readily available.

Treatment of CSSs and/or CS-related often pain requires a different approach than for nocioceptive pain (Latremoliere & Woolf 2009). A number of studies have demonstrated that that tricyclic compounds, serotoninnorepinephrine re-uptake inhibitors (such as duloxetine and

tramadol), and alpha-2-delta ligands (such as pregabalin and gabapentin) are efficacious for CS-related pain disorders and a variety of other related CSSs (Phillips & Clauw 2011). In addition to medication, a biopsychosocial combination of difference desensitizing strategies (e.g. pain neuroscience education, exercise therapy, and cognitive behavioral therapy) has been recommended over monotherapies (Nijs et al 2014-B). In fact, an interdisciplinary treatment approach may be the best option for treating CS-related symptoms of chronic pain (Adams & Turk 2015; Nijs et al 2015; Gatchel & Okifuji 2006).

Conclusion

The CSI was just published in 2012 (Mayer et al 2012). It is still in its infancy. Despite its recent development, it has received quite a bit of international attention and is now available in a number of separate languages. It is anticipated that the number of translations will continue to grow, allowing the CSI to be used and studied in a wide variety of cultures and subject samples. Its positive psychometric properties and varied and substantial evidence of reliability and validity suggest that the CSI has a promising future for clinical and research use.

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