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Chronic pain: relationship with prefrontal symptoms and perceived stress

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ABSTRACT

Objective: The quality of perceived stress coping in chronic pain is related to the performance of the prefrontal cortex as the main structure of control and coordination of superior behavior control. The present study explores the presence of prefrontal symptomatology, in the form of problems to manage cognition, emotions and behavior, and perceived stress in a sample of people suffering from chronic pain.

Material and methods: We studied 78 participants with a diagnosis of chronic pain ranging in age from 27 to 81 years (mean 54.2 and d.t 13.4). Sociodemographic and clinical variables were analyzed together with the results in the 11-item Short Brief Pain Questionnaire (CBD) to assess the intensity and interference of pain, the Prefrontal Symptom Inventory (ISP), both in its complete version of 46 items and in the abbreviated of 20, and the 10-itme Perceived Scale of Perceived Stress (EEP).

Results and discussion: Significant correlations between the prefrontal symptomatology and the intensity (r = 0.32) and the interference (r = 0.53) of the pain, as well as between the stress and the interference of the pain in the mood (r = 0.36). People report more painful feelings when they refer more cognitive and emotional management problems surrounding the environment. The general interference of pain is related to more motivational and attention problems, while the interference that the pain produces in the mood also increases the problems with executive and emotional control. A preliminary structural equation explaining the effect is proposed.

Conclusion: The data suggest that the stress perceived by people with chronic pain depends on the inability of the prefrontal cortex to cope with a changing or threatening situation and this problem is fed back over and over as the person is less able to cope with the environment. Therefore, comprehensive treatment of chronic pain should include psychological interventions focused on coping with stress and cognitive optimization of skills related to prefrontal functioning.

Key words: Chronic pain, cognitive symptoms, prefrontal cortex, stress, neuropsychology.

RESUMEN

Objetivo: La calidad del afrontamiento del estrés percibido en el dolor crónico está relacionada con el rendimiento de la corteza prefrontal como estructura principal de control y coordinación de control superior de la conducta. El presente trabajo estudia la presencia de sintomatología prefrontal, en forma de problemas para gestionar la cognición, las emociones y el comportamiento, y de estrés percibido en una muestra de personas que sufren dolor crónico.

Material y métodos: Se estudiaron 78 participantes con diagnóstico de dolor crónico con edades comprendidas entre 27 y 81 años (media 54,2 y d.t. 13,4). Se analizaron variables sociodemográficas y clínicas junto con los resultados en el Cuestionario Breve de Dolor (CBD) abreviado de 11 ítems para valorar la intensidad e interferencia de dolor, el Inventario

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de Síntomas Prefrontales (ISP), tanto en su versión completa de 46 ítems como en la abreviada de 20, y la Escala de Estrés Percibido (EEP) abreviada de 10 ítems.

Resultados y discusión: Aparecen correlaciones significativas entre la sintomatología prefrontal y la intensidad (r = 0,32) y la interferencia (r = 0,53) del dolor, así como entre el estrés y la interferencia del dolor en el estado del ánimo (r = 0,36). Las personas declaran más sensación dolorosa cuando refieren más problemas de gestión cognitiva y emocional del entorno que las rodea. La interferencia general del dolor se relaciona con más problemas motivacionales y de atención, mientras que la interferencia que el dolor produce en el estado del ánimo incrementa, además, los problemas con el control ejecutivo y emocional. Se propone una ecuación estructural preliminar explicativa del efecto.

Conclusión: Los datos sugieren que el estrés percibido por las personas con dolor crónico depende de la incapacidad de la corteza prefrontal para afrontar una situación cambiante o amenazante, y este problema se retroalimenta una y otra vez al ser la persona cada vez menos capaz de afrontar el ambiente. Por tanto, el tratamiento integral del dolor crónico debe incluir intervenciones psicológicas centradas en el afrontamiento del estrés y la optimización cognitiva de las habilidades relacionadas con el funcionamiento prefrontal.

Palabras clave: Dolor crónico, síntomas cognitivos, corteza prefrontal, estrés, neuropsicología.

INTRODUCTION

Acute pain is an indicator of potential tissue damage, acting as a warning to adapt and respond to a source of pain and avoid it. However, there exist circumstances where pain becomes chronic, growing into a multidetermined, multidimensional perceptual process, more complex than acute pain, and which gives rise to learning (multidetermined and multidimensional) that causes the pain to persist despite being maladaptive (1). This means that, with chronic pain, the warning to adapt provided by acute pain is less efficient and ceases to be a reliable indicator of tissue damage (2), and is a main cause of disability, reduced productivity at work, increased social and health-care costs and, ultimately, poor quality of life (3,4). Recent epidemiological studies show a high prevalence in chronic pain estimates, reaching 37% in developed countries and 41% in developing countries (5). Adult women with low socio-economic status are the most prone to suffering from it (6) in different locations such as low back, knees, head and neck (7).

Since the early explanatory models of chronic pain, it has been suggested that it represents a major source of biological stress by threatening homeostasis and is, therefore, a variable source of psychological stress or perceived stress (8). In this respect, perceived stress is one of the variables that has aroused most interest in recent years given its proven relationship with different physical (9) or psychological (10) health variables, including pain perception (11,12). An increase in perceived stress can arise from inadequate mechanisms to cope with conflict (13) or from an increase in stressful situations themselves as a result of poor coping which, far from solving conflicts, generates a resource loss spiral (14).

The quality of mechanisms to cope with perceived stress is related to PFC performance as the main structure for guiding and coordinating "top-down" control over behavior (15,16). In this respect, for example, dendritic reduction has been observed in the medial prefrontal cortex (17-19) and dendritic growth of neurons in the amygdala and in the orbitofrontal cortex (20). These stress-induced changes in the prefrontal cortex can ultimately lead to dysfunction in attentional / executive performance (21-23) and cause (as in fact occurs in individuals with chronic pain) everyday errors, mistakes and forgetfulness (24), which are perceived as pathological, further increasing perceived stress (25,26).

Furthermore, using functional neuroimaging techniques, functional and structural modifications have been found in brain areas responsible for processing and modulating pain, in what is known as the pain matrix: anterior cingulate cortex, somatosensory cortex (Brodmann areas 1 and 2), insula, amygdala, thalamus and periaqueductal gray matter (27). Differences have also been described in identifying a radiological marker at prefrontal level, insofar as some frontal areas increase in cerebral activity while others appear to be deactivated, suggesting evidence of abnormal prefrontal responses in the presence of chronic pain (28). More recent studies have associated the dorsolateral prefrontal cortex with pain regulation and with generating, maintaining and manipulating cognitive representations. Accordingly, expectations and beliefs were shown to modulate the experience of pain and this, in turn, suggests that expectation-induced analgesia is mediated by prefrontal functions (29,30).

This study therefore aims to analyze the relationship between prefrontal symptomatology, in the form of problems managing cognition, emotions and behavior, and perceived stress, in a sample of individuals suffering from chronic pain. The study's preliminary conclusions will present new hypotheses on which to continue working towards optimizing therapeutic measures in psychological and neuropsychological intervention, fostering increased control and feeling of control, and thus providing improved quality of life both for the patients and for their families.

METHOD

Participants

The initial sample consisted of 90 patients with chronic pain aged between 27 and 81 years old, selected from the

Neurosurgery Department at the Hospital Universitario La Paz in Madrid. However, a total of 12 patients were excluded from the study owing to adverse physical conditions (for example very severe pain) or mental conditions (for example, low intellectual level or depressive mood), preventing them from answering the questionnaires. Accordingly, the study sample consisted of 78 patients whose characteristics are described in Table I. All participants were informed of the evaluation's purpose and gave their signed consent to participate.

Tools

Three questionnaires were administered to assess prefrontal symptomatology, perceived stress and pain intensity and interference. Firstly, the *Prefrontal Symptoms Inventory (PSI)* (31) was applied: this is a self-reported questionnaire that explores symptoms of poor everyday functioning related with neurpsychological alterations that can be attributed to the prefrontal cortex. It consists of three factors: a) Executive problems, which in turn comprise three sub-factors (motivational, attentional and executive control problems); b) Emotional control problems, and c) Social behavior problems. The questionnaire consists of 46 items, with a Likert-type response system (0: never or hardly ever; 1: rarely; 2: sometimes; 3: often; 4: almost always or always). The complete version's 46 items generated the 20 responses of the abbreviated version ISP-20 (32).

Secondly, the *Perceived Stress Scale (PSS)* (33) was applied, adapted for the Spanish population by Remor and Carrobles in 2001 (34). This is a questionnaire consisting of 14 questions regarding stress levels experienced in the previous month, where a higher score indicates greater perceived stress. It uses a Likert-type response system with 5 options (from 0 [never] to 4 [always]). More recent studies find that the 10-item version (PSS-10) obtains better psychometric results, and as the version recommended for use (35), it was the one applied in this study.

Lastly, the *Brief Pain Inventory (BPI)* (36) adapted for the Spanish population by Badia et al. in 2003 (37). In this study, 11 of the BPI's 22 items were included to carry out data analysis. These 11 items have proven their psychometric validity in quantifying pain intensity (items 2, 3, 4 and 5; that is, maxim, minimum, mean and current) and pain interference (through the 7 sections of item 13). Answers to the items used are shown as numerical scales from 0-10, where 0 equals "no pain" and 10 "pain as bad as you can imagine", during the previous week. Item 13, which in turn consists of 7 questions, measures pain's interference in the patient's functioning in their everyday activities (general activity, mood, ability to walk, usual work, relationships with others, sleep and enjoyment of life). It also produces numerical scales from 0-10, where 0 equals "does not interfere" and 10 "interferes completely", during the previous week. The 11 remaining items (1, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21 and 22) were recorded for each patient but were excluded from the data analysis, as they did not offer information relevant to this study's objectives. This tool has proven capable of detecting changes in pain level - high internal consistency of measurements -, intensity ($\alpha = 0.834$) and interference ($\alpha = 0.893$).

Patients were also asked to state their age, sex, education level, marital status and professional situation. Education level was classified into four groups: incomplete primary studies, completed primary studies, completed secondary studies and university graduates. Patient histories provided the clinical variables: diagnosis, age at initiation and pain evolution time, time in treatment, whether or not they received pharmacological and/or psychotherapeutic treatment, and whether or not they received neurostimulator therapy.

Procedure

A cross-sectional study design was used to evaluate the possible relationship between suffering chronic pain and dependent variables: prefrontal symptoms and perceived stress. The self-reported questionnaires were administered by a properly trained psychologist and during hospital consultation hours, on Tuesdays and Thursdays in the months of December 2015 and January and February 2016. The full evaluation lasted approximately 30 minutes per patient. Patients were informed of the investigation's objectives and gave their consent for use of their personal data, guaranteeing its confidentiality and providing each patient with a document to accredit this. The study was approved by the Neurosurgery Department of the Hospital Universitario La Paz in Madrid and by the Ethics Committee of the Universidad Pontificia Comillas.

Statistical analysis

Internal consistency tests were carried out on the scales and sub-scales of all the questionnaires used by means of Cronbach's alpha, considering values above 0.70 to be adequate. The correlation study was carried out using Pearson's r and the Bonferroni correction was applied for multiple correlations to avoid making type I errors. A multivariate analysis of variance procedure was carried out to find differences according to categorical variables (education level and gender), controlling covariates (age). A structural analysis was conducted, based on a joint regression of variables, using the generalized least squares method, and different fit indicators were used to select the best model possible (Confirmatory Fit Index CFI, Adjusted Goodness-

TABLE I
SAMPLE DESCRIPTORS

		Men	*Women*	*Total*
	n (%)	38 (48.7 %)	40 (51.3 %)	78
Age	Mean	54.3	54.0	54.2
	S.D.	13.5	13.4	13.4
	Range	29-81	27-80	27-81
Education	Incomplete primary	21.1	12.5	16.7
	Primary	36.8	32.5	34.6
	Secondary	31.6	32.5	32.1
	Universitary	10.5	22.5	16.7
Marital status	Single	18.4	20.0	19.2
	Married	60.5	65.0	62.8
	Separated/Divorced	21.1	7.5	14.1
	Widow(er)	-	7.5	3.8
Professional situation	In work	7.9	12.5	10.3
	Unemployed	15.8	2.5	9.0
	On leave	18.4	17.5	17.9
	Retired	50.0	35.0	42.3
	Medical/psychological leave	7.9	7.5	7.7
	Housekeeping	-	22.5	11.5
	Other	-	2.5	1.3
Diagnosis	Fibromyalgia	5.3	7.5	6.4
	Back pain	65.8	52.5	59.0
	Headaches	5.3	7.5	6.4
	Pain in limbs	13.2	2.5	7.7
	Axial pain	-	7.5	3.8
	Other	10.5	22.5	16.7
Age at pain initiation	Mean	42.3	40.6	41.4
	S.D.	14.9	13.9	14.4
	Range	16-80	9-72	9-80
Years of pain evolution	Mean	11.1	13.6	12.4
	S.D.	8.5	8.5	8.6
	Range	1-44	1-36	1-44
Years of treatment	Mean	10.1	11.5	10.8
	S.D.	8.8	7.9	8.3
	Range	1-44	1-32	1-44
Drug treatment (%)	Yes	68.4	77.5	73.1
Psychotherapeutic treatment (%)	Yes	50.0	45.0	47.4
Stimulator (%)	Yes	92.1	85.0	88.5

of-Fit Index AGFI, Normed Fit Index NFI and Relative Fit Index RFI). This provided the basis for structural equation modeling, a multivariate statistical technique that can estimate causal relationships from statistical data and make qualitative assumptions regarding such causality. Finally, hierarchical regression analyses were conducted to find out the models' predictive capacity for each of the variables, verifying the proportion of variance predicted by each variable (R^2) and their standardized partial regression coefficient (b), using gender as a dummy variable and education level as an ordinal categorical variable. All the analyses used SPSS 22 and AMOS 18.

RESULTS

Table I shows the characteristics of the 78 patients included in the study.

Firstly, the administered tests' internal consistency was studied. The Cronbach's alpha values obtained were adapted for the PSS, both for the overall test (a= 0.94) and for the sub-scales ($0.78 < a < 0.88$) and the abbreviated version PSI-20 (a= 0.89), for the PSS (a= 0.82), and the BPI sub-scales regarding interference (a= 0.89) and intensity (a= 0.83).

No significant differences were found in any of the variables when education level was used as an independent variable, once age and gender were controlled ($p> 0.05$ in all cases). The same occurred when gender was used as an independent variable and the other two were controlled.

Table II shows the correlations observed among the different study variables. Applying the Bonferroni correction, significant correlations were found among clinical variables, both positive (treatment time and evolution time), and negative (age of initiation and evolution time). Significant correlations were also found among all study variables: prefrontal symptoms correlate, with considerable effect size ($r2 = 0.28$), with mean pain interference, and with smaller effect size ($r2 = 0.10$) with mean intensity, and with perceived stress ($r2 = 0.18$). Conversely, no significance appeared in correlations between stress and pain variables.

A correlation study was then carried out on the subscales relating to pain (intensity and interference) and the variables relating to perceived stress and prefrontal symptomatology sub-scales. Table III shows there is no correlation between the pain and perceived stress parameters, except in the case of the mood sub-scale, though with small effect size ($r^2 = 0.13$). However, correlations did appear among the sub-scales relating to intensity and, very especially, with interference sub-scales, and symptoms of poor behavioral control (motivational, attentional and executive) and poor control of emotions, although not with problems in controlling social behavior. The effect size of these correlations is, in most cases, moderate ($0.20 < r^2 < 0.30$). In order to find out the direction of these relationships, different structural models were assumed, and the model shown in Figure 1 is the one that achieved best fit indicators (CFI = 0.99; AGFI = 0.97; NFI = 0.97; RFI = 0.92). According to this model, pain intensity would predict interference in individuals' functionality, and this interference would directly and indirectly predict, by generating stress, the effects of prefrontal symptoms on everyday life.

The influence of other variables was studied using regression analysis. None of the independent variables used (gender, age, education level, evolution time, treatment time, age at pain initiation, stimulator use, pharmacotherapy and psychotherapy) showed predictive capacity regarding pain

TABLE II
BIVARIATE CORRELATION AMONG DIFFERENT STUDY VARIABLES

	Evolution time	*Age at initiation*	*Treatment time*	*Mean interference*	*Mean intensity*	*Prefrontal symptomss*	*Perceived stress*
Age	0.19	**0.79**	0.27	0.08	-0.05	0.08	-0.06
Evolution time		**-0.39**	**0.76**	-0.10	-0.13	-0.12	0.04
Age at initiation			-0.24	0.22	0.13	0.15	-0.07
Treatment time				-0.13	-0.19	-0.08	0.07
Mean interference					**0.62**	**0.53**	0.31
Mean intensity						**0.32**	0.18
Prefrontal symptoms							**0.42**

Significant correlations after Bonferroni correction are shown in bold ($p < 0.005$)

TABLE III
CORRELATIONS AMONG VARIABLES RELATING TO PAIN AND PREFRONTAL SYMPTOMS AND PERCEIVED STRESS

	Intensity				*Interference*						
	Maximum	*Minimum*	*Mean*	*Current*	*General*	*Mood*	*Walking*	*Work*	*Relationships*	*Sleep*	*Enjoyment*
PSI											
Motivational problems	0.22	0.29	0.24	0.22	**0.37**	**0.55**	0.31	**0.44**	**0.41**	**0.52**	0.37
Executive control problems	0.22	0.31	0.26	0.20	0.33	**0.51**	0.30	**0.45**	**0.46**	**0.45**	0.32
Attentional problems	0.19	0.30	0.20	0.28	**0.38**	**0.50**	0.24	**0.45**	0.35	**0.36**	0.32
Social behavior control problems	0.02	0.06	0.07	0.10	0.05	0.15	0.03	0.05	0.02	0.10	-0.06
Emotional control problems	0.11	0.15	0.13	0.22	0.29	**0.44**	0.11	**0.36**	0.31	**0.41**	0.25
PSI-Screen20	0.22	0.28	0.25	0.30	**0.37**	**0.56**	0.28	**0.45**	**0.43**	**0.48**	0.33
PSS-10	0.10	0.13	0.18	0.19	0.22	**0.36**	0.08	0.31	0.20	0.34	0.21

Significant correlations after Bonferroni correction are shown in bold ($p < 0.001$)

intensity parameters, except in two cases: mean pain intensity was positively predicted by stimulator use ($R^2 = 0.04$; $b = 0.24$; $p < 0.05$) and negatively by treatment time ($R^2 = 0.04$; $b = -0.23$; $p < 0.05$), while current pain intensity was negatively predicted by age ($R^2 = 0.05$; $b = -0.26$; $p < 0.05$). As regards interference, its mean values were negatively predicted by use of drugs ($R^2 = 0.10$; $b = -0.33$; $p < 0.001$), its general estimate was predicted ($p < 0.01$) positively by age at pain initiation ($R^2 = 0.06$; $b = 0.30$) and by education level ($R^2 = 0.05$; $b = 0.25$) and negatively by use of drugs ($R^2 = 0.04$; $b = -0.22$). The use of drugs showed negative predictive capacity regarding all dimensions of interference ($0.07 < R2 < 0.11$), except in terms of work and enjoyment; the latter of these was predicted negatively based on age at pain initiation ($R^2 = 0.07$; $b = -0.29$; $p < 0.05$). The use of drugs ($R^2 = 0.10$; $b = -0.32$) and psychotherapy ($R^2 = 0.05$; $b = -0.24$) negatively predicted the symptoms of poor prefrontal function ($p < 0.001$).

DISCUSSION

This study analyzed the relationship between prefrontal symptomatology and stress perceived with chronic pain, in a clinical sample aged mostly between 50 and 60 years old and who had been diagnosed for over 10 years. In other socio-demographic variables, the sample seems relatively balanced, although the most frequent participant profile was: retired, married and suffering from low back pain as the main source of complaint. As expected, there appears to be a very high statistical relationship between pain evolution time and treatment time; that is, patients begin treatment, either pharmacological or psychotherapeutic, practically from the moment they begin to suffer the chronic pain condition.

As regards prefrontal symptomatology, there appears significant correlation with pain intensity and interference, and with a small to moderate effect size, showing that the greater the feeling of pain reported by the patient,

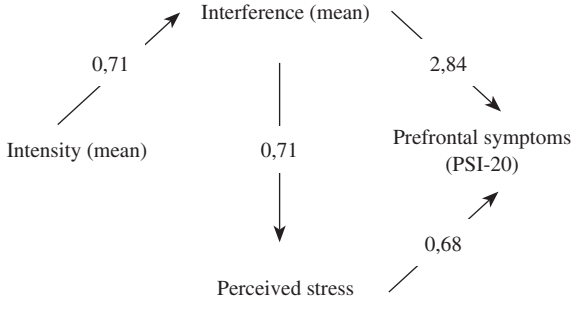

Fig. 1. Structural relationships between model variables (regression weights).

the greater their cognitive and emotional management difficulties with the surrounding environment. For example, pain's general interference is related with more motivational and attentional problems, while pain interference with mood would also increase problems with executive and emotional control. These findings may be interpreted in the light of the main prefrontal functioning models (38,39) to the extent that responding to pain consumes limited central executive resources; resources that, as they can no longer be used to respond to and manage the environment, cause an increased incidence of everyday errors, mistakes and forgetfulness. This is also valid for explaining the incidence of subjective memory complaints among young adults (25,26).

As regards perceived stress, there appears to be a significant relationship between pain interference and mood, a fact that also seems to be explained in the light of the main stress models (13,14). Additionally, we observed the recognized relationship between perceived stress and prefrontal symptoms, to the extent proposed that what are traditionally called executive functions are in fact what come into play when the environment changes, presents a threat or it seems that triggering an automatic response will lead to an error. This may suggest that perceived stress is what occurs when the prefrontal cortex does not know how to cope with changing or threatening circumstances. And this problem feeds into itself as the prefrontal cortex is increasingly unable to cope with the environment as a consequence of the growing stress, which it is increasingly unable to cope with.

This is, in fact, this study's main contribution, shown in Figure 1 as a preliminary structural equation. What may be deduced from the data is that pain intensity increases pain interference and, as a consequence: a) increases the prefrontal cortex's inability to cope with environmental challenges (2,84), and b) increases stress perceived by the individual, which ultimately makes the prefrontal cortex increasingly incapable of governing behavior, managing cognition and controlling emotions. What the data suggests is that integral chronic pain treatment should implement psychological interventions focused on improving mechanisms for coping with stress (40-42), and centered on cognitive optimization of skills related with prefrontal functioning (43,44) with the objective of improving patients' quality of life.

This study's main limitations lie in the low number of participants and how the sample was obtained. The findings from studying an incidental consecutive sample of 78 subjects do not allow the results to be generalized, and it should be considered a preliminary study. Future studies must obtain more representative samples and use control groups, which could be relatives of the affected individuals, so that the relationships observed among variables can be replicated in subjects where pain is not a critical variable. It is to be expected, if the model proposed is adequate, that the relationships observed would be the same in the absence of intense pain.

In applied terms, this study's main value is to provide evidence of the clinical effectiveness of using abbreviated self-reporting to make it easier for professionals to recognize the specific needs of certain patients, suggesting the advisability of intervening in stress and prefrontal symptoms in everyday life. In short, combined administration of the abbreviated Prefrontal Symptoms Inventory (PSI-20) (31,32) and the Perceived Stress Scale (PSS-10) (33-35) may be of interest to health-care professionals who approach the psychological alterations of patients with chronic pain and its consequences on daily life. In other words, with just 30 items that are easy to apply, to correct and to interpret, physicians can recognize specific psychotherapeutic needs, which can improve management of patients and their quality of life.

The variables studied do not exhaust the spectrum of questions that may affect an individual suffering from chronic pain, and which may be much broader, including both internal variables (for example, personality traits) and external variables (for example, social support), but considering the recognized importance of the negative effects of stress and poor executive and emotional control, and because methods with proven effectiveness and efficiency are available to manage both problems, their identification and approach may be extremely useful in improving affected patients' quality of life. Future studies must build on the evidence of this study's results, as well as identify other variables that may be relevant to obtaining greater benefits for patients.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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