Pain catastrophizing is associated with the Val66Met polymorphism of the brain-derived neurotrophic factor in fibromyalgia

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Abstract

Background: Fibromyalgia (FM) is a musculoskeletal chronic pain syndrome that impacts negatively patient's daily lives. Its pathogenesis is characterized by a complex relationship between biological and psychosocial factors not fully understood yet. Pain catastrophizing is associated with FM and is an important predictor of outcomes. This study aimed to answer two questions: (i) whether the allele and genotype frequencies of BDNF Val66Met (rs6265) polymorphism differs between FM patients and healthy controls (HC); and (ii) if the BDNF Val66Met polymorphism is a factor that predicts pain catastrophizing in FM.

Methods: In a cross-sectional design, 108 FM patients and 108 HC were included. FM patients responded to the Brazilian Portuguese version of the Pain Catastrophizing Scale (BP-PCS) to assess pain catastrophizing, as well as other validated tools for anxiety (The State-Trait Anxiety Inventory - STAI), depression (Beck Depression Inventory II – BDI-II) and functional aspects (Fibromyalgia Impact Questionnaire - FIQ; Central Sensitization Inventory validated and adapted for Brazilian population - CSI-BP; Pittsburgh Sleep Quality Index - PSQI; and Resilience Scale). All subjects were genotyped for the BDNF Val66Met polymorphism.

Results: Val allele was significantly more frequent in FM patients compared to the control group ($p < 0.05$). Also, FM patients with Val/Val genotype showed more pain catastrophizing thoughts, and this genotype was significantly associated with magnification and rumination dimensions of BP-PCS ($p < 0.05$). Furthermore, there were significant differences in levels of anxiety and symptoms of depression, years of education, and the functional situation between the FM and control groups.

Conclusions: The findings show an association of BDNF Val66Met polymorphism with pain catastrophizing in FM, which opens new avenues to comprehend the interplay between molecular genetic characteristics and neuroplasticity mechanisms underpinning FM.

Keywords: Fibromyalgia, Pain catastrophizing, BDNF, Single nucleotide polymorphism, Val66Met

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Background

The widespread chronic pain is a recognized cardinal symptom of fibromyalgia [1, 2]. Nevertheless, manifestations of central sensitization syndrome (CSS), such as fatigue, body stiffness, sleep disturbances, depression, anxiety, cognitive problems, and pain catastrophizing co-occur [1, 2]. The CSS refers to an amplification of pain by central nervous system mechanisms, and it is considered a main mechanism generator of pain hypersensitivity in conditions such as FM [3].

Positive and negative emotions and attention state can amplify the pain perception [4]. Pain catastrophizing is an exaggerated negative mental set brought to bear during an actual or an anticipated painful experience [5]. It comprises three dimensions: helplessness, magnification, and rumination [5]. More severe pain, as well as higher levels of pain behavior and disability, is detected in individuals who score higher on measures of pain catastrophizing [6]. Pain catastrophizing is a psychological factor that markedly predicts variability in the perception of pain as well as in the development of chronic pain conditions [6]. It has been associated with increased activity in pain-related areas of the brain [7, 8], and a decrease in the functioning of opioid-mediated endogenous analgesic systems [9]. Notably, the brain-derived neurotrophic factor (BDNF) is involved in central sensitization phenomena [10].

The BDNF is a neurotrophin from the nerve growth factor family implicated in several molecular processes in the central nervous system (CNS) [11, 12] modulating the formation, maturation, and plasticity of neuronal synapses [13]. The BDNF strengthens excitatory (glutamatergic) synapses and weakens inhibitory (GABAergic) synapses. Although preliminary, studies have indicated that the BDNF polymorphisms can be proneness factors to the severity of psychological symptoms associated with chronic pain (e.g., anxiety, depression, etc.) [14, 15]. The most common single nucleotide polymorphism in the BDNF gene (c.196G > A, dbSNP: rs6265) causes an amino acid substitution of valine to methionine at amino acid residue 66 (Val66Met; rs6265). This polymorphism alters intracellular trafficking and packaging of pro-BDNF and, consequently, the regulated secretion of the mature peptide [16]. Individuals with one or two copies of the BDNF Met allele seem to have decreased brain plasticity [17]. According to recent genome-wide study, the Val allele is related to a higher risk of chronic post-surgical pain [18]. And, it has been associated with the severity of depression [19, 20]). Thus, Val66Met polymorphism is a candidate for individual differences observed in neuroplasticity and, therefore, in behavioral pain conditions. Despite the well-known clinical relevance of pain catastrophizing, the neurobiological underpinnings of the phenomenon have just begun to be specified [21]. Furthermore, there is a persistent gap in the literature to investigate whether inter-subject genetic variation on BDNF Val66Met polymorphism might be a predictive factor of pain catastrophizing.

Thus, this study aimed to answer two questions: (i) whether the allele and genotype frequencies of BDNF Val66Met polymorphism differs between FM patients and HC; (ii) if the BDNF Val66Met polymorphism is a factor that markedly predicts pain catastrophizing in FM. Our hypothesis is that catastrophizing may be influenced by genetic factors and pain catastrophizing can predispose patients to more severe symptoms.

Methods

Design, settings and subjects

We conducted an exploratory cross-sectional study. This study was reported following the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines [22]. The Ethics Committee Board of the Hospital de Clínicas de Porto Alegre (HCPA) and Universidade Luterana do Brazil (ULBRA) approved the protocol of this study. All participants consent overtly before their participation.

Recruitment, inclusion and exclusion criteria

We recruited women older than 18. Patients were recruited from outpatient palliative medicine and pain clinics at a private-public hospital, physiotherapy clinics from the metropolitan region of Porto Alegre, Brazil, and by website and social network disclosure. Healthy volunteers were recruited from a blood donation service at the same hospital. Inclusion criteria for patients were: previous diagnosis of FM according to the American College of Rheumatology criteria [23]. Patients who presented illicit drug abuse or comorbidity with oncological disease were excluded. HC included in the study denied any condition of chronic pain, fibromyalgia, systemic lupus erythematosus, arthrosis, or rheumatoid arthritis or use of antidepressant drugs. Both groups were recruited from June 2016 to March 2018. FM patients were matched with controls according to age and gender.

Dependent and independent variables of main interest

The dependent variable was the Brazilian Portuguese version of the Pain Catastrophizing Scale (BP-PCS) (total score) and its domains: helplessness, magnification, and rumination (subscales' scores) [24]. The main interest factors were the genotypes of Val66Met BDNF (rs6265) polymorphism.

Instruments and assessments

All tools, adapted and validated for the Brazilian population, were responded by the clinical group, except the Beck Depression Inventory II (BDI-II) and **S**tate-Trait

Anxiety Inventory (STAI), which were answered by both clinical and control groups.

a) Brazilian Portuguese version of the Pain Catastrophizing Scale (BP-PCS [24];) was applied to assess pain catastrophizing. It consists of 13 items (rated on a 5-point Likert-type scale) to assess patient's thoughts and feelings when they are in pain. The scale is divided into three domains: helplessness (6 items), magnification (3 items), and rumination (4 items). The BP-PCS total score ranges from 0 to 52 points. A cutoff score of 30 represents clinically relevant level of catastrophizing [25].

b) Resilience Scale adapted for the Brazilian population [26] was used to evaluate emotional resilience, defined as levels of positive psychosocial adaptation in the face of important life events. It comprises 25 items rated on a 7-point Likert-type scale and total score ranges from 25 to 175 points. Higher scores indicate higher resilience.

c) Central Sensitization Inventory validated and adapted for Brazilian population (CSI-BP [27]) was applied to assess the severity of central sensitization. The inventory consists of 25 statements rated on 5-point Likert-type scale regarding current health symptoms (part A). Information about Central Sensitization Syndromes and related conditions are collected in part B of the inventory. The cutoff point suggested by CSI-BP is 35. The total score ranges from zero to 100.

d) The Brazilian validated version of the Fibromyalgia Impact Questionnaire (FIQ [28];) was used to assess the impact of FM in quality of life of patients. The questionnaire consists of 10 items, and the higher the score obtained, the greater the impact of fibromyalgia on quality of life (maximum total score is 100).

e) Pittsburgh Sleep Quality Index (PSQI) validated for Brazilian Portuguese [29] was used to evaluate the sleep quality and disturbances over a 1-month period. The index consists of multiple-choice questions that investigate: frequency of sleep disturbances; subjective sleep quality; typical bedtime; time of awakening; sleep latency; and, sleep duration. A global score ranges from zero to 21 whereas scores > 5 suggests poor sleep quality.

f) Brazilian Portuguese version of the Beck Depression Inventory II (BDI-II [30];) was used to evaluate depressive symptoms in patients and controls. The BDI-II consists of 21 sets of statements about depression symptoms regarding the last 15 days, is rated from a zero to 3 ordinal scale (total score ranges from zero to 63 points). Patients can be classified according to severity of symptoms: 0–13, minimal/no depression; 14–19, mild depression; 20–28, moderate depression; and 29–63, severe depression.

g) The State-Trait Anxiety Inventory (STAI) – short version, adapted to Brazilian Portuguese with a shorter version [31] was applied to evaluate anxiety. The scale is Likert-type and divided in two parts for the assessment of two types of anxiety: state-anxiety - a fact-driven transient anxiety; and, trait-anxiety - stable personality disposition, showing general level of fearfulness. The score ranges from 13 to 52 for the state-anxiety scale, and from 12 to 36 for the trait-anxiety scale. Higher scores denote higher levels of anxiety.

h) Standardized Questionnaire was used to assess socio-demographic and health data (with extended medical information questions for FM patients).

Genetic analyses
Blood samples were collected by venipuncture in 4 ml tubes containing Ethylenediamine tetraacetic acid (EDTA), and centrifuged for plasma and cell separation. Total DNA was purified using the method described by Lahiri and Nurnberger [32]. The genotyping of Val66-Met BDNF (rs6265) polymorphism was performed on a StepOnePlus™ Real-Time PCR System (Applied Biosystems Inc., Foster City, USA) using a predesigned TaqMan™ SNP genotyping assay (Thermo Fisher Scientific; catalog 4,351,379, assay ID: C__11592758_10).

Statistical analyses
Descriptive data are presented as mean (M), standard deviation (SD), standard error of mean (S.E.M.), frequency and percentages (%). For the inferential analyses, variables were compared between groups using Student's t test or the nonparametric Mann-Whitney test for continuous variables and the chi-square test for categorical variables. Allele frequencies were determined by direct counting of the alleles and departures from Hardy-Weinberg equilibrium were evaluated by the chi-square test. Correlations between variables were tested by Pearson's *r* coefficient. All tests were two-tailed and performed in SPSS software, version 18.0 (SPSS Inc., USA). $P < 0.05$ was considered statistically significant.

Results
The study recruited 112 subjects with FM, nevertheless 3 subjects were excluded because did not meet the inclusion criteria and one participant was excluded by problems during blood collection. The sample comprises 216 subjects (108 FM and 108 HC). Patients had the same geographic origin and are mainly of European ancestry. The clinical and demographic characteristics of the FM sample and controls groups are shown in Table 1. In the FM

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Table 1 – Socio-demographic and clinical characteristics of FM patients and controls ($n = 216$)

Characteristics	FM($n = 108$)	Controls ($n = 108$)	p
Age (years)	50.2 ± 9.5	49.5 ± 9.5	0.582
Body mass index (Kg/m^2)	28.2 ± 4.6	27.0 ± 4.9	0.073
Years of education	10.3 ± 4.2	12.2 ± 4.1	**0.001**
White skin color	87 (80.6)	88 (81.5)	0.862
Functional situation			**0.002**
Employed	52 (48.1)	76 (70.4)	
Unemployed	17 (15.7)	14 (13.0)	
Retired	36 (33.3)	18 (16.7)	
Other	3 (2.8)	0 (0.0)	
FM diagnosis time (years)	6.4 ± 5.4	–	–
Alcohol consumption	55 (50.9)	–	–
Number of times during the month (mean)	1.2 ± 2.2	–	–
Smoke	22 (20.4)	–	–
Contraceptive pill	19 (17.6)	–	–
Psychiatric disorder[a]	73 (67.6)	–	–
Mood disorders	57 (52.8)	–	–
Anxiety disorders	39 (36.1)	–	–
Other	4 (3.7)	–	–
Psychological or psychiatric treatment	35 (32.4)	–	–
Rheumatic or musculoskeletal condition ($n = 80$)[a]	64 (80.0)	–	–
Hypertension	36 (33.3)	–	–
Diabetes mellitus	9 (8.3)	–	–
Medications aiming pain relief[b]	88 (81.5)	–	–
Central Nervous System active medication	77 (71.3)	–	–
Physical exercise	56 (51.9)	–	–
Number of days per week	1.6 ± 1.9	–	–
Aerobic exercise	32 (29.6)	–	–
Anaerobic exercise	11 (10.2)	–	–
Aerobic and anaerobic exercise	13 (12.0)	–	–
Alternative practice for management pain	63 (58.3)	–	–
Psychological assessment, sleep quality, resilience, quality of life and CS symptoms			
Beck Depression Inventory (BDI – II)	22.0 ± 12.7	3.5 ± 2.8	**< 0.001**
State-Trait Anxiety Inventory (STAI)			
State - anxiety	28.1 ± 7.8	19.8 ± 5.4	**< 0.001**
Trace - anxiety	24.4 ± 5.2	16.4 ± 3.0	**< 0.001**
Total Brazilian Portuguese Catastrophizing Scale (BP-PCS)	32.5 ± 12.2	–	–
BP-PCS - Helplessness	14.2 ± 6.0	–	–
BP-PCS - Magnification	7.5 ± 3.4	–	–
BP-PCS - Rumination	10.7 ± 3.6	–	–
Resilience	128.3 ± 22.5	–	–
Pittsburgh Sleep Quality Index (PSQI - BR)	10.8 ± 4.3	–	–
Central Sensitization (CSI-BP)	58.0 ± 14.8	–	–
Fibromyalgia Impact Questionnaire (FIQ)	61.2 ± 18.1	–	–

Notes. Data are reported as number of subjects (% in parentheses) or mean and standard deviation (± S.D.). Student's *t* test or Mann-Whitney test were used for continuous data and Chi-square test was used for categorical data
[a] Multiple response
[b] Analgesics

sample 81.5% of the patients used pain relief medications, most (51.9%) performed physical exercise, mostly aerobic. And, 58.3% of the patients searched for complementary methods for pain management.

Among FM patients, 30.6% spontaneously reported traumatic life events. Childhood traumatic experiences reported through CSI-BP (item 24) were detected in most patients (51.9%). When we compared socio-demographic characteristics among FM and HC, there were significant differences in years of education and functional situation between groups. Indeed, as expected, there were also significant differences in anxiety and depressive symptoms, between FM and control groups (Table 1).

Allele and genotype frequencies of the Val66Met BDNF polymorphism are shown in Table 2. Allele frequencies were significantly different between FM and control groups ($p < 0.05$). The genotype frequencies are in Hardy-Weinberg equilibrium in both groups.

The score on the BP-PCS was compared between Val/Val and Val/Met genotypes in the FM patients (Fig. 1). Val/Val genotype was significantly associated to magnification and rumination domains (p < 0.05). FM patients carrying the Val/Val genotype displayed higher scores in pain catastrophizing scale (total score) and in the helplessness domain compared to the Val/Met genotype. However, these differences were non-significant. Analysis of endophenotypes involved in FM and their association with Val66Met BDNF polymorphism are shown in Supplementary Table 1.

Total BP-PCS scores and subscores and total FIQ and BP-SCI scores were correlated according to Val66Met genotypes (Table 3). Impact of FM in quality of life of patients showed positive relation with central

Table 2 – Allele and genotype frequencies of the Val66Met variant (n = 216)

	FM (n = 108)	Controls (n = 108)	P
Allele			**0.045**
Val (G)	195 (90.3)	181 (83.8)	
Met (A)	21 (9.7)	35 (16.2)	
Genotype model			**0.069**
Val/Val	87 (80.6)	77 (71.3)	
Val/Met	21 (19.4)	27 (25.0)	
Met/Met	–	4 (3.7)	
Met dominant model[a]			**0.111**
Val/Met + Met/Met	21 (19.4)	31 (28.7)	
Val//Val	87 (80.6)	77 (71.3)	

Notes. Data are presented as frequency and percentage (% in parentheses). *P* values refer to comparison between FM allele and genotype frequencies and controls and are based on Chi-square tests
[a] Met dominant model: OR = 1,67; 95% CI = 0.85–3.32

sensitization symptoms regardless of genotypes. Also, catastrophizing showed positive relation with central sensitization symptoms and impact of FM in quality of life in both groups. However, strong and moderate positive correlations were mostly found in the Val/Met group.

Discussion

In the present study the main findings are that Val allele is more frequent in FM, while the Met allele is most frequent in the control subjects, and that in FM the BDNF Val/Val homozygotes are a potential genetic risk factor associated with higher scores in the Pain Catastrophizing Scale domains: magnification and rumination. From a conceptual perspective, this emerging finding helps to explain the neurobiology processes underpinning pain catastrophizing. Its potential clinical relevance is aligned with the view that pain catastrophizing has been a predictive factor of treatment response [5, 33]. Thus, it may help to integrate the interplay between Val66Met polymorphism and clinical symptoms in the bedside clinical assessment.

In this framework, the higher magnification and rumination levels in the homozygotes Val/Val gives support for this hypothesis that this genotype do not provide sufficient compensatory mechanisms to improve the resilience of the neurobiological system involved in the physiopathology of chronic pain, whereas the severity of these symptoms can be a dysfunctional response related to somatosensory processes. This could an evidence of a distinct subjective pain experience in those with higher levels catastrophizing, somatization, depression, anxiety, and anger [34–36]. As have been noted, these behaviors can indicate the patients have difficulties in recruiting healthy coping strategies and exacerbate psychological and clinical symptoms [37–39].

Accordingly, a previous study showed that individuals Val/Val exposed to stressful events early in life presented increased anxiety and higher volumes of brain structures, such as the amygdala and medial prefrontal gray matter [40]. Furthermore, in another study evaluating anxiety, Val homozygotes had higher levels of trait-anxiety compared to Met allele carriers [14]. Also, an over-representation of the Val allele and lower frequency of the Met allele was detected in patients with bipolar disorders [41]. Likewise, an earlier study with a similar perspective, showed that pain catastrophizing was associated with the rs1176744 polymorphism of the serotonin receptor 3B (5-HT3B) gene in healthy individuals [42].
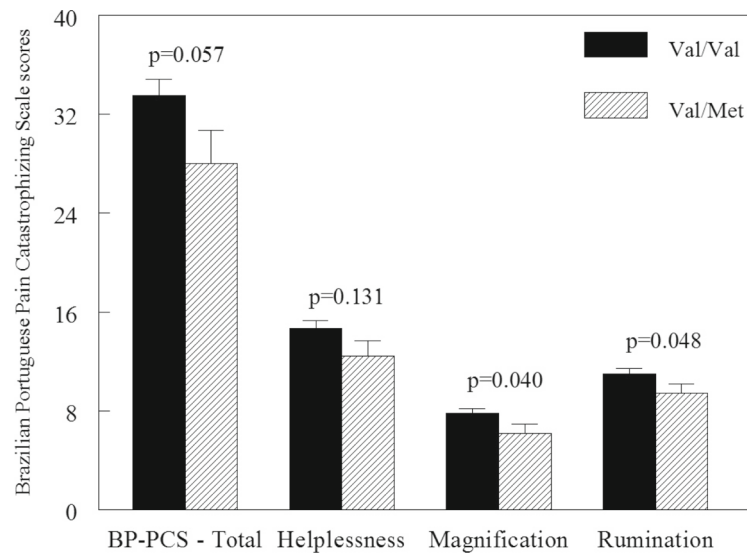
Although the design of this study prevents establishing a cause-consequence relationship between the Val66Met polymorphism and the rumination and magnification in the FM, these findings may hold

Fig. 1 Pain catastrophizing scale (total and sub-scales' scores) in the FM sample according to Val66Met genotypes. Notes. Data are shown as mean and error standard of mean (S.E.M.)

clinical implications. One of them is the idea that some genetic characteristics related to neuroplasticity processes may predispose individuals with FM to more severe clinical symptoms. Besides, they reinforce the assumption that the severity of rumination and magnification is a challenge in the management of pain symptoms because they adversely compromise the prognosis of FM. From the point of view of a coping style, pain catastrophizing may become a maladaptive response, leading to a substantial negative impact in the quality of life of FM patients [43]. Furthermore, it is one of the strongest predictors of the outcomes of therapeutic approaches in chronic pain [5, 33].

The BDNF Val66Met polymorphism has been investigated in several pathological conditions in humans [44–46]. The Met allele was reported as a protective factor against anxiety disorders due to its putative impairment of amygdala-dependent aversive memory acquisition/

consolidation [47]. However, there is controversy regarding which allele of Val66Met polymorphism is associated with risk or protection (harmful or beneficial) in relation to pathological conditions [41, 45–48]. It is possible that the Met allele has pleiotropic effects. The downregulation of synaptic plasticity by Met, particularly in excitatory glutamatergic circuits is discussed as protective against psychiatric disorders [49], despite Met allele being associated with reduced cognitive performance, which suggests decreased brain plasticity [16, 17, 50, 51]. According to an earlier study in a paradigm of use-dependent plasticity, authors found reduced changes in motor cortical excitability in Met carriers [52]. Although we are aware that our results open a way to advance in the comprehension of the complex pathophysiology of FM, which is mediated by multiple systems (i.e., GABAergic, glutamatergic, noradrenergic, serotonergic, etc.), this findings need to be interpreted cautiously.

Table 3 - Correlation between pain catastrophizing, central sensitization and impact of fibromyalgia according to genotype (n = 108)

	Val/ Val (**n** = 87)		Val/Met (**n** = 21)	
	BP-SCI	FIQ	BP-SCI	FIQ
Fibromyalgia Impact Questionnaire (FIQ)	$r = .64^a$		$r = .74^a$	
Pain Catastrophizing Scale (BP-PCS) total score	$r = .39^a$	$r = .36^a$	$r = .68^a$	$r = .55^a$
BP-PCS - Helplessness	$r = .47^a$	$r = .40^a$	$r = .72^a$	$r = .58^a$
BP-PCS - Magnification	$r = .25^b$	$r = .27^b$	$r = .54^b$	$r = .41^a$
BP-PCS - Rumination	$r = .30^a$	$r^2 = .28^a$	$r = .63^a$	$r = .55^b$

a. Correlation is significant at the 0.01 level (2-tailed)
b. Correlation is significant at the 0.05 level (2-tailed)
Brazilian Portuguese Central Sensitization Inventory (BP-SCI); Brazilian Portuguese Pain Catastrophizing Scale (BP-PCS)

Aligned with this perspective of the relationship between the BDNF polymorphism and clinical symptoms, it is plausible that Met allele determine some mechanisms associated with the improvement of dysfunctional circuits involved in the imbalance of excitatory and inhibitory systems underlying pain catastrophizing. This hypothesis finds some support in a previous study that found a positive correlation between pain catastrophizing and cortical disinhibition [2]. Another study gives support for this assumption as well, due to the authors found an association between increased cortical disinhibition and higher serum levels of BDNF in chronic pain [53]. From a theoretical perspective, this association may indicate a deteriorated function of cortical inhibition.

BDNF Val66Met frequencies vary widely among different populations [48]. We detected significant differences in allele frequencies of the BDNF Val66Met polymorphism between FM patients and controls. The frequency of the minor allele (Met) (16.2%) observed in our control group was consistent with those previously reported in control groups of studies performed in the Brazilian population [54, 55].

Certain limitations must be considered in the interpretation of our findings. First, despite our sample size was large in comparison to previous reports in the literature concerning genetic variants of FM [56–61], its statistical power is limited. Second, this is a cross-sectional study, which may limit causality identification of the demographic and clinical variables investigated. Finally, it is not simple to understand how to apply this knowledge about pain catastrophizing and BDNF Val66Met polymorphism in the clinical practice.

Conclusion
In conclusion, the present study showed an association between Val66Met BDNF polymorphism with the FM, providing new insights into the genetically specified processing of pain catastrophizing. However, further studies are needed to elucidate if the role of Val66Met BDNF polymorphism could help to plan personalized therapeutic approaches in FM.

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s42358-020-00141-9.

Additional file 1 Table S1. Psychological and clinical characteristics in the FM sample according to Val66Met genotypes.

Abbreviations
BDI-II: Beck Depression Inventory II; BDNF: Brain-derived neurotrophic factor; BP PCS: Brazilian Portuguese - Pain Catastrophizing Scale; CNS: Central nervous system; CSI-BP: Central Sensitization Inventory validated and adapted for Brazilian population; CSS: Central sensitization syndrome; EDTA: Ethylenediamine tetraacetic acid; FIQ: Fibromyalgia Impact Questionnaire; FM: Fibromyalgia; HC: Healthy controls; HCPA: Hospital de Clínicas de Porto Alegre; PCR: Polymerase chain reaction; PSQI: Pittsburgh Sleep Quality Index; S.E.M: Standard error of mean; SD: Standard deviation; STAI: State-Trait Anxiety Inventory; STROBE: Strengthening the Reporting of Observational studies in Epidemiology; ULBRA: Universidade Luterana do Brasil

Authors' contributions
C.F.S. Alves, W. Caumo and D. Simon designed the study. C.F.S. Alves, J.M. Silvestri, V.S dos Santos, D.F. Cardoso collected the data. C.F.S. Alves, W. Caumo, D. Simon performed the statistical analysis. C.F.S. Alves, W. Caumo, M. Zortea, A. Regner, A.H. de Souza and D. Simon interpreted and discussed the results. C.F.S. Alves, W. Caumo and D. Simon wrote the paper. C.F.S. Alves, W. Caumo, M. Zortea, V.S. dos Santos, A. Regner, A.H. de Souza and D. Simon contributed to the final version of the manuscript. All authors have reviewed and approved the final version of the article, including the authorship list.

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
This study was approved by the Ethics Committee Board of the Hospital de Clínicas de Porto Alegre (HCPA) and Universidade Luterana do Brazil (ULBRA) - Applications No. 1570266 and 1620891. All subjects signed the informed consent form. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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