Central sensitivity in fibromyalgia: testing a model to explain the role of psychological factors on functioning and quality of life

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Abstract

Objective

Central sensitivity (CS) is defined as an increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold inputs. CS has recently been linked to the psychological burden associated with chronic pain, such as fibromyalgia (FM). The primary objective of this study is to investigate the impact of specific psychological constructs on CS in patients with FM. In Study 1, we explore the influence of temperament, personality, childhood trauma, defence mechanisms, and mental pain on CS. In Study 2, our goal is to test the role of the best predictors of CS in influencing quality of life (QoL) and FM functioning through a path analysis model.

Methods

A total of 510 women with FM participated online, completing a self-administered protocol. Data collection took place between April and June of 2023.

Results

In Study 1, higher levels of low sensory threshold (β=0.210), traumatic experiences of physical threat (β=0.141), neurotic defences (β=0.124), and mental pain (β=0.241) emerged as the strongest predictors of increased CS. In Study 2, the presented model demonstrated a satisfactory fit (chi2=27.200; df=10; p=0.002; GFI=0.984; NFI=0.949; CFI=0.967; RMSEA=0.061 [95% CI 0.034-0.090]) with large and medium effect sizes on physical (-0.576) and psychological (-0.190) QoL.

Conclusion

The study underscores the pivotal role of psychological dimensions in influencing CS levels and their relationships with QoL in patients with FM.

Key words

fibromyalgia, chronic pain, nociplastic pain, central sensitisation, environmental sensitivity

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Introduction

Fibromyalgia (FM) is a chronic pain syndrome characterised by generalised musculoskeletal pain and specific tender points, often associated with sleep disorders, fatigue, somatic and cognitive symptomatology, as well as mental diseases (1-4). In the general population, FM diagnosis has a prevalence ranging between 0.2% and 6.6%, with significant higher rates in women (2.4% to 6.8%), showing an increasing trend worldwide (5).

FM presents with multiple physical and mental comorbidities leading to disabling conditions with high psychological and social burden (1, 4, 6). Depression is the most prevalent comorbidity, affecting over half of the patients in their lifetime (7, 8). Other prevalent psychiatric disorders include bipolar disorder, panic disorder, anxiety disorder, or post-traumatic stress disorder, collectively affecting nearly one-third of FM patients (5). Regarding chronic pain (CP) comorbidities, rates range between 39% and 76%, primarily involving tension-type or migraine headache, irritable bowel syndrome, lower back pain, myofascial pain syndrome, and temporomandibular disorders (7). These elements highlight FM as a complex syndrome, associated with both a strong psychological component and other manifestations of chronic pain.

Although the aetiopathology of FM remains complex and largely unknown (1, 9), two main endotypes have been theorised. A peripheral endotype may result from alterations in nociceptive stimuli processing, small fibre neuropathy, inflammation, or autoimmune conditions. In contrast, a central endotype is described as the result of a central sensitisation (CS) process, where psychological (cognitive and affective) factors may play a primary role in symptom onset and maintenance (10). Since more evidence is needed to support these hypotheses, an in-depth study of CS is crucial for advancing our understanding of FM and related treatments.

The International Association for the Study of Pain (IASP) defines CS as an "increased responsiveness of nociceptive neurons in the central nervous system (CNS) to either normal or subthreshold afferent input" (11, 12). CS involves CNS dysfunctions, such as altered sensory processing within the brain, amplified cerebral activity in areas associated with severe pain, and reduced functioning of endogenous analgesia (13-17). Considered a key underlying mechanism of nociplastic pain (NP), CS describes conditions where altered function in pain-related sensory pathways in the periphery and CNS leads to pain, despite no clear evidence of actual or threatened tissue damage, as seen in FM (11, 18, 19). Recent proposals suggest that CS, as the main pathophysiological mechanism of FM, may be linked to sympathetic autonomic deficiencies indicative of small nerve fibre neuropathy (20). Abnormalities in central pain processing, rather than damage or inflammation of peripheral structures, play a crucial role in the development and maintenance of FM (14, 15).

Functional magnetic resonance imaging (fMRI) studies (21-23) have sought to elucidate how CS explains the mechanisms in fibromyalgia. A systematic review on structural and functional brain MRI exploring central sensitisation in fibromyalgia patients reported moderate evidence for region-specific changes in grey matter volume, decreased functional connectivity in the descending pain-modulating system, and increased activity in the pain matrix related to central sensitisation (24, 25). Functional MRI also reveals increased connectivity between the insula and anterior cingulate cortex, regions involved in pain perception and emotional regulation. Molecular mechanism studies (26, 27) indicate that somatosensory information is integrated in SDH lamina I projection neurons, which transmit signals to several brain regions such as the parabrachial nucleus and thalamus (27). In summary, functional neuroimaging studies have provided valuable insights into the pathophysiology of fibromyalgia, suggesting that the brain's response to pain is altered in FM patients.

To study the CS construct, the Central Sensitivity Inventory (CSI) was developed and validated (28) and has recently been used to assess symptom severi-

ty in FM patients (29). An updated systematic review (30) highlights that the CSI may be better aimed at capturing the main psychological characteristics associated with CP (*e.g.* depression, anxiety, pain catastrophising, distress, sleep disorders) rather than serving as a measure of CS *per se*. This emphasizes the central role of psychological experiences in chronic conditions such as FM and, overall, in patients' quality of life (QoL).

Specific psychological dimensions may play a primary role in affecting CS. The temperamental trait of sensory processing sensitivity (SPS) represents an amplified responsivity to positive and negative environmental and social stimuli (31), strongly linked to different CP conditions like FM (32, 33). Personality traits, defined as tendencies and patterns of thinking, feeling, and acting (34) are strongly associated with pain perception (32). Childhood traumatic experiences might contribute to permanently changing the responsiveness of the CNS (35), serving as vulnerability factors for CS progression. For example, significant associations between childhood maltreatment and CP conditions in adulthood have been reported in several systematic reviews (36-40). Defence mechanisms, a group of automatic psychological strategies mediating reactions to inner or exterior stressors or emotional struggles, have also been associated with pain perception (41, 42). A recent study highlighted a significant association between increased disease severity, decreased mature defence mechanisms, and increased immature defence mechanisms in FM patients (24). Additionally, mental pain is a newly defined unitary subjective state of psychological and emotional suffering resulting from behavioural and cognitive processes commonly reported in patients suffering from different CP conditions (43, 44), which may play a role in explaining the CS process. To explore the possible role of these psychological factors in the CS process and, more broadly, their role in determining FM impact and QoL in patients, it is crucial to advance our knowledge of this disease and improve therapeutic proposals for patients.

Aims

The primary objective of this research is to investigate the role of selected psychological constructs in influencing CS in a group of patients with FM (Study 1). In this context, the specific goal of Study 1 is to explore the unique and collective impact of factors such as sensory processing sensitivity (SPS) temperament, personality traits, childhood adverse events, defence mechanisms, and mental pain on CS. It is anticipated that higher scores in SPS, personality traits (such as detachment and psychoticism), childhood traumatic experiences, neurotic and immature defences, and mental pain will predict elevated CSI scores in FM.

The main objective of Study 2 is to assess the role of the best predictors identified in Study 1 through two distinct path diagrams. These diagrams will examine the relationships between psychological domains and CS in predicting physical and psychological quality of life (QoL) (model 1) and the perceived impact of FM (model 2). The hypothesis posits that these selected variables will significantly contribute to predicting deteriorated physical and psychological QoL, as well as a heightened perceived impact of FM through CS.

Materials and methods

Procedures

A total of 529 individuals from Italy participated in this study, recruited through patients' FM associations using official websites and various social media platforms, including Facebook, Instagram, Twitter, and LinkedIn. The survey was administered online via Google Forms, with data collection occurring between April and June of 2023. Participants were required to provide informed consent before engaging in the survey, disclosing details about their FM diagnosis, the year it was determined, and the healthcare professional or medical facility responsible for the diagnosis. The survey ensured anonymity, and participants received no compensation for their involvement. Ethical approval for the project was obtained from the ethical committee of the Department of Dynamic and Clinical Psychology and Health Studies at Sapienza University of Rome, Italy, on November 25, 2022 [protocol no. 0001979 UOR: SI000092 – classified VII/15]. To be eligible, individuals had to identify as cisgender women, be 18 years or older, proficient in Italian, and have received an FM diagnosis from a specialist physician (neurologist or rheumatologist) for at least six months. After excluding nineteen responses (3.59%) due to duplication, falsification, or incomplete records, the final group consisted of 510 participants. Sociodemographic characteristics of this group are summarised in Table I.

Participants

The study participants presented an average age of 45.92 years (ranging from 18 to 75). They predominantly identified as heterosexual, married, and engaged in monogamous relationships. The majority had moderate to moderately high levels of education, with nearly 64% employed. The prevalent ethnic background was white Caucasian, and they primarily resided in small towns or cities with a medium to medium-low socioeconomic status. All participants had received an FM diagnosis between 1982 and 2022, mostly from specialised physicians in neurology and rheumatology. Comorbidities reported included chronic migraine/tension-type headaches, irritable bowel syndrome (IBS), and chronic fatigue syndrome.

Measures

The participants completed nine self-report measures to investigating specific psychological variables aligned with the objectives of the study. The completion time for these assessments was approximately 30 minutes.

Sociodemographic questionnaire. Participants were requested to fill out a concise sociodemographic questionnaire to gather general details such as age, gender, sexual orientation, marital and relational status, level of education, employment status, socioeconomic standing, ethnicity, residential area, and pertinent information related to the diagnosis of FM and other chronic pain conditions.

Table I. Sociodemographic variables description.

Variables		Participants (n=510) M ± ds (min-max)
Age		45.92±12.34 (18-75) Q_3– Q_1: 37-55
		n (%)
Prevalent sexual orientation	Heterosexual	483 (94.71)
	Lesbian	21 (4.12)
	Bisexual, pansexual and polysexual	4 (0.78)
	Asexual, demisexual, grey-sexual	2 (0.39)
Marital status	Unmarried	131 (25.69)
	Married - civil union	252 (49.41)
	Separated - divorced	54 (10.59)
	Widowed	7 (1.37)
	Cohabitant	66 (12.94)
Relational status	Single	116 (22.75)
	Monogamous couple	388 (76.08)
	Non monogamous relationship	6 (1.18)
Education level	Middle School	57 (11.18)
	High School	255 (50.0)
	University	155 (30.39)
	PhD and Postgrads courses	43 (8.43)
Work status	Unemployed	120 (23.53)
	Student	28 (5.49)
	Employed	326 (63.92)
	Retired	36 (7.06)
Socio-economic status	Low	70 (13.73)
	Medium-low	153 (30.0)
	Medium	256 (50.20)
	Medium-high	30 (5.88)
	High	1 (0.20)
Area of residence	Metropolis	31 (6.08)
	City	150 (29.41)
	Suburbs	74 (14.51)
	Village/small town	225 (44.12)
	Rural area	30 (5.88)
Ethnicity	White/Caucasian	499 (97.84)
	Asian/Pacific Ocean	-
	Latin-American/Hispanic	9 (1.76)
	Black/African/Afro-American	-
	Native American	-
	Others (mixed ethnicity)	2 (0.39)
Copresence of other chronic pain conditions	Restless leg syndrome (RLS)	161 (31.57)
	Chronic fatigue syndrome (CFS)	247 (48.43)
	Chronic migraine and tensive headache	267 (52.35)
	Temporomandibular disorders (TMD)	155 (30.39)
	Irritable bowel syndrome (IBS)	287 (56.27)
	Vulvodynia	110 (21.57)

Central sensitisation inventory (CSI). This assessment was designed to appraise the overlapping symptomatic aspects of the central sensitivity syndrome. It serves as a tool for preliminary screening to detect the presence of the syndrome and to alert clinicians to potential symptom-related connections. The inventory comprises two sections: part A yields a total score ranging from 0 to 100 for 25 items concerning current health symptoms, with response options on a scale from never = 0 to always = 4; part B investigates whether patients were previously diagnosed by a physician with any of seven distinct conditions. The CSI demonstrated satisfactory validity among chronic pain patients, wherein higher scores indicate a greater manifestation of central sensitivity. The Cronbach's alpha coefficient for this measure in the present study was 0.87 (total score) (45).

Highly sensitive person scale (HSP-12). This questionnaire delves into the theoretical construct of sensory processing sensitivity, which pertains to a temperamental trait that predisposes individuals to a broader sensory processing of information captured through diverse indicators, extending beyond mere sensitivity to sensory stimuli (31, 46). The survey generates a comprehensive sensitivity score along with three sub-factors: ease of excitation (EOE), aesthetic sensitivity (AES), and low sensory threshold (LST). The psychometric characteristics of the HSP-12 were assessed by Pluess *et al*. (47). Elevated scores indicate a heightened degree of sensitivity. In the current study, the Cronbach's alpha coefficients for this assessment ranged from 0.79 (AES) to 0.89 (LST).

Traumatic experiences checklist (TEC). This instrument explores 29 potential trauma types, encompassing events outlined in criterion A of post-traumatic stress disorder (PTSD), as well as other potentially overwhelming occurrences such as loss of significant individuals, life-threatening illness or aggression, exposure to warehousing, emotional neglect, emotional abuse, physical abuse, sexual harassment, and sexual trauma. The questionnaire comprises a cumulative complex trauma score and five subscales that examine emotional neglect, emotional abuse, physical threat, sexual harassment, and sexual abuse. Enhanced scores signify a heightened presence and significance of traumatic experiences. In the present study, Cronbach's alpha coefficients for this tool ranged from 0.78 (emotional neglect) to 0.87 (physical threat) (48).

Personality inventory for the DSM-5 short form (PID-5-SF). This tool is a condensed version of the PID-5 self-report inventory designed to evaluate the 25 facets associated with pathological personality traits, as well as the five higher-order domains outlined in DSM-5 Criterion B: negative affect, detachment, antagonism, disinhibition, and psychoticism. Each trait domain comprises 5 items. Elevated scores indicate a heightened manifestation of the specific trait. In the present study, the Cronbach's alpha coefficients for this assessment ranged from 0.82 (psychoticism) to 0.90 (detachment) (49).

Table II. Group mean scores of the variables involved in the study.

Variable	Domains	Participants (n=510) M ± ds (min-max)
Central sensitivity inventory	Total score	70.15±13.07 (18-99)
Highly sensitive person scale	Easy of excitation (EOE)	5.53±1.37 (1.2-7)
	Low sensory threshold (LST)	5.32±1.26 (1.33-7)
	Aesthetic sensitivity (AES)	5.39±1.15 (1.25-7)
	Total score	5.43±0.92 (2.08-7)
Traumatic experiences checklist	Traumatic experience total	6.83±4.21 (0-22)
	Emotional neglect	6.48±5.48 (0-18)
	Emotional abuse	5.89±5.12 (0-18)
	Physical abuse	2.34±3.70 (0-18)
	Bodily threat	4.43±3.86 (0-18)
	Sexual harassment	2.27±3.29 (0-18)
	Sexual abuse	1.52±2.83 (0-18)
	Trauma total	22.92±17.53 (0-94)
Personality inventory for DSM-5	Negative Affect	7.56±3.23 (0-15)
	Detachment	5.14±3.00 (0-15)
	Antagonism	3.07±2.33 (0-15)
	Disinhibition	3.73±3.00 (0-15)
	Psychoticism	4.67±3.16 (0-15)
	Total score	24.18±11.50 (0-75)
Defence mechanisms rating scales	Neurotic	25.05±5.95 (4.35-55.56)
	Immature	35.93±9.41 (0-56.41)
	Overall defensive function (ODF)	4.97±0.42 (4.02-6.68)
Mental pain questionnaire	Total score	5.01±2.59 (0-10)
Short Form - 12	Physical QoL	47.65±12.78 (30-95)
	Psychological QoL	48.68±14.92 (21.42-92.82)
Revised Fibromyalgia Impact Questionnaire	Physical functioning	19.46±6.32 (0-30)
	General health status	12.91±5.28 (0-20)
	Symptoms	35.26±7.48 (8-50)
	Total score	67.63±16.84 (10-97.50)

Defence mechanism rating scales - self-report (DMRS-SR-30). (50). This instrument is rooted in the identification of 30 individual defence mechanisms organised hierarchically into various levels based on functional similarity and adaptability. The defence levels are further categorised as mature, neurotic, and immature. For this study, we focused on neurotic and immature defence mechanisms as potential predictors of CSI due to their significant collinearity with mature defences. Elevated scores indicate a greater utilisation of the respective defence mechanism. In the current study, the Cronbach's alpha coefficients for this measure ranged from 0.83 (neurotic) to 0.89 (immature) (50).

Mental pain questionnaire (MPQ). This self-report questionnaire consists of 10 true-false style items and was developed to evaluate mental pain, defined as a subjective state of psychological and emotional distress arising from cognitive and behavioural processes (44). Fava *et al*. (43, 51) provided a comprehensive operationalisation of mental pain, identifying 10 indicators: sensation of pain, feeling of heartbreak, sense of loss, perception of pain being pervasive, constant companionship of pain, inability to comprehend the pain's origin, experience of emptiness, loss of life's meaning, helplessness, and engagement in suicidal behaviours as a means to escape the pain. Elevated scores indicate a greater presence of mental pain. In this study, the Cronbach's alpha coefficient for this assessment was 0.76 (total score).

Short form (SF-12) - Quality of life assessment. The SF-12, derived from the original SF-36, is a concise generic health survey designed to gauge both physical and psychological QoL. It yields two summary measures for self-assessment of physical and mental health, interchangeable with the SF-36 outcomes. Enhanced scores reflect a higher level of QoL in the respective domain. This measure was presented as an optional component of the survey, leading to the participation of 458 respondents out of the final group of 510. In the current study, Cronbach's alpha coefficients for this measure ranged from 0.87 (mental health) to 0.88 (physical health) (52).

Revised fibromyalgia impact questionnaire (FIQR). This questionnaire is recognised as one of the most extensively employed FM-specific tools for comprehensively evaluating the range of issues associated with FM and its response to therapeutic interventions. Furthermore, it has long been regarded as the benchmark for assessing multidimensional function and health related QoL in FM patients. Psychometric investigations have affirmed the reliability, internal consistency, and three/two-dimensional framework of the FIQR within the FM population (encompassing function, symptoms, and general health status). The total score is predominantly utilised for evaluating function and health related QoL in FM patients. Like the SF-12, the FIQR was included as an optional component of the survey, with 458 participants completing it. In the current study, the Cronbach's alpha coefficient for this measure was 0.93 (total score) (53, 54).

Statistical analysis

In the first study, hierarchical multiple regression analyses were conducted using the enter method for each assessed domain to uncover significant predictors of central sensitivity, as presented in Table III. The independent variables encompassed the sub-scales of each questionnaire, while the dependent factor was the total score of the CSI. Following methodological recommendations by Petrocelli (55) and Lewis (56), the regression analyses were executed in six successive stages. These stages were structured as follows: (1) sociodemographics; (2) high sensitivity; (3) traumatic experiences; (4) personality traits; (5) defence mechanisms, and (6) mental pain. In a final step of hierarchical multiple regression analysis, as depicted in Table IV, the significant

Table III. Hierarchical Multiple Regression analyses (n=510).

1. Sociodemographic variables (R^2 = 0.088; F = 12.236; p<0.001)			
	B	***SE***	***β***
Age	0.009	0.045	0.009
Education level	-2.842	0.738	-0.172[1]
Socio-economic status	-3.285	0.716	-0.203[1]
Residence area (From the metropolis to the rural area)	-0.028	0.516	-0.002
[1]Bonferroni corrected p<0.0125			
2. Highly Sensitive Person Scale (R^2 = 0.235; F = 31.007; p<0.001)			
	B	***SE***	***β***
Education level	-1.896	0.687	-0.115[2]
Socio-economic status	-2.021	0.666	-0.125[2]
Easy of Excitation (EOE)	2.276	0.432	0.238[2]
Low Sensory Threshold (LST)	2.487	0.459	0.239[2]
Aesthetic Sensitivity (AES)	-0.740	0.465	-0.065
[2]Bonferroni corrected p<0.010			
3. Traumatic Experiences Checklist (R^2 = 0.190; F = 14.727; p<0.001)			
	B	***SE***	***β***
Education level	-2.636	0.690	-0.159[3]
Socio-economic status	-2.414	0.692	-0.149[3]
Emotional Neglect	0.321	0.123	0.134
Emotional Abuse	0.060	0.135	0.023
Physical Abuse	-0.126	0.189	-0.036
Bodily Threat	0.491	0.158	0.145[3]
Sexual Harassment	0.479	0.223	0.121
Sexual Abuse	0.243	0.249	0.053
[3]Bonferroni corrected p<0.006			
4. Personality Inventory for DSM-5 (R^2 = 0.208; F = 18.816; p<0.001)			
	B	***SE***	***β***
Education level	-1.781	0.697	-0.108
Socio-economic status	-2.126	0.683	-0.132[4]
Negative Affect	0.246	0.217	0.061
Detachment	0.655	0.245	0.151
Antagonism	-0.105	0.291	-0.019
Disinhibition	0.282	0.212	0.065
Psychoticism	0.731	0.236	0.177[4]
[4]Bonferroni corrected p<0.007			
5. Defense Mechanisms Rating Scales (R^2 = 0.168; F = 25.432; p<0.001)			
	B	***SE***	***β***
Education level	-1.890	0.714	-0.114[5]
Socio-economic status	-2.718	0.683	-0.168[5]
Neurotic defenses	0.370	0.093	0.168[5]
Immature defenses	0.371	0.058	0.267[5]
[5]Bonferroni corrected p<0.0125			
6. Mental Pain Questionnaire (R^2 = 0.233; F = 51.290; p<0.001)			
	B	***SE***	***β***
Education level	-2.121	0.671	-0.128[6]
Socio-economic status	-1.895	0.665	-0.117[6]
Mental Pain	1.991	0.204	0.395[6]
[6]Bonferroni corrected p<0.017			

variables identified in the preceding regressions were incorporated to identify the most robust predictors of central sensitivity using the enter method. To control for potential confounding, socio-demographic variables found to be significant in stage 1 (education level and socio-economic status) were introduced as covariates in all hierarchical multiple regression analyses. To mitigate the risk of false positives (error type 1), the Bonferroni multiple-comparison correction was applied at each stage of the hierarchical multiple regression analysis.

For the second study, a path analysis model grounded in theoretical considerations was constructed. This model aimed to examine more enduring traits hypothesised to influence central sensitisation, alongside the resulting health outcomes, namely psychological and physical QoL variables depicted in Figure 1, and the total score of the FIQR as portrayed in Figure 2. To gauge the model's fit, various fit indices including chi-squared, goodness of fit (GFI), normed fit index (NFI), comparative fit index (CFI), and root mean square error of approximation (RMSEA) were employed. The model's effects, encompassing total, direct and indirect pathways, were reported. The statistical analyses were carried out utilising IBM SPSS v. 27.0 (SPSS Inc., Chicago, IL, USA) and SPSS AMOS.

Results

Study 1

Table II reports the descriptive statistics of psychological variables assessed for the current study. To ensure sufficient statistical power (0.80), a predetermined minimum of 160 participants was calculated a priori for the subsequent analyses. These analyses encompassed 21 predictors and necessitated a minimum effect size of 0.15. The effective sample size for the hierarchical multiple regression analyses ultimately reached 510 participants, resulting in a *post-hoc* observed statistical power of 0.99.

To test the best predictors of central sensitivity in FM patients, a series of multiple hierarchical regression analyses were run utilising the enter method (Table III). Education level and socio-economic status were retained as covariates from step 2 on, while each questionnaire domain served as an independent variable. Predictors that emerged as statistically significant were EOE, LST, bodily threat experiences, traits indicative of psychoticism, employment of neurotic and immature defence mechanisms, and the presence of mental pain. Specifically, higher CSI levels were associated with lower education and socio-economic status (sociodemographic), heightened responsiveness to stimuli (EOE) and reduced sensory thresholds (LST), an increased presence and impact of traumatic experiences related to bodily threat, higher scores in psychoticism traits, higher employment of neurotic and immature defence mechanisms, and amplified mental pain.

To identify the strongest predictors of CS, a final hierarchical multiple regres-

Table IV. Final Hierarchical Multiple Regression analyses on best predictors emerged (n=510).

Final regression – Central Sensitization Best Predictors (R^2 = 0.366; F = 31.990; p<0.001)			
	B	***SE***	***β***
Step 1 (covariates)			
Education level	-2.863	0.727	-0.173[a]
Socio-economic status	-3.248	0.709	-0.201[a]
[a]*Bonferroni corrected p<.025*			
Step 2			
Education level	-1.242	0.630	-0.075
Socio-economic status	-1.186	0.616	-0.073
Easy of Excitation (EOE)	0.722	0.421	0.075
Low Sensory Threshold (LST)	2.186	0.425	0.210[b]
Bodily Threat	0.477	0.127	0.141[b]
Psychoticism	0.429	0.178	0.103
Neurotic defences	0.274	0.086	0.124[b]
Immature defences	0.122	0.061	0.088
Mental Pain	1.214	0.213	0.241[b]
[b]*Bonferroni corrected p<0.0056*			

sion analysis was executed. Education level and socio-economic status were maintained as covariates (Table IV, Step 1), while factors that exhibited significance in the preceding analyses were employed as possible predictors (Table IV, Step 2). The model was statistically significant, explaining 37% of the variance in central sensitivity ($F_{(9,499)} = 31.990, p<0.001, \Delta R^2=0.366$). Among the various factors considered, LST, experiences related to bodily threats, neurotic defences, mental pain emerged again as significant predictors of CS in the final round, with mental pain as the strongest one (t=5.691).

Study 2

The objective of the second study was to test a model describing the interaction between the psychological factors that emerged in Study 1 in predicting CS values considering the potential impact, on one side, on psychological and physical QoL, and, on the other side, on the FM functioning. Figure 1 portrays the constructed path diagram, which considers not only the direct effects of psychological variables on CS and psychological and physical QoL, but also their interactions. Neurotic defences and LST, held a prominent position in the model's outset. Additionally, bodily threat was established as an endogenous variable contingent upon LST. Similarly, mental pain was categorised as an endogenous variable, influenced by neurotic defences, LST, and bodily threat. Psychological and physical QoL were positioned at the model's end, both influenced by central sensitisation. Notably, a direct pathway was depicted from mental pain to psychological QoL.

The model was tested with 458 participants among the original 510 from Study 1 who had completed the supplementary QoL measure. Considering the potential reduction in statistical power for chi-squared-based analyses when surpassing 200 participants, the model displayed a satisfactory fit to the data (chi^2=27.200; df=10; p=0.002; GFI=0.984; NFI=0.949; CFI=0.967; RMSEA=0.061 [95% CI 0.034–0.090]). All endogenous paths were determined to be statistically significant (Fig. 1). The comprehensive effects, encompassing total, direct, and indirect influences, are reported in Table V. The standardised total effects of LST and neurotic defences on central sensitisation exhibited large and small effect sizes (LST=0.364; neurotic defences = 0.094). Similarly, the impact of mental pain on CS was also large (0.352). Regarding the cumulative effects of CS on general health, large and medium effects were observed on physical (-0.576) and psychological QoL (-0.190). This model explained 31.9% of the variance in CS, 20.8% in psychological QoL, and 33.1% in physical QoL.

Furthermore, the authors endeavoured to extend their examination to include the effects of psychological variables on the FIQR total score, an established index used to gauge the impact of FM on

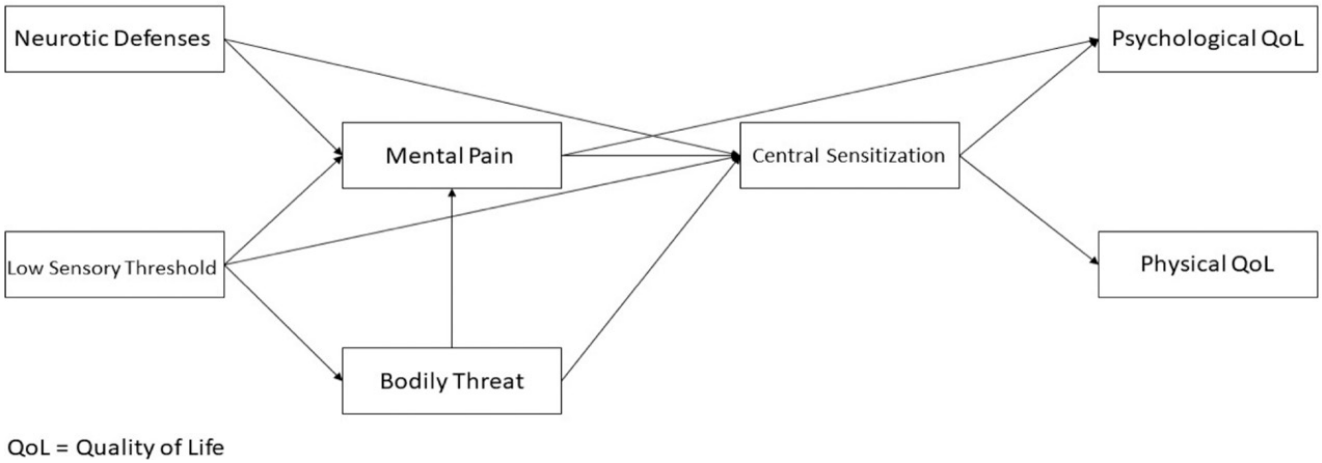

Fig. 1. Path diagram model of neurotic defences and low sensory threshold on central sensitisation and quality of life.

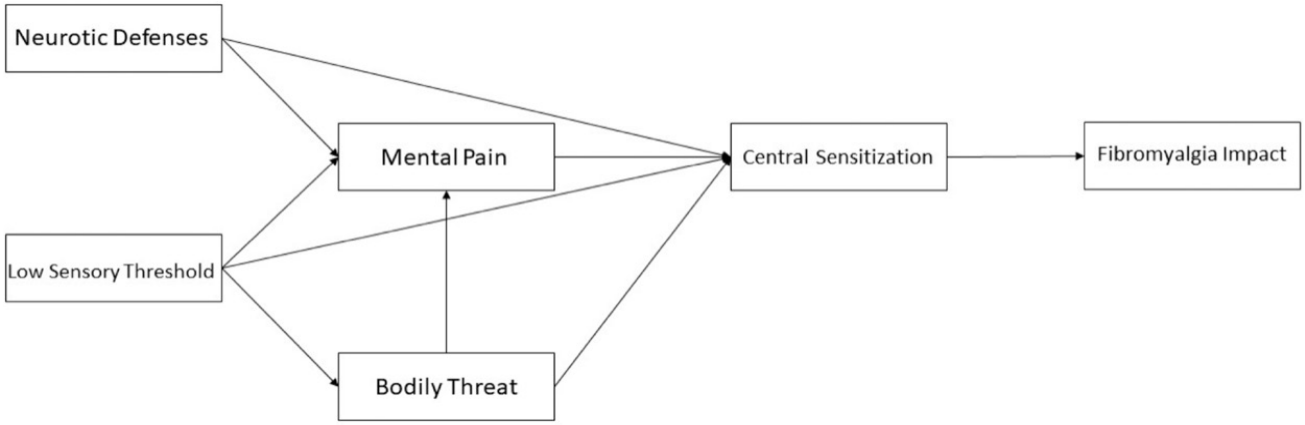

Fig. 2. Path diagram model of neurotic defences and low sensory threshold on central sensitization and fibromyalgia impact on patients.

Table V. Standardised total, direct, and indirect effects of the model (n=458).

	Low sensory threshold	Neurotic defences	Bodily threat	Mental pain	Central sensitisation
Total effects					
Bodily threat	0.223**	-	-	-	-
Mental pain	0.171**	0.094***	0.127***	-	-
Central sensitisation	0.364**	0.178**	0.199**	0.352**	-
Physical QoL	-0.209**	-0.102**	-0.114**	-0.203**	-0.576**
Psychological QoL	-0.127**	-0.066**	-0.081**	-0.407**	-0.190**
Direct effects					
Bodily threat	0.223**	-	-	-	-
Mental pain	0.143**	0.094***	0.127***	-	-
Central sensitisation	0.269**	0.144**	0.154**	0.352**	-
Physical QoL	-	-	-	-	-0.576**
Psychological QoL	-	-	-	-0.340**	-0.190**
Indirect effects					
Bodily threat	-	-	-	-	-
Mental pain	0.028***	-	-	-	-
Central sensitisation	0.095**	0.033***	0.045**	-	-
Physical QoL	-0.209**	-0.102**	-0.114**	-0.203**	-
Psychological QoL	-0.127**	-0.066**	-0.081**	-0.067**	-

Two-tailed significance bootstrap on 500 samples; bias corrected percentile method.
*p<0.001 **p<0.01 ***p<0.05.

patients. Figure 2 shows the same path diagram tested in Figure 1, where the FIQR total score were posed at the model's culmination, dependent on CS. The results of the model's assessment indicated satisfactory data fit (chi^2=17.191; df=6; p=0.009; GFI=0.988; NFI=0.964; CFI=0.976; RMSEA=0.064 [95% CI 0.030–0.100]). Every endogenous path within the diagram was found to carry statistical significance. A comprehensive account of the effects, including total, direct, and indirect, is provided in Table VI. The standardised total impact of CS on the FIQR was large (-0.645). This model counted for 31.9% of the variance in CS and 41.6% in the FIQR total score.

Discussion

The principal aim of Study 1 was to explore the role of sensory processing sensitivity, personality traits, childhood adversities, defence mechanisms and mental pain in influencing CS in a group of patients with FM. Multiple regression analysis, controlled for educational level and socioeconomic status, showed that higher EOE, lower LST, greater bodily threat experiences, higher presence of psychoticism personality dimension, greater immature and neurotic defence mechanisms, and higher level of mental pain predicted higher CSI scores. The final hierarchical regression model highlighted a stronger predictive role on CS scores for LST, bodily threat experiences, neurotic defences and mental pain. These findings seem to confirm the hypothesis that specific psychological factors are directly related to CS and, consequently, may influence the patient's health status.

The findings showed to be in accordance to the broader literature to FM (57-59) producing further evidences for a specific psychological profile associated to CS process. In particular, a low sensory threshold represents a temperamental trait predisposing a greater responsivity to environmental and social stimuli (60). Highly sensitive people appear to be more reactive to both positive and negative stimuli, and may be predisposed to greater CS activation, especially in cases of CP diseases such as FM (61). Another psychological dimension resulting a significant predictor of CS scores was the experience of bodily threat during childhood. It refers directly to the experience of physical pain and death (even if only supposed) which does not only concern violent acts perpetrated by an abuser, but also illnesses or accidents that have threatened the person's integrity. This appears to be in line with the studies showing that adverse childhood experiences seem to improve the risk of developing FM in adulthood (1, 62, 63).

Moreover, neurotic defence mechanisms were significantly associated to high CSI scores. Considering neurotic defences such as intellectualisation, isolation of affect and displacement (42), these could be interpreted as psychological unconscious strategies of

Table VI. Standardised total, direct, and indirect effects of the model (n=458).

	Low sensory threshold	Neurotic defences	Bodily threat	Mental pain	Central sensitisation
Total effects					
Bodily threat	0.223**	-	-	-	-
Mental pain	0.171**	0.094***	0.127***	-	-
Central sensitisation	0.364**	0.178**	0.199**	0.352**	-
FIQR total score	0.235**	0.115**	0.128**	0.227**	0.645**
Direct effects					
Bodily threat	0.223**	-	-	-	-
Mental pain	0.143**	0.094***	0.127***	-	-
Central sensitisation	0.269**	0.144**	0.154**	0.352**	-
FIQR total score	-	-	-	-	0.645**
Indirect effects					
Bodily threat	-	-	-	-	-
Mental pain	0.028***	-	-	-	-
Central sensitisation	0.095**	0.033***	0.045**	-	-
FIQR total score	0.235**	0.115**	0.128**	0.227**	-

Two-tailed significance bootstrap on 500 samples; bias corrected percentile method.
*p<0.001 **p<0.01 ***p<0.05.

harm avoidance involved in the process of sensibilisation and reinforcement of painful experiences. In this sense, neurotic defences may play a relevant role in the chronicisation of NP when extensively applied by the patients as pain avoidance strategy. In this light, harm avoidance and maladaptive defence style resulted as significant predictors of patients' psychological distress, determining a worsening in the general QoL in FM patients (64). Interestingly, mental pain seems to be the most important predictor of CS in the current sample of FM patients. This psychological construct proposed by Fava *et al*. (43) defined a condition linking bodily sensations to the subjective perception and cognitive interpretation of pain. Hence, it is reasonable to suppose that in the current study mental pain, together with other psychological dimensions, may contribute, on the one hand, to the onset of FM, and, on the other one, to the maintenance of the vicious cycle through the CS. This might be especially relevant in FM conditions in which a genetic and environmental predisposition was sustained (65), such as in the case of FM central endotype (10). Taking charge of the elements that emerged in this study by the clinical team can favour a more holistic approach to the patient with FM, not only oriented towards the painful symptom, but towards an improvement in functioning and QoL. Specifically, the clinician should investigate these areas in the diagnostic process and evaluate the role and need for an integrated psychosomatic intervention.

The second study aimed to test the role of the best predictors emerged in study 1 in two similar path diagrams examining the relationships between the main variables related to CS and their role in predicting the QoL and the perceived FM impact. The path analysis supported the model in which neurotic defence mechanisms and low sensory threshold held a central position, with neurotic defences showing a smaller magnitude on central sensitisation (0.094) than low sensory threshold (0.364). Similarly, the impact of mental pain on central sensitisation was large (0.352). Interestingly, a direct influence of mental pain on psychological QoL has been confirmed, supporting a central negative effect on psychological wellbeing of typical manifestations of mental pain such as guilt, anguish, fear, panic, loneliness, and helplessness (43).

The model presented is useful for directing the clinical psychological treatment of some patients with FM with the aim of improving their QoL. In other words, FM patients may benefit from a specific psychotherapeutic intervention aimed at improving the QoL and reducing distress through a specific work on mental pain and on the elaboration of traumatic experiences (62). About the effects of CS on QoL, the model showed a large and medium effect on physical and psychological QoL, respectively. Hence, CS seems to have a central role in determining the wellbeing of patients suffering from FM. A very similar discussion can be made for the second model which varies only by the function of the CSI on the impact of FM.

The key message of this research is that psychological aspects are central to QoL and FM impact. In this sense, the CSI appears to be a tool that summarises all these factors and can be used in a simple and agile way even by those without psychometric experience as it is a self-administered measure. 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 (66). This appeared particularly relevant in FM considering the high psychopathological comorbidity shown by FM patients. However, we do not know whether this mechanism is specific of FM or shared with other chronic pain conditions as migraine (67).

Future studies should explore to what extent the psychological variables identified in the current research can identify different subgroups of patients with unique clinical specificities, as well as test the effectiveness of specific treatments for example on trauma and defence mechanisms in FM.

Although this study presents promising new findings, some limitations need to be discussed: (i) Participants were recruited using a "snowball" technique on institutional websites and social media of patients' associations, so the results may not be generalisable to the entire FM population, despite the good variability of participants involved. (ii) The study relied on self-report questionnaires, which may introduce response bias if participants falsify their responses. (iii) Diagnoses were self-reported by participants without differentiation of specific sub-types. While validation information for the diagnosis was collected in the survey, such as year of diagnosis and referral to specialists, cases

of self-diagnosis cannot be entirely ruled out. Hence, the evidence presented should be considered preliminary and needs to be confirmed and further explored in future studies.

Conclusion

This study underscores the central role of specific psychological factors (namely SPS temperament, personality traits, childhood adverse events, defence mechanisms, and mental pain) in the process of CS in patients with FM and represents a small step forward in the search for stronger evidence that various manifestations of FM and NP in general may exist. Specifically, in the opinion of the authors, this study goes in the direction of the hypothesis that at least two FM endotypes may exist (peripheral and central), and that the central FM endotype might be interpreted as the result of a central sensitisation (CS) process, in which psychological factors play a primary role in the onset and maintenance of the symptoms (10). But much remains to be done to have strong evidence in this sense, towards a more in-depth study of CS in FM and other CP conditions.

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