Central Sensitization and Physical Functioning in patients with Chronic Low Back Pain

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A pilot study in the association between Waddell Non-Organic Signs and Central Sensitization

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ABSTRACT

Study Design. A cross-sectional observational multicenter pilot-study was performed within care as usual in three rehabilitation centers in the Netherlands.

Objective. To explore the relationship between Waddell's non-organic signs (NOS) and central sensitization (CS) in patients with chronic back pain.

Summary of Background Data. A possible relationship between NOS and CS is theoretically plausible, but it has never been tested.

Methods. A cross-sectional observational multicenter pilot-study was performed in three rehabilitation centers in the Netherlands. Patients with chronic back pain were included. Main measures were Waddell's NOS, a battery of eight clinical tests performed during a physical examination, and Central Sensitization Inventory (CSI), a questionnaire measuring symptoms originating from CS. Analyses included Spearman correlation and univariate multiple regression analysis with NOS as dependent variable, CSI as independent, and controlled for confounders (psychosocial variables).

Results. Data of n=56 patients (59% female, mean age 42.6 years) were obtained. Correlation between NOS and CSI was r_s=0.34 (p=0.01). After controlling for confounders, CSI did not independently predict NOS.

Conclusion. In this pilot study, CS was moderately related to NOS, but CS did not independently contribute to NOS after controlling for confounders. The results suggest that NOS may not exclusively be non-organic tests, although questions remain. The results of this pilot study can help to develop larger studies to allow replication and more detailed analyses.

INTRODUCTION

In 1980, Gordon Waddell introduced eight simple clinical tests, called 'Non-organic signs' (NOS) to identify non-organic symptoms in the physical evaluation of patients with chronic back pain (CBP) [1,2]. This battery of tests contain the examination of superficial and deep tenderness, simulated axial loading and spinal rotation, distracted straight leg raising, regional sensory disturbances and weakness, and overreaction to the examination. These signs were named 'Non-organic' because they were then assumed to have a non-organic basis [2] and they were considered behavioral responses to a physical examination [1]. The presence of multiple NOS can alert clinicians to the presence of altered psychosocial and behavioral aspects of patients with CBP. Indeed, later studies have revealed an association between NOS and psychosocial factors such as depression, anxiety, and distress [3–6].

In 1983, central sensitization (CS) was introduced as a possible pathophysiological mechanism in several chronic pain conditions [7], including a subgroup of patients with CBP [8]. In CS, a structural or functional changes of the central nervous system occur, leading to an altered processing of pain [9]. Clinical manifestations of this altered processing are allodynia, hyperesthesia, pain distribution beyond the original injury region, temporal summation of pain, and hypersensitivity of senses unrelated to the musculoskeletal system [10]. Recognition is growing that it is important to consider CS for the diagnosis and treatment of many chronic musculoskeletal pain conditions [11] and CS should, therefore, be one of the factors that need to be considered during the multidimensional assessment of pain.

Considering the knowledge development of the last decades regarding chronic pain and in particular CS, there is ample evidence that altered processing of pain should be considered organic [12], while influenced by organic and non-organic factors (psychosocial and behavioral factors) [13]. A closer analysis to both NOS and CS reveals an overlap in the manifestations of symptoms; for example, an 'overreaction' (NOS sign) may refer to hyperesthesia (CS symptom), and a 'regional sensory disturbance' (NOS sign) may also be regarded as pain distribution beyond the original injury region (CS symptom). A possible relationship between NOS and CS has been suggested by others [14], but it has never been tested to the authors' knowledge. The aim of this pilot study was to explore the relationship between CS and NOS in patients with CBP, while controlled for psychosocial variables. The assumption, of an exploratory nature, that NOS should not be interpreted as only non-organic was considered plausible, when the strength of the association between NOS and CS is at least moderate ($r \geq 0.30$), and when CS would independently contribute to a multiple

regression model explaining NOS after controlling for several psychosocial factors.

METHODS

Design

A cross-sectional observational study was conducted within the current Vocational Rehabilitation (VR) programs from October 2018 to June 2019. Data were gathered from three outpatient rehabilitation centers affiliated with the 'Vroege Interventie' network across the Netherlands. NOS and CS data were collected during patients' intake assessment at the rehabilitation centers. Additional data, including self-reported questionnaires, were collected from patients' medical files. All patients meeting the inclusion criteria signed informed consent. A waiver from the Ethical committee was obtained for this study (M18.238357). The ethical standards of the Helsinki Declaration of 1975 and revised in 2014 were followed in this study [15].

Patients

All eligible patients were consecutively included based on in- and exclusion criteria. Inclusion criteria were: adult patients aged between 18 and 65 years, admitted to VR, diagnosed with CBP (ICD-11 code: MG30.02) of at least three months duration, and with sufficient language skills to understand instructions and fill out questionnaires independently. Exclusion criteria were: pregnancy, being diagnosed of specific back pain related conditions (e.g. tumors, infections, fractures, 3rd and 4th degree spondylolisthesis, or radicular syndromes), and relevant comorbidities which could influence VR results (e.g. psychiatric or cardiovascular conditions).

Measurements

Dependent variable

Non-organic signs during the physical examination were measured with the NOS, consisting of eight clinical tests assessing five categories of signs: tenderness, simulation, distraction, regional disturbance, and overreaction [2]. A description of the tests is presented in the Appendix. The presence of any individual sign on each of the tests counts as positive, thus, the NOS score ranges from 0 to 8. A sum score of 3 or more positive tests was considered indicative of the presence of altered psychosocial and behavioral aspects. A Dutch study found that the inter-observer reliability of NOS in patients with CBP is moderate and the intra-observer reliability is good for trained observers [16,17].

Independent variables

CS was measured with the CS Inventory part A (CSI-A), a self-reported questionnaire to quantify the severity of symptoms originating from CS [18]. The CSI-A consists of 25 questions related to somatic and emotional indices of CS syndromes. The answers (Likert scale 0–4) for all 25 questions are summed in a score ranging from 0–100; a higher score reflects more severity of CS symptoms. The Dutch translation of the CSI has excellent test-retest reliability and good internal consistency for three out of four domains [18,19].

Pain disability was measured with the Pain Disability Index, Dutch Language Version (PDI-DLV) [20]. This seven-item questionnaire measures across seven categories of activities: family/home responsibilities, recreation, social activity, occupation, sexual behavior, self-care, and life-support activity. The score for each item ranges from 0 to 10; with 0 being no interference and 10 being total interference. The total maximum sum score for the PDI is 70 points which indicates total interference in activities of daily living. Clinimetric properties of the PDI-DLV are sufficient [20].

Pain and fatigue intensities were measured with the Numeric Rating Scale (NRS). The scale consists of 11 numbers from 0 (no pain/fatigue at all) until 10 (worst pain/fatigue imaginable) [21]. Clinimetric properties of the NRS are sufficient [21].

Psychosocial factors that could contribute to maintaining CBP and increase the risk of long-term work absenteeism were measured with the Work Reintegration Questionnaire (in Dutch: Vragenlijst ArbeidsReintergratie; VAR). This 78-item questionnaire consists of eight scales: distress, perceived disability, job strain, control, job dissatisfaction, avoidance/insecurity, perfectionism, and stressful home situations. Each of the items has a 1–4 score range. The total sum of all item scores (78–312) is used in this study; higher score indicates a higher risk for non or delayed work resumption. The clinimetric properties of the VAR are sufficient [22–24].

Data-analyses and interpretation

Datasets from all centers were merged into one dataset and entered into SPSS (SPSS Statistics version 25, IBM Corp., USA) for analyses. This dataset was checked for missing data and outliers. If a case had more than 50% missing data, the case was excluded. Substitution by means was used to replace for any missing items in the questionnaires. The influence of outliers (larger than three SD) was examined with Cook's distance and leverage values. The association

between NOS and CSI-A, both for the total score and for each of the items of the NOS, was tested with a Spearman correlation. A correlation of r_s=0.10–0.30 was considered weak, of r_s=0.30–0.60 moderate, and of r_s≥0.60 strong [25]. The univariate multiple regression analysis between NOS and CS consisted of two steps. Step 1: Spearman correlation analysis between NOS and CSI-A and each of the psychosocial variables to identify confounders. Those correlating significantly ($p<0.10$) with both NOS and CSI-A were progressed to the next step. Step 2: univariate multiple regression analysis with CSI-A fixed and the independent variables significant at step 1 entering the model using the stepwise forward method. The regression assumptions were checked: multi-collinearity was checked using a correlation matrix, and the residual errors were checked using histograms and P-P plots. Results were expressed in explained variance (R^2), unstandardized beta (B), standard errors (SE), 95% confidence intervals (95% CI), and p-values. Results of the regression analysis were considered significant at $p<0.05$.

RESULTS

A total of n=56 patients participated in this study, of which n=33 (59%) were female. Demographic and clinical characteristics are presented in Table 1. Results of the correlation analyses are presented in Tables 2 and 3.

Table 1. Demographic and clinical characteristics of the study sample (n=56).

	mean ± SD / n and %
Age (years)	42.6 ± 13.2
BMI (kg/m2)	26.3 ± 4.8
Pain disability (PDI, 0–70) [a]	34.0 ± 12.8
Pain intensity (NRS pain, 0–10)	4.8 ± 2.2
Fatigue intensity (NRS fatigue, 0–10)	4.3 ± 2.8
CS (CSI-A, 0–100)	34.7 ± 13.1
NOS positive total (0–8)	2.1 ± 2.0
Superficial tenderness	11 19.6%
Deep tenderness	29 51.8%
Axial loading	14 25.0%
Rotation	28 50.0%
Straight leg raising	6 10.7%
Sensory disturbance	5 8.9%
Weakness	11 19.6%
Overreaction	15 26.8%
Occupational psychosocial factors (VAR, 78–312) [b]	178.8 ± 29.4
Distress (13–52)	26.0 ± 7.0
Perceived disability (10–40)	28.8 ± 7.4
Job strain (7–28)	14.5 ± 4.7
Control (6–24)	17.2 ± 5.0
Job dissatisfaction (12–48)	24.2 ± 7.8
Avoidance/insecurity (11–44)	21.1 ± 5.2
Perfectionism (12–48)	35.3 ± 6.1
Stressful home situation (7–28)	12.5 ± 4.4

Sample size: [a], n=51; [b], n=48. Abbreviations: BMI, Body Mass Index; CSI-A, Central Sensitization Inventory part A; NOS, Non-Organic Signs; NRS, Numeric Rating Scale; PDI, Pain Disability Index; VAR, Vragenlijst ArbeidsReïntegratie (Work Reintegration Questionnaire).

Table 2. Spearman correlation of NOS with CSI-A (n=56).

	CSI-A	
	r_s	p
NOS positive total	0.34	0.011
Superficial tenderness	0.33	0.013
Deep tenderness	0.12	0.398
Axial loading	0.33	0.013
Rotation	0.04	0.796
Straight leg raising	0.10	0.463
Sensory disturbance	0.37	0.005
Weakness	0.24	0.072
Overreaction	0.25	0.064

Abbreviations: CSI-A, Central Sensitization Inventory part A; NOS, Non-Organic Signs.

Table 3. Spearman correlation between covariates and NOS and covariates and CSI-A.

	r_s	
	NOS	CSI-A
Age (years)	0.06	0.22
BMI (kg/m^2)	0.08	0.15
Pain disability (PDI)	0.45**	0.53***
Pain intensity (NRS pain)	0.44**	0.50***
Fatigue intensity (NRS fatigue)	0.43**	0.65***
Occupational psychosocial factors (VAR)	0.31*	0.66***
Distress	0.36**	0.67***
Perceived disability	0.53***	0.45**
Job strain	0.31*	0.46**
Control	0.14	0.20
Job dissatisfaction	0.07	0.32*
Avoidance/insecurity	-0.13	0.38**
Perfectionism	0.18	0.36**
Stressful home situation	0.00	0.37**

Significance level: *, p<0.05; **, p<0.01; ***, p<0.001.Abbreviations: BMI, Body Mass Index; CSI-A, Central Sensitization Inventory part A; NOS, Non-Organic Signs; NRS, Numeric Rating Scale; PDI, Pain Disability Index; VAR, Vragenlijst ArbeidsReïntegratie (Work Reintegration Questionnaire).

Regression analysis

Based on the p-values of the correlation analyses (Tables 2 and 3), next to CSI-A, the following psychosocial confounders progressed to the regression analysis: pain disability (PDI), pain intensity (NRS pain), fatigue intensity (NRS fatigue), and occupational psychosocial factors (VAR). In the regression model the contributions of pain intensity, fatigue intensity and occupational psychosocial factors were not significant and, therefore, excluded from the model. This resulted in a final model for NOS consisting of CS and pain disability (Table 4). The model explained 30% of the variance; CS did not contribute significantly, while pain disability did (model R^2=0.303, adjusted R^2=0.274; tolerance=0.665; variance inflating factors=1.503).

Table 4. Results of univariate multiple regression analysis for predicting NOS (n=56).

				95% CI	
	B	**SE**	**p**	**LB**	**UB**
Constant	-0.88	0.77	0.254	-2.42	0.66
CS (CSI-A)	0.01	0.02	0.835	-0.04	0.05
Pain disability (PDI)	0.08	0.02	0.001	0.04	0.13

Abbreviations: CSI-A, Central Sensitization Inventory part A; PDI, Pain Disability Index.

DISCUSSION

In this pilot study, a moderate relation between CS and NOS was observed, but no independent contribution of CS on NOS was observed when controlling for confounders. Although not both a priori assumptions were met, these results suggest that NOS may not exclusively be interpreted as a non-organic test. NOS were named as such because they were originally assumed to have a non-organic basis and they were considered behavioral responses to a physical examination [2]. Previous studies confirmed correlations between psychosocial features and NOS [3–6], but explained variances left space for additional explanations. As demonstrated by this pilot study, one of these additional explanations may be CS. While after this study we cannot rule out (or in) behavioral aspects, this study adds some early evidence for a biological/organic explanation of NOS and gives plausibility for future studies. Consequently, we need to regard the NOS from a biopsychosocial framework, and not only from a psychosocial or behavioral one.

To the authors' knowledge, there are no other studies where measures of CS and NOS were correlated. Therefore, the results of the present pilot study cannot be compared to earlier findings. There are specific features of this study that may have influenced the results; these may need to be considered in the planning and design of future studies: CS measurement instrument, sample and system characteristics, blinding, sample size and cross-sectional design. Firstly, the CS measurement instrument, CSI, has demonstrated moderate correlation with measures of pain disability [26] and this is also observed in our sample (Table 3). Looking closely at the CSI-A, some items that are reflective of consequences of CS are measured, such as pain disability, rather than manifestations of CS itself. This suggests that the CSI may not be a gold standard for self-reported CS, even though it is a widely used instrument. In future research and clinical care, other instruments should also be considered for measuring CS, including other self-report instruments as well as non-self-reported instruments such as quantitative sensory testing [13]. As demonstrated in Table 1, the sample characteristics could be interpreted as being somewhat less severe regarding CBP and disability compared to other studies in secondary care [20,27]. At present, it is unknown how severity influences the relation between CS and NOS, and this should be subject of further investigation. Secondly, the sample and system characteristics limit the generalization of the results to all patients with CBP. This study was performed within an outpatient vocational rehabilitation setting in the Netherlands, and similar studies in other settings and healthcare and social security systems should be performed to study external validity of the results. Thirdly, because this pilot study was performed within usual care, the clinician was not blinded for the CSI-A and NOS results, which may have introduced bias. The direction and extent of this bias are unknown and should be subject to further study. Fourthly, the sample size was sufficient for correlation testing but limited for introducing many independent variables in the regression model. Fifthly, detailed itemized analyses with separate NOS could not be done because of risk of type I errors, but these analyses may be relevant because some items are theoretically more feasibly related to CS than others. Additionally, distribution of positive item occurrence varied, leading to floor-effects at item-level. Future studies should consider larger samples to enable more detailed analyses. Sixth and lastly, the cross-sectional study design prevents us from drawing causal relationship between NOS and CS. Future studies may include a longitudinal study design and appropriate analyses to study a causal relation. Although the present study is indefinite about the direction of the association, based on theoretical assumptions, future longitudinal studies should test the hypothesis that a reduction of CS is a prerequisite for a reduction in NOS.

In this pilot study, CS was moderately related to NOS, but CS did not independently contribute to NOS after controlling for confounders. The results suggest that NOS may not exclusively be non-organic and that results of NOS testing are determined by organic and non-organic features. The results of this study can help to develop future longitudinal studies with a sufficient sample size to allow replication and more detailed analyses and analytic approaches directed at studying causal mechanisms

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APPENDIX

Appendix 1.– The Waddell Non-organic Signs (NOS) [2].

Tenderness	
1.Superficial	The skin is tender to light pinch over a wide lumbar area. A localised band in a posterior primary ramus distribution may be caused by nerve irritation and should be discounted.
2. Deep	Tenderness is felt over a wide area. It is not localized to one structure and often extends to the thoracic spine, sacrum, or pelvis.
Simulation tests	
3. Axial loading	LBP is reported on vertical loading over the standing subject's skull by the examiner's hands. Neck pain is common and should be discounted.
4. Rotation	LBP is reported when shoulders and pelvis are passively rotated in the same plane as the subject stands relaxed with the feet together. In the presence of root irritation leg pain may be produced and should be discounted.
Distraction test	
5. Straight leg raising	Straight leg raising is the most useful distraction test. The subject whose back pain has a nonorganic component shows marked improvement in straight leg raising on distraction as compared with formal testing.
Regional disturbances	
6. Sensory	Sensory disturbances include diminished sensation to light touch pinprick and sometimes other modalities fitting a "stocking" rather than a dermatomal pattern.
7. Weakness	Weakness is demonstrated on formal testing by a partial cogwheel "giving way" of many muscle groups that cannot be explained on a localized neurological basis.
Overreaction	
8. Overreaction	Overreaction during examination may take the form of disproportionate verbalization, facial expressions, muscle tension and tremor, collapsing or sweating judgements should, however, be made with caution, minimizing cultural variations, and it is very easy to introduce observer bias or to provoke this type of response unconsciously.