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Psychological distress and widespread pain contribute to the variance of the central sensitization inventory: A cross-sectional study in patients with chronic pain

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Abstract

Objectives

Central sensitization (CS) implies increased sensitivity of the nervous system, resulting in increased pain sensitivity as well as widespread pain. Recently, the Central Sensitization Inventory (CSI) was developed to assess symptoms of CS and central sensitivity syndromes. The aim of this study was to examine the convergent validity of the CSI by comparing the outcome to psychosocial factors and clinical features of CS.

Methods

In a cross-sectional explorative study, patients with chronic pain completed multiple questionnaires, including the CSI, pain catastrophizing scale, SCL-90 for psychological distress, duration of pain, intensity of pain, widespread pain, and lateralization of pain. Based on bivariate correlations, relevant predictors of CS were selected and used to fit an exploratory structural equation model (SEM) of CS.

Results

In total 114 patients with chronic pain were included, 56.1 % being women. The average pain duration was 88 months. The mean total score on the CSI was 36.09 (15.26). The CSI was strongly related to known contributing and related factors of CS. SEM analysis showed that both psychological distress and widespread pain contributed significantly to the variance in symptoms of CS in patients with chronic pain.

Conclusion

In this study, the convergent validity of the CSI was measured with demonstration of a strong relationship between contributing factors and clinical features of CS. These findings of convergent validity, considering former studies of the CSI, underline the use of the questionnaire in the clinical practice.

Key words: central sensitization, psychology, validity, chronic pain

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Introduction

Pain research has changed the clinical view on pain, from a 'strict' bio-medical model towards the acceptance of a more bio-psycho-social understanding of pain [1]. Milestones in this new view were the 'gate control theory' of Melzack and Wall (1965) [2] followed by more recent findings indicating the involvement of central sensitization [3,4] and neural plasticity [2]. These findings have led to a better understanding of the chronicity of pain syndromes, as well as a phenomenological difference between acute and chronic pain [5].

In the 20th century, several chronic pain syndromes were described based on perceived symptoms rather than sound etiology or pathogenesis. These syndromes have consequently been called 'somatically unexplained' symptoms, 'functional' or 'functional somatic' syndromes. Alternatively, Yunus (2007) proposed a list of 13 central sensitivity related syndromes such as; fibromyalgia, irritable bowel syndrome, whiplash associated disorder, temporomandibular disorder, myofascial pain syndrome, tension type headache, and proposed to label these as 'central sensitivity syndromes' [6]. Numerous studies confirmed that central sensitization is (part of) the explanation for other well know (subgroups of) chronic pain conditions such as low back pain [7], osteoarthritis [8], subacromial impingement syndrome [9] and tendinopathy [10].

Central sensitivity, central sensitization (CS) or central mediated pain are all terms suggesting augmentation of responsiveness of central neurons to input of uni-and polimodal receptors, resulting in increased pain sensitivity as well as widespread pain and disproportional pain [11]. CS and somatosensory changes can be induced by bottom up, nociceptive C-fiber input, and/or by top-down modulation. This top-down modulation may encompass malfunction of descending pain inhibitory pathways or enhanced pain facilitation by psychosocial factors. Well-known psychosocial risk factors for CS and somatosensory changes are depression, fear, stress, and cognitive factors including

catastrophizing and inadequate illness perceptions [12]. In a worldwide survey of 17 countries investigating neck and back pain, mood and anxiety disorders were strongly related to chronic low back and neck pain [13]. Results from a meta-analysis of 41 studies indicate that anxiety sensitivity was strongly associated with fearful appraisals of pain and pain thresholds [14]. Neblett et al., (2016) found associations between the outcome of the Central Sensitization Inventory (CSI), a questionnaire developed to assess symptoms of CS, and depressive symptoms, disability, sleep disturbance and pain intensity [15].

Since central sensitivity syndromes are common in healthcare, clinical tools that can aid in the diagnosis or recognition of predominant central sensitization are needed. A first step is to determine the clinical features of predominant CS. Disproportional pain, an implausible neuroanatomical pain distribution and sensory hypersensitivity were proposed as main clinical features of predominant CS [16]. In addition, quantitative measures can also be found in the Quantitative Sensory Testing (QST) tools, which are used to demonstrate altered pain threshold, sensitivity, heat or cold, as well as allodynia and hyperalgesia [17]. These standardized tests are used with mechanical and thermal stimuli to characterize somatosensory profiles in patients. For daily clinical care, QST is time consuming, norm scores are not available, and the data from QST are difficult to interpret because sensory abnormalities are often bilateral, frustrating the left-right comparison [18].

Recently, Mayer et al. (2012) developed a questionnaire attempting to measure signs of central sensitization, the Central Sensitization Inventory (CSI) [19]. The original CSI contains two parts in which the first part (A) contains 25 items representing pain related, psychosocial, cognitive, and functional items. The second part (B) contains seven different central sensitivity syndromes (CSS), which are restless legs, chronic fatigue syndrome, fibromyalgia, temporomandibular joint disorder, migraine or tension headache, irritable bowel, and multiple chemical sensitivities and three disorders relate to CSS, namely neck pain (whiplash), depression and anxiety or panic attacks. The questionnaire was tested in a group of patients with fibromyalgia (M_{CSI} = 58.2, SD = 10.5), chronic widespread pain (M_{CSI} = 47.5, SD = 14.9), low back pain (M_{CSI} = 41.6, SD = 14.8), and a normative healthy control group (M_{CSI} = 28.9, SD = 13.5). Significance differences were presented on the CSI

total score among the groups. Furthermore a 4-factor structure was found, and a good test-retest reliability (r = .82), good internal consistency (Cronbach's α = .88) and promising construct validity based on comparisons of three subgroups of patients and a healthy control group [19]. The same group also described norm scores for the CSI [15, 20] using a group of 121 patients from multidisciplinary pain center of which 89 (74 %) had one or more central sensitivity syndromes. A score of 40 in this study was found to best distinguish between control subjects and patients diagnosed with CSSs. Though one might assume that all of the patients with a CSS did indeed have some level of CS, no objective testing of CS was performed in this study. Compared to a non-patient group a score of 40 had an 81 % sensitivity (true positive rate) and 75 % specificity (true negative rate) score [20]. In a study using the CSI to identify chronic pain patients with, and without, an objective CSS diagnosis, the sensitivity was 82.8 % and specificity was 54.8 % [21]. Similarly, the Dutch version of the CSI showed a four-factor solution, good discriminative validity and excellent test-retest reliability [22]. In this study 368 patients with chronic pain from primary multidisciplinary and monodisciplinary physical therapy settings in Belgium and the Netherlands were included.

Although the CSI has been tested for several psychometric properties, the convergent validity of the questionnaire remains unknown. Since no gold standard is available for assessing CS, convergent validity should be evaluated by relating the CSI to the described clinical features of CS and psycho-social risk factors related to CS, such as catastrophizing, anxiety and levels of psychological distress.

Taken together, there are two research questions to investigate the convergent validity of the CSI. First, is the CSI related to the contributing psychosocial factors for central sensitization such as catastrophizing and psychological distress? Second, what is the relation between the CSI and clinical features of CS?

METHODS

Subjects

114 consecutive patients were included via referral to a transdisciplinary pain-management center (Transcare, The Netherlands) by their medical specialist or general practitioner. This center works with transdisciplinary teams with physicians, psychologists and physical therapist. The diagnosis for referral was chronic pain unresponsive to traditional medical treatment or other primary care treatments. The majority of patients were women (56.1%) and the age range was broad with the youngest patient being 16 years old and the oldest patient in our sample being 88 years old (see Table 1).

Study design and setting

In this cross-sectional explorative study, all patients filled out a standardized list of questionnaires before admission to a transdisciplinary outpatient pain clinic. Sociodemographic data (gender, age) were collected as part of a standard diagnostic procedure. All patients filled out an informed consent for using these clinical data for scientific research. Since these measures were part of standard medical care, separate Medical Ethical approval was not needed.

The set of standard questionnaires was sent to the patients by regular mail. All patients filled out the questionnaire and returned it by regular mail with an included prepaid envelope. Patients filled out the questionnaires without supervision of a researcher in order to get valid and unbiased information. In case of missing data on 2 or less items of the total questionnaire, patients were asked to complete their questionnaires before the assessment in the presence of the researcher. Patients with missing data on more than 2 items were excluded from the study. Patients were included from January 2013 until June 2015. All questionnaires were imported in SPSS by one researcher.

Variables

All patients filled out socio-demographics (gender, age) and the following measures; a numbered Visual Analogue Scale (0 no pain - 10 worst pain; for their average pain over the last week), duration of pain in months, Central Sensitization Inventory (CSI) - Dutch version, Pain Catastrophizing Scale (PCS), Symptom Checklist 90 (SCL-90) and the Widespread Pain Index (WPI).

The translated *CSI-Dutch version*, described by Kregel et al. (2015), was filled out by all patients [22]. The CSI consists of two parts. Part A contains 25 items presenting the pain related psychosocial, cognitive and functional items. Part B was not used in the present study.

The *WPI* was originally developed for patients with Fibromyalgia containing 19 pain-sites in an anatomical drawing. For this study we also included the head as one of the potential pain-sites leading to a maximum score of 20 pain-sites [23]. Besides the potential widespread pain, we also used the WPI data to create a binary variable named lateralization of pain to determine if the reported pain was one-sided or two-sided.

The *PCS* is a self-reported questionnaire assessing pain catastrophizing. It is a 13-item scale in which patients are asked to reflect on past painful experiences and indicate the degree to which they experienced thoughts or feelings during pain on a five-point scale. In the present study the total score of the PCS was used. Total scores are counted by adding up all individual items scores. Higher scores correspond to more severe catastrophic thoughts about pain. The psychometric properties of the PCS are adequate. [24,25]

The *SCL-90* is a multidimensional self-report inventory to assess current psychological symptoms. The SCL-90 yields 8 symptom domains of which the dimensions phobic anxiety, anxiety, depression, somatization, insufficiency of thinking and acting, interpersonal sensitivity, hostility and quality of sleep were assessed and used. Participants were asked to rate on a 5-point scale from 1 (not at all) to 5 (extreme) how much each item had distressed or bothered them during the last 7 days, including the day of the examination. The total score of this questionnaire can be calculated resulting

in a psychological distress score. The SCL-90 is a worldwide used questionnaire and the psychometric properties have been considered adequate [26].

Statistical analysis

First, we calculated the means, standard deviation, and range of each demographic variable and pain related measures and questionnaires. The bivariate correlations between the total score on the CSI, PCS, SCL-90, duration of pain complaints, intensity of pain experienced last week (VAS), WPI, lateralization of pain and possible confounders age and gender were then analyzed using Pearson correlations. Spearman's rank correlations were used when one or more variables were skewed. Third, based on these correlations, we selected relevant predictors of patient-reported CS-related symptoms measured by the CSI and used these to fit a basic regression model followed by an explorative structural equation model (SEM) of central sensitization. These path analyses contain five manifest predictor variables with five estimated standardized path coefficients in the basic regression analysis and thirteen estimated standardized path coefficients in the explorative SEM. With our sample size of 114 subjects, we meet the criteria of an adequate sample size for the basic regression analysis. For the SEM we were a few participants short to meet those sample size criteria [27], however, this analysis is an exploratory one and performed to generate hypotheses instead of answering them. Furthermore we would like to note that fitting data in a structural equation model does not prove the causal assumptions that we make, but it makes them tentatively more plausible [28]

The goodness-of-fit was evaluated with the following descriptive fit indices: (1) the Satorra-Bentler scaled χ^2 global goodness of fit, which takes the non-normality into account; (2) the root mean square error of approximation (RMSEA); (3) the comparative fit index (CFI); (4) the standardized root mean square residual (SRMR). The Satorra-Bentler scaled χ^2 should yield p-values of >.05 indicating a good fit. The RMSEA and SMRS should yield values <.06 indicating a good fit [27] and values <.08 are indicative of an acceptable fit [27]. For the CFI values >.95 indicate a good fit [27]. Bivariate correlations and standardized path coefficients are presented and following Cohen (1988), coefficients

of .1 are small, .3 are moderate, and .5 are large in magnitude [29]. The STATA 14 statistical software package was used for all analyses [30). An alpha of .05 was considered statistically significant.

Results

The average pain duration was 88 months (range 3-480 months) and the mean pain intensity as measured by the VAS was 6.61 (1.73). Eighty-eight out of 114 patients (77.2%) reported bilateral pain. The mean total score on the CSI was 36.09 (15.26) (Table 1).

The bivariate correlations are presented in Table 2. It is notable that gender was not significantly correlated with any of the other variables. Age showed small to moderate correlations with duration of pain and the SCL-90 total score. The total score on the SCL-90, PCS, and WPI, as well as pain intensity experienced in the last week and lateralization of pain all showed positive associations with the total score on the CSI.

Based on these correlations, we decided to use every variable that had a significant correlation with the CSI into the structural equation model starting with a basic regression model where every variable had a direct causal relation with total score on the CSI. This model yielded only 2 significant relations, with a moderate effect found for WPI ($\beta = .29$, $p<.001$) and a large effect for the total score on SCL-90 ($\beta = .56$, $p<.001$). This regression model was further used to explore if some of the variables that did not show a significant direct relation (PCS, lateralization of pain, and pain experienced last week) could influence CSI in an indirect way. The determination of the directions of the causal relations was based on current knowledge of existing literature. Lateralization of pain was not significantly

associated with any of the other variables in the model and was dropped from the final model (see Figure 1).

The final model fit the data well (Satorra-Bentler scaled $\chi^2(4)=2.76$, p=.60; RMSEA and SMRS both <.05, CFI=1.00). We found a strong association between the SCL-90 and the CSI ($\beta = .57$, $p<.001$). The WPI had a moderately direct association with the CSI ($\beta = .33$, $p<.001$) and an indirect effect via the SCL 90. The PCS did not have a direct association with CSI, but a significant indirect association via SCL-90 was found. Finally, the pain VAS did not show a direct effect on CSI, but an indirect effect through PCS and SCL-90.

Discussion

In this study, for the we found an association between psychological distress and symptoms of CS using the CSI for patients with chronic pain. In relation to the convergent validity of the CSI, it was shown that the outcome of the CSI showed moderate to large associations with known contributing and related factors of CS. Likewise, it was found that both psychological distress, measured using the SCL-90, and widespread pain, measured with the WPI, contributed significantly to the variance in symptoms of CS in patients with chronic pain. In addition to psychological distress and widespread pain, it was found that pain catastrophizing did not contribute uniquely to the variance in symptoms of CS in patients with chronic pain.

We found a strong association of $\beta = .57$ for the CSI and the total score of the SCL-90 as well as a significant association of $\beta = .33$ for widespread pain. This relationship is consistent with previous research, where the relationship between chronic pain and psychological factors was emphasized [15, 33, 34, 35]. The relationship between central sensitization and chronic widespread pain has also been emphasized before mainly in central sensitivity related syndromes [16, 36, 37].

In this explorative study of the CSI, we only used the total score of the SCL 90. This finding seems an argument to further explore the relationship of the CSI with specific domains of the SCL 90

such as depression, fear, somatization and sleep. The size of our sample did not allow for examination of possible associations between symptoms of central sensitization and specific SCL-90 domains, therefore, this is an important issue for further work in this area. Furthermore, future research should focus on possible relationships between the SCL-90 domains and the total score on the CSI as well as the specific domains of the CSI described in the factor analyses by Mayer et al. (2012) and Kregel et al. (2015) [19, 21].

The WPI showed a strong relation with the CSI outcome, as expected based on the algorithm by Nijs et al (2014), in which diffuse or neuroanatomical illogical pain is proposed as a crucial sign of CS [16]. This finding was also in agreement with the work done by a Delphi study on clinical indicators of nociceptive versus neuropathic and central sensitization pain, showing that 'widespread, non-anatomical distribution of pain' obtained up to 96% consensus level agreement among expert clinicians as a clinical indicator of central sensitization pain [38]. Similarly, a study of 464 low back pain (LBP) patients, 'non-segmental/diffuse areas of tenderness on palpation' was identified as one of the four key predictors of CS LBP versus peripheral neuropathic and nociceptive LBP [39]. Looking at our data, the observed widespread pain seems to confirm a diffuse pain distribution, although exact definitions of both these features should be described more precisely.

Catastrophizing did not show a direct significant relation in our model with the outcome of the CSI, although catastrophizing has been described as one of the modulating factors associated with alterations in supraspinal endogenous pain-inhibitory and -facilitatory processes, and therefore a factor in maintaining and or aggravating CS pain [40, 41]. Catastrophizing was originally used to describe a maladaptive cognitive strategy employed by patients with anxiety and depressive disorders [42]. In relation to pain, catastrophizing was characterized by the tendency to magnify the threat value of pain, ruminate about pain, and feel helpless in the context of pain, essentially an inability to inhibit pain-related thoughts in anticipation of, during or following a painful encounter [40]. This study, however, showed that the association between catastrophizing and the CSI might be mediated by psychological distress.

No relationship was found between the CSI total scores and the duration of pain. A period of 3 to 6 months has been used for defining chronic pain. In our study the average pain duration was 88 months (range 3 – 480 months). Future studies should also include pain patients with a pain duration of less than one year and examine whether pain duration is related with CS. No relationship was found between lateralization of pain and the CSI, although 77.2% of the patients showed pain on both sides. Perhaps this can be an important clinical feature, but in the same analyses with widespread pain, lateralization did not contribute significantly since a strong relationship between these two features was found.

For clinicians, this study examined the relationship between several clinical features of patients with long lasting pain and established contributing factors. In the last decade, several studies have used the mechanism of CS to explain long lasting pain in patients in which no somatic cause can be found. We are aware of the fact that more evidence is needed to understand these features before it is usable in clinical practice, but this study gives some first insight for implementation in further studies and clinical use. The psychometric properties found in former studies of the CSI establish the use of the CSI as a tool for assessing symptoms related to CS and Central Sensitivity Syndromes' [15, 19, 20, 21]. The findings of convergent validity in this study also underline the use of the questionnaire in the clinical practice.

The study has several limitations and several strengths. All patients in the current study had long persisting pain, which means that the conclusion of this study cannot be generalized to all chronic pain patients, especially not the chronic pain patients with a shorter duration of pain. Furthermore, we included only patients referred to a pain management center, which might explain why the mean score on the CSI was lower compared to other studies describing the CSI. Second, while we used the SCL-90 total score, in future studies, the separate domains of the SCL 90 should be used to further explore if specific domains are related to symptoms of CS. The present study is cross-sectional in nature; therefore the directions of the paths in the SEM model are based on theory and previous research.

However, even though the good statistical fit of this proposed SEM model with the data does not prove the causal assumptions made, it does make them tentatively more plausible. Longitudinal studies would aid in developing more sound evidence for this theoretical model. Study strengths include the originality of the study: this is one of the first clinical studies exploring associations between several psycho-(patho)logical features of chronic pain and symptoms of CS. Therefore the study will contribute to a better understanding of symptoms of CS in chronic pain patients seen in clinical practice. Finally, the use of validated measures and clear standardization of measures requires mentioning as study strength.

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References

1) Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull. 2007;133:581-624.
2) Melzack R. From the gate to the neuromatrix. Pain 1999; Supplement 6: S121-S126.
3) Woolf CJ. "Windup and central sensitization are not equivalent." Pain 1996;66:105-108.
4) Woolf CJ. "Central sensitization: implications for the diagnosis and treatment of pain." Pain 2011;152:S2-15.
5) Nijs J, Van Houdenhove B. From acute musculoskeletal pain to chronic widespread pain and fibromyalgia: Application of pain neurophysiology in manual therapy practice. Man Ther. 2009;14:3-12.
6) Yunus MB. Fibromyalgia and overlapping disorders; the unifying concept of central sensitivity syndrome. Semin arthritis rheum. 2007;36:339-356.

7) Giesecke T, Gracely RH, Grant MA, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis Rheumatism 2004;50:613-623.

8) Mease PJ, Hanna S, Frakes EP, Altman RD. Pain mechanisms in osteoarthritis: understanding the role of central pain and current approaches to its treatment. J Rheumatol. 2011;38:1546-1551.

9) Paul TM, Soo Hoo J, Chae J, Wilson RD. Central hypersensitivity in patients with subacromial impingement syndrome. Arch Phys Med Rehabil. 2012;93:2206-2209.

10) Plinsinga ML, Brink MS, Vicenzino B, van Wilgen CP. Evidence of Nervous System Sensitization in Commonly Presenting and Persistent Painful Tendinopathies: A Systematic Review. J Orthop Sports Phys Ther. 2015;45:864-875.

11) Woolf CJ. What to call the amplification of nociceptive signals in the central nervous system that contribute to widespread pain? Pain 2014;155:1911-1912.

12) Brosschot JF. Cognitive-emotional sensitization and somatic health complaints. Scand J Psychol. 2002;43:113-121.

13) Demyttenaere K, Bruffaerts R, Lee S, et al. Mental disorders among persons with chronic back or neck pain: Results from the world mental health surveys, Pain 2007;129:332–342.

14) Ocañez KL, McHugh RK, Otto MW. A meta-analytic review of the association between anxiety sensitivity and pain. Depress Anxiety. 2010;27:760-767.

15) Neblett R, Hartzell MM, Mayer TG, Cohen H, Gatchel RD. Establishing Clinically Relevant Severity Levels for the Central Sensitization Inventory. Pain Pract. 2017;17 (2):166-175.

16) Nijs J, Torres-Cueco R, van Wilgen CP, et al. Applying modern pain neuroscience in clinical practice: criteria for the classification of central sensitization pain. Pain physician 2014;17:447-457.

17) Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain. 2006;123:231–243.

18) Konopka KH, Harbers M, Houghton A, et al. Bilateral sensory abnormalities in patients with

unilateral neuropathic pain; a quantitative sensory testing (QST) study. PLoS One. 2012;7:e37524.

19) Mayer TG, Neblett R, Cohen H, et al. The development and psychometric validation of the central sensitization inventory. Pain Pract. 2012;12:276-285.

20) Neblett, R, Cohen H, Choi Y, et al. The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. J Pain. 2013;14;438-445.

21) Neblett R, Hartzell MM, Cohen H, et.al Ability of the Central Sensitization Inventory to Identify Central Sensitivity Syndromes in an Outpatient Chronic Pain Sample Clinical Journal of Pain. 2015;31(4):323-332.

22) Kregel J, Vuijk PJ, Descheemaeker F, et al. The Dutch Central Sensitization Inventory (CSI): Factor Analysis, Discriminative Power and Test-Retest Reliability. Clin J Pain. 2016;32:624-630.

23) Wolfe F, Clauw DJ, Fitzcharles MA, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol. 2011;38:1113-22.

24) Sullivan MJ, Bishop SR, Pivik J. The pain catastrophizing scale: Development and validation, Psychol Assess 1995;4**:**524–32.

25) Severeijnse R, Hout van den MA, Vlaeyen JWS, Picavet HS. Pain catastrophizing and general health status in a large Dutch community sample. Pain 2002;99:367-76.

26) Arrindel WA, & Ettema J. SCL-90: manual of a multidimensional psychopathology indicator. Lisse: Swets & Zeitlinger 2003.

27) Kline, Rex B. "Principles and Practice of Structural Equation Modeling, Methodology In The Social Sciences. New York: Guilford press; 2004.

28) Bollen, K.A. & Pearl, J. (2013) Eight Myths About Causality and Structural Equation Models. In S.L. Morgan (Ed.), *Handbook of Causal Analysis for Social Research*, (pp. 301-28). *Dordrecht*, The Netherlands: Springer

29) Cohen, J. (1988). *Statistical power analysis for the behavioral sciences (2nd ed.).* Hillsdale,

NJ: Erlbaum.

30) StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.

31) Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Structural Equation Modeling 1999;6:55.

32) Bollen KA, Long JSE. Alternative ways of assessing model fit. Testing structural equation models Newbury Park, California: Sage Publications, 1993:136 - 162.

33) Linton SJ, Bergbom S. Understanding the link between depression and pain. Scandinavian Journal of Pain 2011;2:47-54.

34) Turk DC, Okifuji A. Psychological factors in chronic pain: evolution and revolution. J Consult Clin psychol 2002;70:678-90.

35) Visscher CM, Lobbezoo F, De Boer W, van der Meulen M, Naeije M. Psychological distress in chronic craniomandibular and cervical spinal pain patients. Eur J of Oral Sci. 2001;109:165–171.

36) Lluch Girbés E, Dueñas L, Barbero M, Falla D, Baert IA, Meeus M, Sánchez-Frutos J, Aguilella L, Nijs J. Expanded Distribution of Pain as a Sign of Central Sensitization in Individuals With Symptomatic Knee Osteoarthritis. Phys Ther. 2016; 96(8):1196-207

37) Noten S, Struyf F, Lluch E, D'Hoore M, Van Looveren E, Meeus M. Central Pain Processing in Patients with Shoulder Pain: A Review of the Literature. Pain Pract. 2016 [Epub ahead of print]

38) Smart KM, Blake C, Staines A, Doody C. Clinical indicators of 'nociceptive', 'peripheral neuropathic' and 'central' mechanisms of musculoskeletal pain. A Delphi survey of expert clinicians. Man Ther 2010;15:80-87.

39) Smart KM, Blake C, Staines A. Tacker M, Doody C. Mechanisms-based classifications of musculoskeletal pain: part 1 of 3: symptoms and signs of central sensitisation in patients with low back (+/- leg) pain. Man Ther 2012;17:336-344.

40) Quartana PJ, Campbell CM, Edwards RR. Pain Catastrophizing: A Critical Review. Expert rev neurother. 2009;9:745–758.

41) Campbell CM, Buenaver LF, Finan P. et al. Sleep, Pain Catastrophizing, and Central Sensitization in Knee Osteoarthritis Patients With and Without Insomnia. Arthritis care res. 2015;67,1387.

42) Beck AT, Rush AJ, Shaw BF, Emery G. Cognitive Therapy of Depression. Guilford Press: NY; 1979.

Table 1. Age, sex, and outcome of the pain related measures and questionnaires of the study sample (n=114)

Variables	**Mean (SD)**	**Range**
Age	46.73 (15.95)	16-88
Gender; n (%) female	64 (56.1%)	
Pain related measures		
Duration pain complaints (in months)	88.46 (103.94)	3-480
Pain last week (VAS)	6.61 (1.73)	1-10
WPI	5.97 (4.67)	1-20
Lateralization of pain; n (%) two-sided	88 (77.2%)	
Questionnaires		
CSI	36.09 (15.26)	3-72
PCS	19.87 (11.25)	1-51
SCL-90	146.74 (42.83)	90-316

VAS = Visual Analogue Scale; WPI = Widespread Pain Index; CSI= Central Sensitization Inventory; PCS = Pain Catastrophizing Scale; SCL-90 = Symptom Checklist 90 items

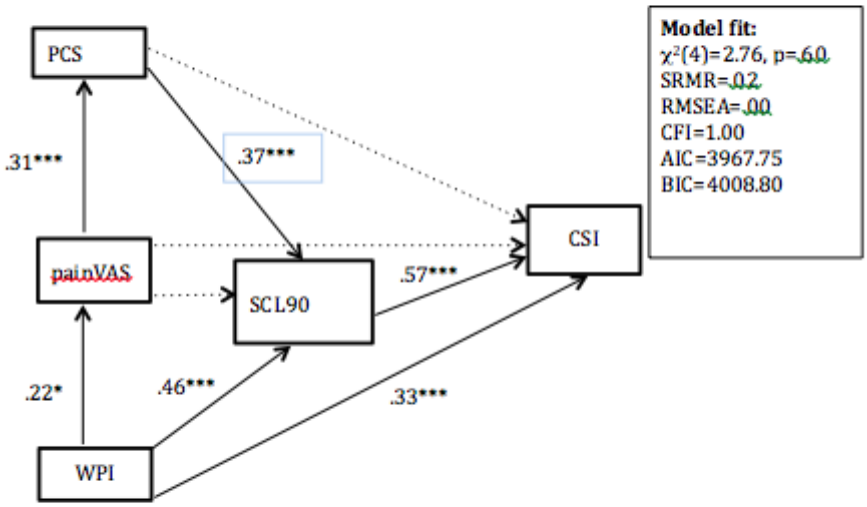
Table 2. Bivariate correlations between the demographic variables, pain related variables, and questionnaires

	CSI	Age	Gender	Duration pain complaints (in months)	Pain last week (VAS)	WPI	Lateralization of pain; n (%) two-sided	PCS	SCL 90
CSI	-								
Age	-.12	-							
Gender	-.18	.02	-						
Duration pain complaints (in months)	.26†	.21†*	-.07†	-					
Pain last week (VAS)	.29†**	.05†	-.14†	.12†	-				
WPI	.58†***	-.03†	-.16†	.16†	.20†*	-			
Lateralization of pain; n (%) two-sided	.33***	-.04	-.11	.13†	.16†	.57†***	-		
PCS	.27**	.05	.11	-.05†	.29†**	.04†	-.02	-	
SCL-90	.75†***	-.23†*	-.07†	.02†	.16†	.47†***	.23†*	.44†***	-

Note. † = Spearman's rank correlation; *<.05, **<.01, ***<.001

CSI= Central Sensitization Inventory; VAS = Visual Analogue Scale; WPI = Widespread Pain Index; PCS = Pain Catastrophizing Scale; SCL-90 = Symptom Checklist 90 items

Figure 1. Structural equation model explaining Central Sensitization Inventory outcome in 114 patients with long lasting pain



Note. Standardized regression coefficients are presented; Dotted lines are non-significant associations; *<.05, **<.01, ***<.001