Establishing central sensitization-related symptom severity subgroups: A multicountry study of chronic pain and healthy subjects using the Central Sensitization Inventory (CSI)

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Abstract (up to 250 words)

The main goal of this study was to identify central sensitization-related symptoms subgroups in a large sample of patients having chronic pain using the Central Sensitization Inventory (CSI). A large, pooled international (n=8 countries) sample of chronic pain patients and healthy subjects (n= 2,620) was randomly divided into two subsamples for cross-validation purposes. First, a hierarchical cluster analysis was performed using CSI item-level data as clustering variables (test sample; n= 1,312). Second, a latent profile analysis was conducted to confirm the optimal number of CSI clusters (validation sample; n= 1,308). Finally, to promote the implementation in real-world clinical practice, we built a free online CSI cluster calculator.

Keywords: Central Sensitization Inventory; central sensitization; central sensitivity syndrome, chronic pain, hierarchical cluster analysis; latent profile analysis

INTRODUCTION

Patient-reported outcome measures (PROMs) are frequently used in research and clinical practice to assess health-related outcome domains (e.g. pain intensity, physical functioning, depressive or anxiety symptoms, etc.). A total PROM score can indicate a higher or lower level or severity of the target domain(s). Some PROMs also provide subscale scores for different sub-domains, often based on factor analyses. The quality of a PROM is dependent on its psychometric properties (i.e. validity, reliability and responsiveness). However, even PROMs with very good psychometrics have limited usefulness without values that can provide meaning and interpretation to an instrument's score, especially when they are used in clinical settings (Field et al., 2019; Holmes et al., 2017). For example, what scores can indicate that a patient likely meets criteria for a specific diagnoses or disease process? When comparing between-group differences, what scores can suggest that a symptom domain in one group is more severe than in another? When assessing clinical changes over time, or responsiveness to treatment, how much score change can be considered clinically meaningful?

Some PROMS offer cut-off scores, indicating that a patient is more or less likely to reach a clinical meaningfulness threshold or meet some type of symptom criteria for a specific disease or symptom domain. Cut-off scores are usually determined by comparing two groups of subjects (one positive and one negative for a specific disease), using receiver operating characteristic analyses. Use of minimal important change (MIC) to interpret score changes has been proposed for some PROMs, suggesting that a symptom improvement or worsening is clinically important. However, the use of MICs has been criticized due to methodological limitations in determining them and problems with generalizing the results across different patient populations (Gatchel, Lurie, & Mayer, 2010; Sedaghat, 2019). Especially in clinical settings, severity ranges are most useful for aiding clinical interpretation and assessing treatment responsiveness.

There is no gold standard methodological guideline for determining severity ranges for a PROM, but two general methods are frequently used: mean profiles analyses and cluster analyses. A mean profiles analysis determines severity level score cut-off scores from the total score distribution of a target subject sample. A cluster analysis assesses patterns from each individual PROM item response to form patient subgroups. Cluster analyses classify subjects into the fewest number of groups that explain the most variance (Meece & Holt, 1993). The goal is for individuals within each subgroup to be as similar as possible to others within their group (creating high within-group homogeneity) and as different as possible to those in other groups (creating low between-group homogeneity) (Clatworthy et al., 2005).

The CSI is a 25-item measure, with a score range of 0 to 100, designed to evaluate symptoms related to central sensitization (CS) and central sensitivity syndromes (CSS) (Neblett, 2018). Central sensitization (CS) refers to hypersensitivity and enhancement of pain sensations in the central nervous system (Woolf, 2011), and CSSs are disorders for which CS is thought to

be a common etiology (e.g. fibromyalgia, irritable bowel syndrome, migraine, temporomandibular disorder, etc.) (Yunus, 2007). The CSI has been translated in multiple languages (available at www.pridedallas/questionnaires) and has been found to be psychometrically sound in all published studies to date, with intraclass correlation coefficients for test-retest reliability ranging from 0.85 to 0.97, and total score Cronbach's α values from 0.88 to 0.91 (Scerbo, Colasurdo et al. 2018). Evidence of validity (including convergent, discriminant, and predictive) has been demonstrated with both patient-reported and objective variables (including quantitative sensory testing, brain gamma aminobutyric acid levels, serum brain-derived neurotrophic factor) (Neblett, 2018). Moreover, a comprehensive factor analysis, with pooled multi-country subject data determined that one general factor, representing "CS-Related Symptoms," showed substantial reliability and unidimensionality (Cronbach α = 0.92; Omega ω = 0.95; and omega hierarchical ω-h = 0.89) (Cuesta-Vargas et al., 2018). A cutoff score of 40 has been recommended for alerting health care professionals that a patient's symptom presentation may be related to CS and/or indicate the presence of a CSS (Neblett et al., 2013; Nijs et al., 2014). Severity levels (from subclinical to extreme), which were previously determined with a mean profile analysis, have also been proposed for clinical interpretation (Neblett et al., 2017).

Since the seminal work by Bradley et al (1978) who identified chronic pain subgroups by administering the Minnesota Multiphasic Personality Inventory (MMPI; Hathaway & McKinley, 1943), several researchers have attempted to establish chronic pain subgroups by means of cluster analyses of clinical features (Table 1). The goal of this study was to determine CS-related symptom severity subgroups for the CSI and to develop a free online CSI cluster calculator, which we hope will provide additional aid to clinical interpretation of CSI scores. To determine the severity subgroups, CSI data from a large international sample of chronic pain patients and healthy subjects was pooled for a hierarchical cluster analysis and latent profile analysis.

Insert Table 1

METHODS

Participants

CSI item-level data from 2,620 subjects, recruited in eight countries, were pooled into a single database. All participants agreed to participate by signing an informed consent. Each single study obtained an Institutional Review Board (IRB) approval. As detailed elsewhere (Cuesta-Vargas et al., 2018), because data collection in The Netherlands was performed during routine physical therapy sessions, IRB approval is exempted under Dutch law. Nevertheless, all Dutch participants agreed to include their CSI data in this study and signed a written informed consent. Approval for data collection in Belgium was granted by the medical ethical committee of the University Hospital Ghent. Approval for data collection in France was granted by the IRB

at Comité d'Ethique Hospitalo-Facultaire, Cliniques Universitaires Saint-Luc. Approval for data collection in Brazil was granted by the local ethics committee at Postgraduate Research Group at Hospital de Clínicas de Porto Alegre. Approval for data collection in Serbia was granted by the Ethical Board of Clinical Centre of Vojvodina. Approval for data collection in Italy was granted by the Internal Ethical Board of the Department of Internal Medicine at the University of Genova. Approval for data collection in Spain was granted by the Tribunal of Review of Human Subjects at the University of Malaga. Approval for data collection in Japan was granted by the Institutional Ethics Committee of Konan Women's University in Kōbe. Data in the U.S. sample were collected as part of each patient's standard medical files, with Health Insurance Portability and Accountability Act (HIPAA) protection of de-identified data. Therefore, the study was granted exemption status by the IRB at the University of Texas at Arlington.

Table 2 shows the main characteristics of the eight samples. Most participants were suffering chronic pain conditions, with heterogeneous diagnoses. To augment the variability of the pooled sample, non-clinical participants (n= 192) were also included because clinical samples score higher on the CSI, whereas pain-free individuals score lower (Neblett, 2018). Including both types of samples provided the widest possible distribution of CSI scores in the pooled sample for the clustering analyses. As described elsewhere (Cuesta-Vargas, et al., 2018), different recruitment methods were used in each study, as shown in Table 3. Most subjects had been study participants in published CSI validation manuscripts (see Table 2). Some additional subjects were included in the Dutch, Japanese and English samples.

Insert Table 2

Central Sensitization Inventory (CSI)

The CSI (Mayer et al., 2012) has two separate sections. Part A of the CSI includes 25 items that evaluate somatic and emotional health-related symptoms that are common in CS-related disorders. Each item is scored on a 5-point scale with the end points (0) "never" and (4) "always", resulting in a total possible score of 100. Higher scores indicate a higher degree of self-reported symptomatology. Part B assesses 7 CS-related conditions (tension headaches/migraines, fibromyalgia, irritable bowel syndrome, restless leg syndrome, temporomandibular joint disorder, chronic fatigue syndrome, and multiple chemical sensitivities), and three related diagnoses (depression, anxiety/panic attacks, and neck injury). Respondents are asked: 1) if they have previously been diagnosed by a doctor with each of the conditions; and 2) what year they were diagnosed. Only Part A was used for the present study. The English version of the CSI is provided as supplementary material.

Statistical analyses

We pooled data across the eight studies and the overall sample (n= 2,620) was then randomly divided into two subsamples to: 1) explore the optimal number of clusters (test

sample; n= 1,312), and 2) to validate the identified cluster solution (validation sample; n= 1,308). SPSS v22.0 was used to compute the analyses.

First, in order to identify homogeneous subtypes of patients based on their CSI responses, we conducted an exploratory hierarchical cluster analysis using the Ward's linkage method to form clusters at each stage, with squared Euclidean distances included in the proximities matrix. As a first step, all CSI scores were standardized (z-scores). Agglomeration coefficients were examined and plotted to identify the cluster solution that best represented the data. The percentage change between adjacent cluster solutions and plot characteristics were taken into account. The dendrogram, which represents the relationships of similarity among the group of clusters, was also visually inspected to decide the number of clusters.

Second, to confirm the optimal number of clusters in our validation sample, LPAs were conducted using maximum likelihood estimation with robust standard errors in Mplus v7.4. The main aim of LPA is to categorize patients from a heterogeneous population into smaller, more homogenous subgroups (latent classes) using continuous variables (Muthén, 2002). LPA can be distinguished from classical cluster analysis, which has frequently been used in previous research on chronic pain subtypes, in that it treats the type variable as "latent" and therefore takes measurement error into account. To ensure all participants were included in the LPA, the variance of any variable with missing data was estimated as part of the model, assuming that data were missing at random. For parsimony reasons, latent profile models containing 1 to a maximum of 5 profiles were fit to the data. The best fitting model was determined by the *sample size-adjusted Bayesian Information Criterion* (sBIC), with lower values on this fit statistic indicating a better model fit. Additionally, we used the *Lo-Mendell-Rubin likelihood ratio test* (LMR-LRT) and the *bootstrap likelihood ratio test* (BLRT) to compare the fit between neighboring class models. If the LMR-LRT and BLRT p-values are significant, it suggests that a k profile model fits better than a k-1 profile model. Entropy values (which can range from 0 to 1) are also a measures of classification accuracy (higher probability values for each group indicate better classification). There is no established cut-off value for deciding whether an entropy value is adequate, but values greater than 0.80 are considered to indicate adequate classification quality. Finally, models were also evaluated in terms of interpretability to decide whether the classes represented different categories of patients. For example, small classes (i.e., $\leq$ 5% of the sample) are usually considered spurious, so the number of participants categorized into each class was considered important (Hipp & Bauer, 2006). Latent profile models were also computed in the whole sample. However, model comparisons by study sample were not computed due to non-identification of the models in Mplus.

Finally, we computed an ordinal regression analysis (Harrell, 2001), using the CSI items as independent variables and the final cluster categories as the dependent variables, to create a cluster calculator. It was our intention to make this calculator freely available online for clinical and research use. Using centroids for each CSI item response, the cluster calculator takes the

sum of Euclidian distances between the item values (0-4) and their corresponding centroids. Subsequently, the calculator selects which cluster has a lower value for this sum and assigns it to the subject. To determine the level of agreement between the original cluster assignments and the calculator's derived cluster assignments, a kappa coefficient was calculated using the same sample to estimate the accord (intra-class correlation).

RESULTS

Hierarchical cluster analysis

The dendrogram indicated that participants could be homogeneously separated into three well-defined clusters with different levels of central sensitization symptom severity, accounting for 30.7%, 34.8% and 34.5% of the test sample (n= 1,219 valid cases), respectively. The pairwise comparisons showed statistically significant differences among each cluster group, demonstrating that each group was clearly distinguished from the other two groups. Clusters were labelled as follows: (i) *Mild CS-Related Symptoms*, (ii) *Moderate CS-Related Symptoms*, and (iii) *Severe CS-Related Symptoms*. In contrast, a 4-cluster solution showed overlapping CSI clusters. Figure 1 displays the distribution of the CSI items' mean score for the 3- and 4-cluster solution.

Insert Figure 1

Latent profile analysis

Table 4 shows model fit statistics for the 2, 3, 4 and 5-profile solutions that were evaluated. Entropy values (all > .80) suggested that participants were overall well classified in all class solutions in the validation sample (n= 1,245 valid cases). The BIC and ABIC values as well the BLRT *p*-values suggested the superiority of the 5-class model. In contrast, the LMR-LRT *p*-values suggested that the 5-class model did not provide further improvement compared to a 4-class model. The profile plot of the 5-class solution showed overlapping CSI profiles whereas the profile plot of the 4-class solution showed non-ordered CSI profiles. Among profile solutions with comparable model fit and entropy values, as found in the present study, preference is usually given to the most parsimonious and theoretically interpretable solution. On the basis of the tests of statistical significance, profile sizes, and visual inspection of profile plots (see Figure 2), the 3-profile solution was preferred. Good discrimination between profiles was revealed, with the average latent class probabilities for most likely latent class membership being high (class 1 = .958; class 2 =.941; class 3 = .965). In total, 37.5% of patients were classified into class 1, 37.9% into class 2, 24.6% into class 3. Results reported above were replicated in the total sample (n= 2,479 valid cases), providing support for the three cluster profiles (Mild, Moderate, and Severe CS-related symptoms).

Insert Table 3

Insert Figure 2

Cluster calculator

The kappa coefficient analysis indicated a substantial level of agreement between the original cluster assignments and the cluster calculator's derived cluster assignments (*k*= .82). To promote the use of the 3 CSI CS-related symptom severity clusters among clinicians and researchers, a free cluster calculator can be found at https://www.pridedallas.com/questionnaires or by clicking on the following link:

DISCUSSION

The present study pooled CSI data from a large international sample of chronic pain and healthy subjects (n= 2,260) from 8 countries for a hierarchical cluster analysis and a latent profile analysis to determine CS-related symptom severity subgroups. This led to the identification of a three-cluster solution, with mild, moderate and severe CS-related symptoms as cluster labels. This 3-cluster solution was chosen based on the statistical significance, profile sizes, and visual inspection of profile plots (Table 3, Figure 1). Good discrimination between profiles was revealed, with 37.5% of subjects classified into the mild severity class, 37.9% into the moderate severity class, and 24.6% into the severe severity class. Importantly, these findings were replicated in the total sample (n= 2,479 valid cases), which confirmed the three profiles (Figure 2?).

Potentially every single person experiencing pain can develop CS, but only a minority will. CS appears to be a continuum of altered nociceptive processing mechanisms, in which more profound central nervous system changes lead to a greater number and severity of CS-related symptoms. CS predicts poor outcomes in patients with many painful disorders, including tennis elbow (Coombes, et al., 2015), chronic pain following whiplash injury (Sterling et al., 2006), low back pain (Aguilar Ferrandiz et al., 2016), and osteoarthritis (Kim et al., 2015). This includes poor outcome following physiotherapy and rehabilitation (Aguilar-Ferrandiz et al., 2016; Jull et al., 2007) and surgical interventions (Bennett, et al., 2017; Gwilym et al., 2011; Yarnitsky et al., 2008). It is important to recognize signs of CS when evaluating patients in clinical practice so the most appropriate and effective treatments can be provided. The typical profile of a patient with CS includes severe pain, disproportionate to what one expects based on the available tissue damage or presumed source of nociception, together with spreading pain and additional cognitive, emotional and somatic symptoms related to CS (Nijs et al., 2014). The combination and severity of symptoms associated with CS can be easily assessed with the CSI. The present study provides added value above what was previously known about how to interpret CSI total scores.

The CSI is a psychometrically sound PROM that has shown adequate fit to a unidimensional model in a similar large international sample (ref). It has gained popularity among researchers and clinicians, in part because of it is easy to use, requires little burden for patients for completion, and takes little time for clinicians to score. CSI items are believed to reflect symptoms of CS in patients having chronic pain. However, the content validity of the

CSI cannot be directly verified. Evidence supporting the idea that the symptoms included in the CSI are the result of CS in patients with chronic pain is limited, due to the lack of a gold standard measure of CS. In many people with chronic non-specific pain, CS can explain why they suffer from pain in the absence of a clear origin of nociceptive input, or in the absence of enough tissue damage to explain the experienced pain severity, disability and other symptoms. CS encompasses various related dysfunctions within the central nervous system, all contributing to increased responsiveness to a variety of stimuli like mechanical pressure, chemical substances, light, sound, cold, heat, stress and electricity. This makes it plausible to interpret many of the symptoms included in the CSI as symptoms reflecting CS. Still, research examining this assumption is needed.

Up to now, recommendations for clinical interpretation of CSI scores have included the validated cut-off score of 40/100 (Neblett et al., 2013; Nijs et al., 2014), as an indication that a patient's symptom presentation may indicate the presence of CS, and mean profile analysis-derived severity levels (from subclinical to extreme) (Neblett et al., 2017). Compared to a mean profile analysis, the CSI cluster analyses in present work can be considered a more sophisticated and valid method for determining CS-related symptom severity levels. The 3-cluster result determined in the present study adds substantially to the ability of clinicians and researchers to interpret CSI scores. To promote the use of this 3-cluster distribution among clinicians and researchers, a cluster calculator was constructed and has been made available online. This free online calculator provides accessible support to clinicians around the globe for the clinical interpretation of CSI scores obtained from patients having chronic pain.

This work has strengths and limitations. Its main strengths include the large sample size, the multi-cultural nature of the analyzed data (with patients from 8 countries represented), and the well-established statistical approach to identify clusters (ref?). However, further research on the mild, moderate, and severed CSI CS-related symptom clusters will be needed to verify their usefulness in clinical and research settings. For instance, the CSI clusters identified in this study can be assessed in future longitudinal studies to evaluate their prognostic value, or in future randomized clinical trials to evaluate heterogeneity of treatment effects in the diverse clusters.

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Table Legends

Table 1. Subgroups of chronic pain patients by clinical features (1978-2018)

Table 2. Samples description, demographics (age and gender), and recruitment methods [extended from Cuesta-Vargas et al., 2018]

Table 3. Model fit for the 2–5 latent profile solutions in the validation sample (n= 1,245 valid cases)

Table Legends

Figure 1. Hierarchical cluster analysis: Three- and four-cluster solutions based on the Central Sensitization Inventory (CSI) in the test sample (n= 1,219 valid cases)

Figure 2. Three latent profiles plot based on the Central Sensitization Inventory (CSI) in the validation sample (n= 1,245 valid cases) and total sample (n= 2,479 valid cases).

Note: The three profiles are labelled as follows: *Mild CS* (green), *Moderate CS* (yellow), and *Severe CS* (red).