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Psychological burden in nociplastic pain: Central Sensitivity as possible discriminating construct within different chronic pain conditions and healthy population

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Abstract

Background: Central Sensitivity (CS) is defined as an increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold inputs. CS has been linked to the psychological burden associated with suffering from various chronic pain (CP) conditions, including fibromyalgia (FM) and chronic headache (CH). The present study aims to investigate whether CS can distinguish between CP conditions and healthy controls (HCs), as well as among different CP conditions, specifically CH, FM, and FM with CH.

Methods: A total of 737 women (n=220 CH; n=200 FM; n=209 FM with CH; n=108 HCs) completed an online self-administered protocol consisting of the Central Sensitivity Inventory (CSI) and socio-anamnestic information. A general linear model ANCOVA was performed to test differences in CSI scores, covarying for sociodemographic variables showing a significant different distribution among groups (age, social and working status and educational level).

Results: Data analysis showed a good fit for the model (R^2 Adjusted=.407; df=7; F=73.172; p<.001) and a significant difference between groups in CSI scores (p<.001). The only covariate included in the model showing a significant effect was educational level (F= 32.208; p<.001). Post hoc tests using the Bonferroni method revealed that all clinical groups scored significantly higher than HCs (all p < .001). Additionally, FM with comorbid CH showed CSI scores significantly higher than all other clinical groups.

Conclusions: CS appears to have a discriminating role among CP conditions, particularly in FM associated with CH. Including this dimension in the clinical evaluation of CP patients seems relevant to better understand the complex connection between CP and mental health.

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1. Introduction

Chronic pain (CP) represents the greatest widespread disease, showing a prevalence rate of 43.5% (Fayaz et al., 2016; Galli, 2023), causing a considerable disability in people worldwide and a huge socioeconomic burden (James et al., 2018; Nijs, Lahousse, et al., 2021). CP does not affect all individuals equally, in this direction the Centre for Disease Control and Prevention produced data indicating higher prevalence rates among women, people from lower socioeconomic backgrounds, and those living in rural areas (Dahlhamer et al., 2018). Pain is the primary reason people seek medical attention, with osteoarthritis, back pain, and headaches being three of the main causes. Among the four leading causes of years lost to disability, three CP conditions (Cohen et al., 2021). The biopsychosocial model suggests that pain and related disability result from the multidimensional, dynamic interactions among biological, psychological, and social factors that mutually influence each other (Meints & Edwards, 2018). Although it is widely acknowledged that psychological characteristics (i.e. depression, anxiety, sleep disturbance, adverse social conditions, etc.) can result from CP, it is less commonly known that these psychological factors can also predispose individuals to develop CP conditions (Cohen et al., 2021).

Pain can be categorised as nociceptive (i.e. tissue injury), neuropathic (i.e. nerve injury), or nociplastic (due to a sensitised nervous system). In this direction, the term Central Sensitivity (CS) was proposed to elucidate the regional and diffuse pain hypersensitivity associated with several CP conditions, including peripheral neuropathic pain, fibromyalgia (FM), chronic headache (CH), temporomandibular disorder, irritable bowel syndrome (IBS), and interstitial cystitis (Fitzcharles et al., 2021; Fitzcharles & Yunus, 2012). The International Association for the Study of Pain (IASP) defines the CS as an "increased responsiveness of nociceptive neurons in the central nervous system (CNS) to either normal or subthreshold afferent input" (IASP, International Association for the Study of Pain, 2017; Woolf, 2011), encompassing different CNS dysfunctions (i.e. altered sensory processing within the brain, amplified cerebral activity in brain areas associated in the experience of severe pain feelings, as well as a reduce functioning endogenous analgesia), that allow to deepen and enrich clinicians' understanding about CP knowledge and care (Bosma et al., 2016; Nijs, George, et al., 2021; Nijs, Lahousse, et al., 2021; Staud et al., 2008; Van Ettinger-Veenstra et al., 2019). To study CS, the Central Sensitivity Inventory (CSI) was developed and validated (Neblett et al., 2013) and recently used to assess symptom severity in FM and CH patients (Bosma et al., 2016; Galli, 2023; Nijs, George, et al., 2021; Staud et al., 2008). Nevertheless, an updated systematic review (Adams et al., 2023) highlighted that the CSI may better capture the main psychological characteristics associated to CP (e.g., depression, anxiety, pain catastrophizing, distress, sleep disorders) than measure CS

per se, emphasizing the centrality of psychological experience in painful chronic conditions. Thus, a deeper exploration of the role of CS in CP appears as an important research question also for improving precision pain medicine in clinical practices, identifying patients with specific psychological needs, and tailoring treatment to individual patient characteristics. Indeed, people suffering from CP conditions undergo numerous treatments that often fail to provide substantial benefits for the majority of patients, thus generating frustration, hopelessness and increasing the psychophysical burden (Edwards et al., 2023). This has highlighted the importance of spurring intensive efforts to match patients with the most effective treatment for them emphasizing the importance of personalized medicine also in the CP context (Edwards et al., 2023; Turk, 1990).

Accordingly, present study aims to investigate if CS discriminates between CP conditions and healthy controls (HCs) as well as between different CPs (CH, FM and FM with CH) thus highlighting particularly frail populations. The hypotheses were: a) that clinical groups will obtain higher scores than HCs and, b) FM with CH will show the highest scores among the clinical groups, hypothesizing the greater psychological burden due to suffering from multiple CP conditions.

2. Method

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval for the project was granted by the ethical committee of the Department of Dynamic and Clinical Psychology and Health Studies at Sapienza University of Rome on November 25, 2022 [Protocol number 0001979 UOR: SI000092—Classified VII/15]. Data collection was realized through a Google Forms between April and May 2023. Participants were recruited using a snowball sampling technique through associations for CH (Al.Ce. Alleanza Cefalalgici) and FM (Associazione Italiana Sindrome Fibromialgica), which disseminated the web survey via their official websites and social media platforms, including Facebook, Instagram, X, and LinkedIn. Before participating in this studies, individuals were required to provide informed consent.Participant anonymity was ensured.

The inclusion criteria for the clinical groups required participants to be 18 years or older, be fluent in Italian, and have a diagnosis of CH or FM made by a specialized medical doctor (e.g., neurologist, rheumatologist, etc.) for at least 6 months. For individuals who did not meet the inclusion criteria, the survey ended without the possibility to complete the study protocol. A total of 651 patients resulted eligible to participate in the study but due to the low male

participation (n=22) only female participants were included in the data analysis. As regards CH patients, we considered only the frequency of attacks (> 15 headaches for month for at least three months), because the online nature of the survey did not allow us to discriminate between the different sub-types (chronic migraine or chronic tension-type headache) according to the international classification of headache disorders ('Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd Edition', 2018). The final clinical sample was composed by 629 women (n=220 CH; n=200 FM; n=209 FM with CH).

A convenience sample of HCs was than recruited accordingly to the following inclusion criteria: female gender, 18 years or older, be fluent in Italian no history of CP in general and specifically related to the diagnoses considered in this study. For individual not meeting the inclusion criteria, the survey ended without the possibility to complete the study protocol. A total of 108 eligible woman gave their consent to participate in the study and completed the same online survey of clinical groups. The analyses have been performed on a total sample of 737 participants. A full description of participants is reported in Table 1.

Table 1. Socio-anamnestic data and differences between groups

	Chronic Headache (CM) (n = 220)	**Fibromyalgia (FM) (n = 200)**	**Fibromyalgia and Chronic Headache (FM+CH) (n = 209)**	**Healthy Controls (HCs) (n = 108)**	**Significance**		
	M ± SD	**M ± SD**	**M ± SD**	**M ± SD**	**F**	**Bonferroni Post-hoc**	**Partial Eta²**
Age	39.6 ± 12.2	46.8 ± 12.2	46.5 ± 11.7	36.9±14.4	26.004 df = 3 $p < 0.001$	CH, HCs < FM, FibroMig	0.096
	n (%)	**n (%)**	**n (%)**	**n (%)**	**Chi-squared**		
Civil status							
Single	92 (41.8)	46 (23)	56 (26.8)	60 (55.5)			
Married/Civil Union	84 (38.2)	105 (52.5)	101 (48.4)	26 (24.1)	52.384 df = 12		
Separated/Divorced	14 (6.4)	18 (9.0)	23 (11)	7 (3.3)	$p < 0.001$		
Widowed	0	2 (1.0)	4 (1.9)	1 (0.9)			
Cohabitant	30 (13.6)	29 (14.5)	25 (11.9)	14 (6.7)			
Education degree							
Middle school	9 (4.10)	23 (11.5)	25 (11.9)	2 (1.8)	60.555 df = 9 $p = < 0.001$		
High school	88 (40.0)	99 (49.5)	111 (53.1)	31 (28.7)			
Degree	93 (42.3)	64 (32.0)	53 (25.4)	53 (49.1)			
Post-degree	30 (13.7)	14 (7.0)	20 (9.6)	22 (20.4)			

Work Status					
Unemployed	49 (22.3)	43 (21.5)	54 (25.8)	10 (9.2)	60.555 df = 9 p = < 0.001
Student	31 (14.1)	7 (3.5)	9 (4.3)	27 (25.0)	
Employed	134 (60.9)	132 (66.0)	133 (63.7)	63 (58.3)	
Retired	6 (2.7)	18 (9.0)	13 (6.2)	8 (7.5)	
Socio-economic status					
Low	20 (9.1)	27 (13.5)	27 (12.9)	10 (9.2)	
Middle-Low	52 (23.7)	60 (30.0)	58 (27.7)	24 (22.2)	68.447 df = 12
Middle	120 (54.5)	100 (50.00)	113(54.1)	61 (56.5)	p = 0.103
Middle-High	26 (11.8)	13 (6.5)	11 (5.3)	13 (12.1)	
High	2 (0.9)	0	0	0	

2.1 Measurements

Sociodemographic questionnaire: Participants were asked to complete a brief sociodemographic form to gather general information such as age, gender, social status, education level, work status, socioeconomic status, and for clinical groups details regarding their CP diagnosis, such as the healthcare professional or institution responsible for the diagnosis and treatment.

Central Sensitization Inventory (CSI) (Chiarotto et al., 2018) assessed the overlapping symptomatic dimensions of the central sensitivity syndrome. It serves as a screening tool to help identify the presence of the syndrome and alert clinicians that presenting symptoms may be related to it. In patients with CP, the CSI has demonstrated satisfactory validity, with higher scores indicating a higher presence of CS. The Cronbach's alpha value for this measure in the current study was 0.87 (total score).

2.2 Statistical Analysis

JAMOVI (2.4.11) was employed to conduct statistical analysis. Data are presented ad means and standard deviation for continuous variables and as frequencies and percentage for discrete variables. A general linear model ANCOVA was performed to test differences in CSI scores covariate for age values, social and work status and educational level (all variables showing a statistically different distribution between groups). Social status as well as working status have been transformed in dichotomous variable, specifically social status was transformed in 0= not in a relationship (single, separated/divorced, widowed); 1= in a relationship (married/civil union, cohabitant), whereas work status was transformed in 0= not occupied (unoccupied and retired); 1= occupied (employed and student). Bonferroni correction was applied. A $p<.05$ was considered significant.

3. Results

Data analysis showed a good fit of the model (R2 Adjusted=.407; df=7; F=73.172; p<.001) and a significant difference between groups in CSI scores (p<.001). The only covariate variable included in the model that shows a significant effect was educational level (F= 32.208; p<.001) in the direction of a higher educational level associated to lower CSI scores regardless clinical condition. Post hoc test with Bonferroni test were performed showing that all the clinical groups scored significantly higher than HCs (all p<.001); FM and FM with CH clinical groups scored significantly higher than CH group (both p<.001), FM with CH scored significantly higher than FM (p=.007), thus FM with CH in comorbidity reported scored significantly higher to all other groups (see Figure 1). Figure 1 showed the trend of CSI scored obtained.

Figure 1. Differences between groups on CSI scores covariated for age, social and work status and educational level

	Chronic Headache (CH) (n = 220)	Fibromyalgia (FM) (n = 200)	Fibromyalgia and Chronic Headache (FM+CH) (n = 209)	Healthy Controls (HCs) (n = 108)	Significance		
	M ± SD	M ± SD	M ± SD	M ± SD	F	Bonferroni Post-hoc	Partial Eta²
CSI SCORE	59.51± 11.74	67.07 ± 12.80	71.47 ± 12.52	38.91 ± 19.40	113.106 df=3 $p < 0.001$	HCs < CH < FM < FM+CH	0.315

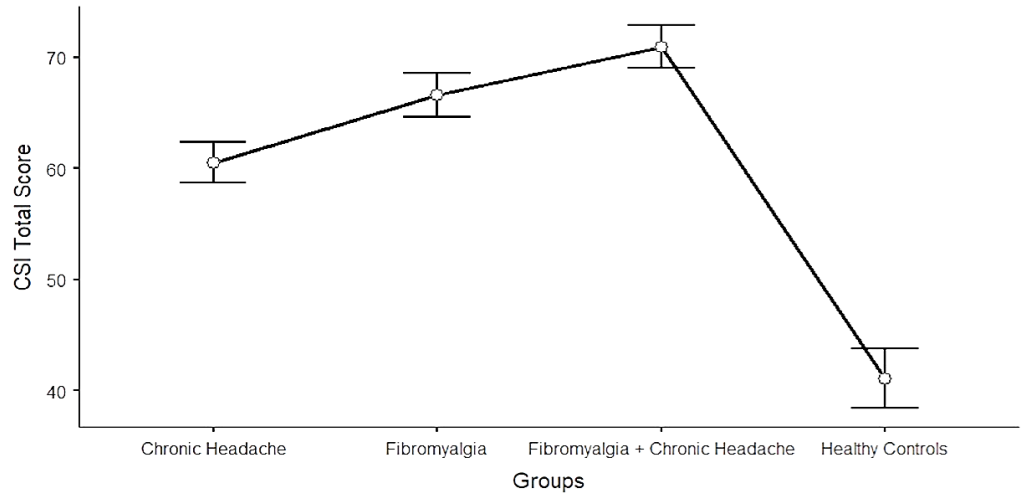

Figure 1. Differences between groups on CSI scores covariated for age, social, work status and educational level

4. Discussion

In accordance with study's hypothesis the HCs reported the lowest CSI scores compared to clinical groups, thus confirming the clinical relevance of CS in different CP conditions. Moreover, a discriminating role of CS seems conceivable also among CP conditions, especially in FM associated to CH.

In accordance with previous literature CSI is associated to different CP conditions with higher scores in clinical populations than in healthy controls (Adams et al., 2023; Falling et al., 2021).

Moreover, present findings seem to be in accordance with the international literature arising questions about the nature of this widely employed inventory that appear to assess high sensitivity in a broader sense than the one regarding the animal kingdom (i.e. increased summation of nociception, reduced inhibition of pain, hypervigilance to noxious and non-noxious stimuli etc.) including feelings of anxiety and depression, as well as cognitive impairment (Adams et al., 2021, 2023). In this light, CSI may be thus considered as an help in evaluating specific psychological profiles rather than simply centrally enhanced nociceptive responsivity (Adams et al., 2021, 2023). Psychological dimensions seem to be crucial, it should be considered that several features (as low affect regulation capabilities and high negative/dysphoric emotions) resulted to play a significant role in the perception of pain and patients' ability to manage it in several CP conditions, as patients suffering from migraine (Giri et al., 2022; Kocakaya et al., 2023) and fibromyalgia (Frumer et al., 2023; Galvez-Sánchez et al., 2020; Rost et al., 2021; Schmitz et al., 2021). In a recent study with episodic migraine patients (Guerra et al., 2024), a reduced quality of life was associated to a reduced affect regulation capabilities with related reduced possibility to effectively manage negative emotions, originating difficulties in integrated physical and mental symptoms, thus resulting in poor health management and higher pain perception.

As regards the differences between CPs conditions, a recent review (Arendt-Nielsen et al., 2018) sustained that although it is evident that CS is present to a greater or lesser extent across different CP conditions, it is not possible to rank them according to most or least CS. Nevertheless, it has been concluded that there seems to be a tendency that deep somatic or visceral chronic conditions have the most profound effect on the development of generalised sensitisation (Arendt-Nielsen et al., 2018). In this light, patients with musculoskeletal pain, as FM patients, are among those who are to live the largest percentage of their life with their disability chronic pain condition, thus time aspect may play a role for the central manifestations (Arendt-Nielsen et al., 2018).

On the other hand, if sensitization of cerebral pain pathways and persistent activation occurred in patients experiencing headache episodes, this alteration in brain activation could significantly contribute to the heightened risk of developing more widespread fibromyalgia pain (Marcus et al., 2005). These data support a hypothesis that ongoing headache activity results in a widespread dysregulation of pain mechanisms, which may increase risk for the development of other CP syndromes, like fibromyalgia (Marcus et al., 2005; Okifuji et al., 1999). In a large cohort study of primary headache patients (De Tommaso et al., 2011), headache frequency, anxiety, poor sleep quality, and physical disability emerged as the most discriminating elements for a FM

comorbidity with patients suffering from chronic migraine and chronic tension-type headache showing a greater probability of exhibiting the FM profile.

In the same direction also to suffer from several CP conditions may represent a risk factor for higher CS scores (Arendt-Nielsen et al., 2018). Psychological distress has been considered as negative prognostic factors for treatment of chronic migraine (Bottiroli et al., 2016). An association between psychological distress and symptoms of CS using the CSI has been evidenced, with both psychological distress and widespread pain significantly contributing to the variance in symptoms of CS (Van Wilgen et al., 2018).

Present study highlights also the role of educational level in the direction of more years of study associated to less CSI scores regardless the suffered clinical condition, in line with previous findings reporting that greater levels of completed schooling are correlated with lower pain prevalence (Haas & Fosse, 2008; Kennedy et al., 2014; Zimmer & Zajacova, 2018).

Present findings need to be interpreted in the light of some limits: a) the on-line data collection through institutional websites and social media of patients' associations, that may introduce a generalizability bias, b) self-reported diagnosis, that may be not precise as those reported by clinician in medical department, c) the lack of inclusion of psychological construct that may have a relevant role in these CP conditions. Hence, present findings should be considered preliminary and needs to be confirmed and further explored in future studies realized in clinical settings.

In conclusion, it appears relevant to include CSI dimension in the clinical evaluation performed with CP patients in order to better understand the complex connection between CP and mental health. In this sense, the CSI appears to be a tool that summarizes a series of psychological burden dimensions and can be used in a simple and agile way also by those without psychometric experience as it is a self-administered measure. This resulted to be in line with previous research findings performed on these clinical populations, supporting how CSI is strongly associated to both physical and psychological quality of life with the well know bidirectional effect on pathology severity and process of chronicity (Nimbi et al., 2023, 2024). Thus, CS assessment may be used to identify patients with specific psychological needs, and tailor treatment to individual patient characteristics thus improving precision pain medicine in clinical practices (Macfarlane et al., 2017).

Ethical approval

The institutional ethic committee of the Department of Dynamic and Clinical Psychology, and Health Studies at Sapienza University of Rome approved this study [Protocol number 0001979 UOR: SI000092—Classified VII/15-25 November 2022].

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data that support the findings of this study are available upon request from the author [FMN].

Conflict of interest statement

The author declare that the research was conducted in the absence of any potential conflict of interest

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