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Serum cortisol levels and neuropsychological impairments in patients diagnosed with Fibromyalgia

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Objective. To describe the relationship between neuropsychological variables and serum cortisol levels as a measure of physiological stress in patients with fibromyalgia.

Methodology. A sample of 60 women was intentionally selected: 30 with Fibromyalgia diagnosis and 30 with normal controls. Cortisol levels were determined using two blood samples (AM and PM) and a neuropsychological and emotional battery was applied with a standardized protocol in Colombian population to evaluate different cognitive domains. Comparative and correlational non-parametric analyzes were performed, a multiple regression analysis to determine influences between variables.

Results. Significant differences between the study groups in the neuropsychological variables (attention, memory, language, visual-constructive praxis and executive functions (EF), ($p<0.05$) were found, obtaining better scores in the control group. Significant correlations between the cortisol profile, with false acknowledgments of Rey auditory-verbal learning test, and with perseverative errors of the Wisconsin test were found. Multiple regression analysis predicts the influence of memory and EF variables on the cortisol profile in an 88.7%.

Conclusions. The findings show that, in patients with FM, there are neuropsychological alterations, mainly in executive functioning (cognitive flexibility) and episodic memory (evocation and storage). Likewise, executive dysfunction is related to physiological stress reciprocally and in turn are conditioned by emotional alterations such as symptoms of depression, which supports the neurophysiological model that compromises the hypothalamic-pituitary-adrenal axis and the prefrontal cortex, rich in corticosteroid receptors.

Key Words: Pain, Fibromyalgia, Cortisol, Neuropsychological impairments

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Niveles de cortisol sérico y alteraciones neuropsicológicas en pacientes con diagnóstico de Fibromialgia

Objetivo. Describir la relación entre variables neuropsicológicas y niveles de cortisol sérico; como una medida de estrés fisiológico; en pacientes con fibromialgia.

Metodología. Se seleccionó intencionalmente una muestra de 60 mujeres: 30 con diagnóstico de Fibromialgia y 30 controles normales. Se determinaron los niveles de cortisol mediante dos muestras de sangre (AM y PM) y se realizó una batería neuropsicológica y emocional, con un protocolo estandarizado en población colombiana para evaluar diferentes dominios cognitivos. Se hicieron análisis comparativo y correlacional no paramétrico, un análisis de regresión múltiple para determinar influencias entre las variables.

Resultados. Se encontraron diferencias significativas entre los grupos de estudio en las variables neuropsicológicas (atención, memoria, lenguaje, praxis viso-constructiva y funciones ejecutivas (FE), ($p<0,05$), obteniendo mejores puntajes el grupo control. Se hallaron correlaciones significativas entre el perfil de cortisol, con falsos reconocimientos del test de aprendizaje auditivo verbal de Rey y con errores perseverativos del test de Wisconsin. El análisis de regresión

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múltiple predice la influencia de las variables de memoria y FE en el perfil de cortisol en un 88,7%.

Conclusiones. Los hallazgos demuestran que, en pacientes con FM, existen alteraciones neuropsicológicas, principalmente en funcionamiento ejecutivo (flexibilidad cognitiva) y memoria episódica (evocación y almacenamiento). Igualmente, la disfunción ejecutiva está relacionada con el estrés fisiológico de manera recíproca y a su vez son condicionadas por alteraciones emocionales como síntomas de depresión, lo cual soporta el modelo neurofisiológico que compromete el eje hipotálamo-hipófisis-adrenal y la corteza pre-frontal, rica en receptores de córticoesteroides.

Palabras Clave: Dolor, Fibromialgia, Cortisol, Alteraciones Neuropsicológicas

INTRODUCTION

Fibromyalgia (FM) is a syndrome of chronic affection characterized mainly by generalized musculoskeletal pain of non-inflammatory cause, accompanied by cognitive complaints, sleep disorders, anxiety and depression. According to the criteria established in 2010 by the American College of Rheumatology (ACR), these symptoms, to be valid, must be reported by the patient persistently in the last 3 months[1,2].

FM has a prevalence of 2.1% to 2.9% in the general population, being more frequent in women (2.4%) than in men (1.8%), showing increases with age: <40 years (0.8%), 40-59.9 years (2.5%) and <60 (3.0%); and the presence of somatic symptoms, anxiety and depression in the manifestation of the disease[3-5]. In Latin America, there was an increase in cases from 2009 to 2011, probably due to a greater recognition of the syndrome by the medical community[6].

One of the aspects that makes its approach more difficult are the associated affective-behavioral symptoms. It has been found that the coexistence of generalized pain with psychiatric conditions leads to a detriment in the quality of life of people with FM[7]. In a sample of 5,501 patients attending a medical unit in Madrid, it was found that 58% had psychiatric illness (non-severe depressive disorder, dysthymia, anxiety disorders, phobias, personality disorders and adaptive disorders)[8]. It is also considered that FM can be part of a set of syndromes that go through sensitization and central hypersensitivity processes, which explains the presence of pain and its associated symptoms[9].

The repeated presence of pain has also been associated with a significant deterioration of cognitive functions, which may be affected by the concurrence of affective symptoms such as associated anxiety and depression[10]. Various studies have made evident that patients with FM show greater deficits in attention, work memory, episodic memory and executive functions (inhibitory control, information processing speed and decision making), which has also been referred to in the literature as "Fibrofog", understood as a variety of cognitive complaints that include precisely difficulties in memory, concentration and mental confusion[11-13]. Other investigators have found difficulties in the response of inhibition and attentional control as measured by evoked potentials during the execution of an emotional stroop task[14].

The neurobiological bases of this pathology have not yet been defined with certainty, some studies reveal that the existence of a sympathetic hyperactivity of the neurons responsible for the release of corticotropin in the hypothalamic-pituitary-adrenal (HPA) axis, could explain the symptoms of the disease and specifically the deficit at cognitive level[15]. It has been shown that cortisol as a steroid hormone released by the adrenal cortex has effects on memory, brain aging and the endocrine response to stress[16], as well as in the fluctuations of perceived pain[17]. The exacerbated response of pain also causes changes in neuroplasticity, which perpetuate its symptoms over time[18].

At present, the diseases associated with the presence of chronic pain, are becoming increasingly epidemiological relevance because of the high impact they represent in the productivity of the individual and in most aspects of daily life and high costs for the systems of health. Due to the complexity of the symptomatology and the chronicity in the evolution of the natural history of FM, it is important to identify the neuropsychological and physiological mechanisms underlying this syndrome, in order to propose new treatment options.

The objective of this research was to study the presence of neuropsychological alterations and to determine the influence that they have on cortisol as a physiological measure of stress in patients with FM.

MATERIAL AND METHODS

Design

The present cross - sectional study was carried out through a correlational - causal design, with case - control analysis.

Patients

The sample of subjects with FM was taken from the population of patients attending the Colombian Institute of Neuropedagogy (Barranquilla, Colombia). The calculation of the sample size showed 30 subjects in each study group, having as parameters a confidence level of 95% and a test

power of 80%, average level of cortisol in the morning of 8.0±0.2 (micrograms/dl) in the control group[19] and a minimum standardized mean difference with respect to fibromyalgia patients 0.73 (micrograms/dl). The sample size was calculated using the program developed by the Information Service of the Public Health of General Directorate of the of Public Health (Xunta de Galicia), (Directorate General of Public Health of the Department of Health, Galicia), in collaboration with the Pan American Health Organization (PAHO-WHO) Health Analysis and Systems Information.

The inclusion of the subjects was carried out in an incidental, intentional, non-probabilistic manner provided that they met the following inclusion and exclusion criteria: patients with fibromyalgia diagnosis according to the diagnostic criteria of the American College of Rheumatology[2], age between 30 and 70 years of age, schooling of 5 years or more, and not having a diagnosis of connective tissue diseases or a history of cerebrovascular disease (CVD), traumatic brain injury, major psychiatric disorders, use of psychoactive substances or drugs with action in central nervous system, cognitive disability or learning disorders at premorbid level, inquired through a semi-structured interview in the patient's medical history. For the control group, 30 subjects with no pathology or major neurological or psychiatric history were selected selected according to age, gender and schooling criteria according to the group of cases. All subjects signed informed consent to participate in the study.

Thus, 60 subjects were selected, in their entirety of the female gender, which were divided into the two study groups: Case Group with FM (30 subjects) and Control Group (30 subjects).

INSTRUMENTS

For the evaluation of neuropsychological variables, a protocol of validated evaluation was selected in the Colombian population[20] which includes the following instruments:

1. **Minimental State Examination – (MMSE):** A screening test used to measure general cognitive functioning in the areas of orientation, memory, attention, language and visual-constructive praxis. Sensitive to evaluate symptoms of dementia or cognitive impairment.
2. **Boston Naming Test:** It was used as a measure of the nominative function of the language. This test is part of the Boston Aphasia Exam, using in this study the 60 reagent version.
3. **Controlled Oral Word Association Test (COWAT):** A word search procedure, used as a measure of language fluency and information processing speed.
4. **Rey-Osterrieth Complex Figure Test (ROCF):** As a measure of visuo-constructive praxis and the ability to organize the perception of complex visual stimuli. The evocation section was used as a measure of visual memory.
5. **Rey Auditory-Verbal Learning Test (RAVLT):** Represents an acoustic-mnemic task that allows the evaluation of verbal episodic memory, ability to learn through rehearsal and deferred recall.
6. **Trail Making Test (TMT):** A task that involves the ability to locate elements in the space used as a selective attention measure (Part A) and to follow sequences as a measure of executive functions (Part B).
7. **Symbol Digit Test (SDMT):** Measures the ability to focus and execute efficiently (selective attention) the working memory, as well as oculomotor agility in the written version.
8. **Stroop color-word Test:** Taken as a measure of selective attention, divided attention and inhibitory control (section word-color).
9. **Token Test:** Used as a measure of perception and comprehension of language by means of verbal instructions of increasing complexity.
10. **Auditory Continuous Performance Test (ACPT):** Continuous monitoring task that allows assessing the ability to focus and maintain attention (sustained attention).
11. **Benton Visual Retention Test (BVRT):** In addition to being sensitive to altered visual memory, it is used as a measure of exploration of the ability to sustain attention as well as resistance to perseveration.
12. **Wisconsin Card Sorting Test (WCST):** Used as an executive performance measure that assesses the ability to form abstract concepts and cognitive flexibility.
13. **Mental Control - Wechsler Memory Scale Subtest:** Used to measure attention control and speed of information processing.
14. **Hamilton Anxiety Scale and the Beck Depression Inventory:** Used to measure the degree of intensity of anxiety and depression symptoms.

Also, blood levels of cortisol (serum free from hemolysis) were evaluated as a measure of physiological stress. Samples were taken at two times: Serum cortisol AM levels (8:00-9:00h), with reference values: 4.46-22.7 ug/dl. Serum levels of PM cortisol (4:00-5:00h), with reference values: 1.7-14.1 ug/dl. In addition to the values obtained in the study group and control group, the difference between AM and PM cor-

tisol was considered for each of the subjects (Profile AM -PM).

Statistical analysis

The data were analyzed using the SPSS Version 20 for social science statistical package. To determine significant differences between the study variables, a comparative analysis was performed using the non-parametric U test of Mann Witney. Subsequently, in the correlation analysis, the Sperman statistic was used to establish the relationship between the study variables, and finally, a multiple regression model was applied to evaluate the effect or influence of neuropsychological variables on cortisol and a multivariate analysis of variance to analyze the influence of affective symptoms (anxiety and depression) on the neuropsychological profile.

Ethical considerations

All investigative processes were guided by ethical standards established for human research: the Helsinki Declaration of the 2008 World Medical Association, Resolution No. 008430 of October 4, 1993, of the Ministry of Health of Colombia, on the scientific, technical and administrative standards for health research, classifying this research as minimum risk and the statutes of the Colombian College of Psychologists, COLPSIC: Law 1090 of September 6, 2006. In this way, during the development of research, the nature of the process and the rights that would be guaranteed were socialized with the participants.

RESULTS

In the present investigation, two previously defined groups were evaluated: group of cases with diagnosis of FM (30 subjects) and control group without some type of pathology (30 subjects). For the FM group, the mean age was 52 (SD=8.9), with 5 to 12 years of schooling (M=10.2 SD=2.7) belonging to an average socio-economic level, which on a scale of 1 to 6 corresponds to a socio-economic level 3 and 4 (M=3.9 SD=1.0). With respect to the time of evolution of the disease, 9 women had <1 year of diagnosis, 10 between 2 and 5 years, 8 between 6 and 10 years, and 3 more than 10 years. Pain intensity was assessed using the Visual Analog Scale of the McGill Pain Inventory[21], finding that on a scale of 1 to 10, patients reported a level of pain ranging from 6 to 10 points (ME=7.9 SD=1.86). The patients included in the study were not on pharmacological treatment with drugs of action on the central nervous system.

For the control group, the mean age was 48.7 years (SD=11.1), the average years of schooling was 11.7 (SD=0.6) and belong to an average socio-economic level (M=4.0, SD=1.4). The control group did not report pain according to McGill Visual Analog Scale (ME=0.2, SD=0.81). No differences were found in relation to the variables of age, socio-economic stratum and educational level. All subjects stated in writing to be willing to participate in the study.

In the descriptive - comparative analysis, significant differences ($p<0.01$) were found with respect to the neuropsychological variables between the study groups (Table 1). The group with FM, obtained a worse performance in the attention tests (TMT-A, Stroop word-color, written and oral digit symbol, auditory continuous performance test, Benton visual retention test), language (Boston test, Controlled Oral Word Association Test, Token test), memory (Rey auditory verbal learning test, section A1, A5, A7 trials and recognition), viso-constructive praxis (Rey-Osterrieth Complex Figure Test - Copy) and Executive Functions (Stroop Word-color, wisconsin test, mental control). There were no significant differences in performance in the Minimental state examination, false recognition of Rey auditory-verbal learning test and TMT B. Regarding the values obtained from the plasma cortisol test AM, PM and the difference between the two values (Profile AM-PM), there were no significant differences between the study groups (Table 1).

The Spearman correlational analysis of variables for non-parametric samples indicates statistically significant correlations in the FM group (Table 2): a moderate negative correlation was found between the cortisol profile (AM-PM Difference) and False Recognition of the Rey Verbal-Auditory Learning Test and perseverative errors of the Wisconsin test. No correlation was found between the neuropsychological variables and the independent measurements of AM and PM cortisol. With regard to the control group, significant correlations ($p<0.05$) were found between Cortisol AM with Wisconsin Categories (negative correlation), and Cortisol FM with Phonological Verbal Fluency, and with Wisconsin Persevering Errors (Positive Correlations) (Table 3).

Subsequent, to estimate which is the variable that best predicts the behavior of the cortisol profile, a multiple regression analysis was performed. The dependent variable is the cortisol profile, and the neuropsychological variables, anxiety (Hamilton Scale) and depression (Beck Inventory), as independent variables. This model explains, in 88.7% (R2) the variability of the cortisol profile (corrected R2=77.4%), influencing jointly and linearly on this (p-value=0.000).

In the model estimates, the variables with significant values ($p<0.05$) were observed: Minimental State Examination, Auditory Continuous Performance Test, Controlled oral word association test (phonological and semantic verbal fluency),

Table 1 Description and comparison analysis between study groups

		Control Group			Group with fibromyalgia			P-Value*
		Mean	SD	Median	Mean	SD	Median	
Physiological stress	CORTISOL AM	9.23	5.91	8.50	10.31	4.70	10.00	0.134
	CORTISOL PM	4.10	1.42	4.00	5.87	3.76	5.00	0.092
	PROFILE AM-PM	5.06	5.10	4.00	4.53	3.81	4.00	0.790
Mental status and attention	MMSE	29.73	0.69	30.00	29.29	1.42	30.00	0.206
	TMT - A	41.03	14.62	40.00	57.48	26.46	49.00	0.007
	STR WORD	107.20	16.93	100.00	85.32	25.16	94.00	0.001
	STR COL	71.20	12.55	70.00	60.19	16.04	60.00	0.009
	SDMT.WRITTEN	46.53	9.36	48.00	36.71	11.24	35.00	0.000
	SDMT ORAL	52.97	11.46	54.50	41.71	11.71	40.00	0.000
	ACPT	15.90	0.31	16.00	14.68	2.30	16.00	0.001
	BVRT	6.87	1.48	7.00	6.52	4.65	6.00	0.018
Language	BOSTON	49.70	4.87	50.00	43.61	7.87	44.00	0.001
	COWAT.SEM	35.13	5.34	37.00	29.61	6.34	29.00	0.001
	COWAT.PHON	42.20	12.24	42.00	30.61	10.75	31.00	0.001
	TOKEN	34.27	1.55	35.00	29.71	6.60	32.00	0.000
Memory	RAVLT.A1	5.40	1.30	5.00	4.35	0.84	4.00	0.001
	RAVLT.A5	12.77	1.36	13.00	10.39	2.26	10.00	0.000
	RAVLT A7	10.90	2.38	11.00	8.06	2.95	8.00	0.000
	RAVLT REC	14.53	0.68	15.00	12.19	3.35	13.00	0.000
	RAVLT FREC	14.43	0.68	15.00	14.10	1.40	15.00	0.495
	ROCF COP	19.73	4.52	19.50	15.61	7.69	15.00	0.005
Viso-constructive Praxis	ROCF EV	35.23	1.33	36.00	32.42	5.08	35.00	0.016
Executive function	STR WORD-COL	40.87	9.25	40.00	29.94	14.07	30.00	0.000
	WCST CAT	5.30	1.18	6.00	3.45	1.95	4.00	0.000
	WCST PERSEV.ERR	16.47	11.10	13.00	34.26	23.47	29.00	0.000
	TMT- B	98.97	40.37	83.00	130.61	64.71	119.00	0.052
		6.70	1.60	7.00	5.03	2.46	6.00	0.006

* Test U of Mann-Whitney with significance 0.05
MMSE: Minimental State Examination; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; SDMT.WRITTEN: Written Digit Symbol; SDMT ORAL: Oral Digit Symbol; ACPT: Auditory continuous performance test; BVRT: Benton visual retention test; BOSTON: Test of denomination of Boston COWAT.SEM: Controlled Oral Word Association Test - Semantic Fluidity; COWAT.PHON: Controlled Oral Word Association Test - Phonologic Fluidity; TOKEN: Token test; RAVLT: Rey auditory-verbal test (A1 Trial, A5 Trial, A7 Trial); REC Recognition; FREC False Recognition; ROCF EV: Rey-Osterrieth complex figure test - Evocation; FIG.REY.COP: Rey-Osterrieth complex figure test - Copy; STR.WORD: Stroop Word; STR.COL: Stroop Color; STR.WORD.COL: Stroop Word Color; WCST CAT: Test of Wisconsin Categories; WCSN PERSEV.ERR: Wisconsin card sorting - Perseverative errors; CONTROL MEN: Subscale of Wechsler of Mental Control.

Table 2 Sperman Correlation between cortisol levels and neuropsychological variables in cases group

Neuropsychological Tests		Cortisol AM	Cortisol PM	Difference AM-PM
MMSE	Correlation coefficient	0.061	0.294	-0.030
TMT A	Correlation coefficient	0.090	-0.129	0.228
TMT B	Correlation coefficient	0.129	-0.141	0.333
SDMT.WRITTEN	Correlation coefficient	-0.251	-0.091	-0.279
SDMT ORAL	Correlation coefficient	-0.144	0.016	-0.285
ACPT	Correlation coefficient	-0.094	0.262	-0.316
TRVB	Correlation coefficient	-0.270	0.004	-0.314
BOSTON	Correlation coefficient	-0.064	0.087	-0.068
COWAT.SEM	Correlation coefficient	-0.126	0.217	-0.311
COWAT.PHON	Correlation coefficient	-0.138	0.091	-0.239
TOKEN	Correlation coefficient	-0.203	0.018	-0.149
RAVLT.A1	Correlation coefficient	0.060	-0.051	0.208
RAVLT.A5	Correlation coefficient	0.252	0.321	0.060
RAVLT A7	Correlation coefficient	0.202	0.302	-0.054
RAVLT REC	Correlation coefficient	-0.177	0.013	-0.257
RAVLT FREC	Correlation coefficient	-0.204	0.069	-0.428*
ROCF EV	Correlation coefficient	-0.354	-0.126	-0.351
ROCF COP	Correlation coefficient	0.202	0.239	0.057
STR WORD	Correlation coefficient	-0.134	0.175	-0.295
STR COL	Correlation coefficient	-0.004	0.226	-0.200
STR WORD-COL	Correlation coefficient	-0.001	0.242	-0.240
WCST CAT	Correlation coefficient	0.279	0.120	0.283
WCST PERSEV.ERR	Correlation coefficient	-0.162	0.095	-0.369*
MENTAL CON	Correlation coefficient	-0.049	0.316	-0.229

*Significant Correlation at 95%** Significant Correlation at 99%.
MMSE: Minimental State Examination; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; SDMT.WRITTEN: Written Digit Symbol; SDMT ORAL: Oral Digit Symbol; ACPT: Auditory continuous performance test; BVRT: Benton visual retention test; BOSTON: Test of denomination of Boston COWAT.SEM: Controlled Oral Word Association Test - Semantic Fluidity; COWAT.PHON: Controlled Oral Word Association Test - Phonologic Fluidity; TOKEN: Token test; RAVLT: Rey auditory-verbal test (A1 Trial, A5 Trial, A7 Trial); REC Recognition; FREC False Recognition; ROCF EV: Rey-Osterrieth complex figure test - Evocation; FIG.REY.COP: Rey-Osterrieth complex figure test - Copy; STR.WORD: Stroop Word; STR.COL: Stroop Color; STR. WORD.COL: Stroop Word Color; WCST CAT: Test of Wisconsin Categories; WCSN PERSEV.ERR: Wisconsin card sorting - Perseverative errors; CONTROL MEN: Subscale of Wechsler of Mental Control.

Rey Verbal-Auditory learning test (A1, A5 trials, recognition and false recognition); Rey-Osterrieth complex figure test (evocation), Mental Control, Wisconsin Card sorting Test (categories and perseverative errors) and TMT B and Beck Depression Inventory. In addition, the variables that most influence the cortisol profile are: Rey Verbal- auditory Rey test (Recognition) and the Wisconsin Card Sorting Test (Perseverative errors and categories), variables related to memory storage processes and Executive Functions (cognitive flexibility and abstraction capacity), respectively (Table 4).

Table 3 **Sperman Correlation between cortisol levels and neuropsychological variables in control group**

	Neuropsychological Tests	Cortisol AM	Cortisol PM	Diference AM-PM
MMSE	Correlation Coefficient	0.064	-0.072	0.067
TMT A	Correlation Coefficient	0.094	-0.072	0.117
TMT B	Correlation Coefficient	0.022	-0.112	-0.002
SDMT.WRITTEN	Correlation Coefficient	-0.190	0.009	-0.134
SDMT ORAL	Correlation Coefficient	-0.205	0.085	-0.172
ACPT	Correlation Coefficient	-0.045	-0.188	0.162
TRVB	Correlation Coefficient	-0.082	0.012	-0.061
BOSTON	Correlation Coefficient	-0.257	-0.271	-0.274
COWAT.SEM	Correlation Coefficient	-0.218	-0.133	-0.070
COWAT.PHON	Correlation Coefficient	0.025	-0.390*	0.160
TOKEN	Correlation Coefficient	-0.319	-0.147	-0.265
RAVLT.A1	Correlation Coefficient	0.344	0.063	0.290
RAVLT.A5	Correlation Coefficient	-0.232	-0.286	-0.184
RAVLT A7	Correlation Coefficient	-0.162	-0.253	-0.133
RAVLT REC	Correlation Coefficient	-0.014	0.153	-0.068
RAVLT FREC	Correlation Coefficient	-0.120	-0.253	-0.092
ROCF EV	Correlation Coefficient	-0.216	0.012	-0.270
ROCF COP	Correlation Coefficient	0.021	0.061	-0.016
STR WORD	Correlation Coefficient	0.005	0.003	0.031
STR COL	Correlation Coefficient	-0.207	-0.186	-0.061
STR WORD-COL	Correlation Coefficient	-0.264	0.009	-0.226
WCST CAT	Correlation Coefficient	-0.430*	-0.244	-0.321
WCST PERSEV.ERR	Correlation Coefficient	0.326	0.414*	0.224
MENTAL CON	Correlation Coefficient	0.049	-0.105	0.102

*Significant Correlation at 95%** Significant Correlation at 99%.
MMSE: Minimental State Examination; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; SDMT.WRITTEN: Written Digit Symbol; SDMT ORAL: Oral Digit Symbol; ACPT: Auditory continuous performance test; BVRT: Benton visual retention test; BOSTON: Test of denomination of Boston COWAT.SEM: Controlled Oral Word Association Test - Semantic Fluidity; COWAT.PHON: Controlled Oral Word Association Test - Phonologic Fluidity; TOKEN: Token test; RAVLT: Rey auditory-verbal test (A1 Trial, A5 Trial, A7 Trial); REC Recognition; FREC False Recognition; ROCF EV: Rey-Osterrieth complex figure test - Evocation; FIG.REY.COP: Rey-Osterrieth complex figure test - Copy; STR.WORD: Stroop Word; STR.COL: Stroop Color; STR. WORD.COL: Stroop Word Color; WCST CAT: Test of Wisconsin Categories; WCSN PERSEV.ERR: Wisconsin card sorting - Perseverative errors; CONTROL MEN: Subscale of Wechsler of Mental Control.

It should be noted that neuropsychological variables do not show interdependence in the model. It is ruled out that there is multicollinearity, or linear autocorrelation. The first aspect measured by the inflation factors of variance that did not exceed 10, the diagnoses of collinearity less than 30 and the coefficient above 0.9. The second aspect obtained by the Dubin-Watson statistic is 2.111, which assumes that the residuals are independent and complies with the fact that there is no serial autocorrelation. Also, when applying the test of normality to the waste (Kolmogorov-Smirnov test)

generates a Z statistic of 0.379, with a p-value=0.996. This indicates that the assumption of the normality of the residues is fulfilled.

The linear regression model performed in the control group did not show significant results (p<0.73); similarly, the model only accounts for 43.5% of the variability of the cortisol profile, which implies a low adjustment. Thus, significance values above 0.05 are found in the different neuropsychological and emotional variables included in the model (Table 4).

CONCLUSIONS

The group of patients with FM present significant neuropsychological alterations, mainly in the attention, memory, language and executive functions, as compared to the control group; being specifically of relation and influence of the alterations of episodic memory and cognitive flexibility with the profile of serum cortisol, as a measure of physiological stress.

Previous studies have shown that the functions of selective attention and working memory are more susceptible to deficit in the presence of pain[22]. Likewise, patients with FM have worse performance in Stroop word-color and symbol digit test as a measure of attention / executive function and processing speed, respectively[23], as well as in the ability to effectively access verbal information stored in memory[24]. These evident difficulties in diminished cognitive performance suggest alterations in the underlying brain mechanisms, especially those related to reward / punishment and pain systems (decreased dopaminergic activity in the ventral tegmental area and decreased gray matter in regions of the cingulate cortex, Prefrontal medial, parahippocampal gyrus, fusiform cortex and cerebellum areas), evidenced in functional magnetic resonance imaging (MRI)[25,26].

On the other hand, when measuring the physiological stress variable by means of the AM-PM cortisol test, and analyzing the difference of both measures (cortisol profile), it was found that there are no significant differences between patients with FM and the control group, contrary to what has been found in previous reviews[15]. However, the findings show that, in the FM group, there are significant correlations between the cortisol profile and memory storage capacity and the ability to be flexible and change strategy against the demands of the environment. This negative correlation, indicates that the greater the stress, the lower the performance in memory activities and cognitive flexibility, which suggests that physiological stress can be considered a factor that interferes in the neuropsychological alterations of these patients, especially in work memory tasks and surveillance, which are related to salivary cortisol measurements, as reported in previous studies[27]. Likewise, in the control group, similar correlations were found; which may suggest that stress in non-pathological subjects may influence cognitive performance specifically in attention, memory, or executive functions, even though these difficulties are not clinically significant[28].

In the same vein, the results of the multiple regression analysis indicate that some of the neuropsychological alterations found mainly in memory and executive functions, as well as the symptoms of depression, are related to and predict the variability in cortisol levels, this due to the existing and documented relationship of cognitive processes and the neuroendocrine system: the stress associated with glucocorticoid activation that causes declining declarative memory[29], poor self-regulation capacity and inhibition of executive function responses that maintains the chronic pain condition[30] and the symptoms of anxiety and depression are related to alterations in the endocrine system, which sustained over time affects the cognitive processes[31]. On the other hand, it has been demonstrated that there is a relationship between cortisol levels and cognitive functions, probably mediated by the activation and feedback of the hypothalamic-pituitary-adrenal system, with the prefrontal cortex, which has high concentrations of corticosteroid receptors and are responsible for the regulation of affect, autonomic reactions to harmful stimuli, learning and memory[32].

The findings of this study, besides confirming alterations in specific cognitive domains in FM patients and demonstrating the probably two-way relationship between physiological stress, neuropsychological variables and depression, suggest the presence of more complex mechanisms underlying the symptoms of disease, involving the participation of different functional brain systems. On the other hand, cognitive and affective systems have been shown to be involved in disorders related to pain perception; specifically, the ventromedial prefrontal cortex and the accumbens nucleus, which form a system that evaluates the relevance and affective value of the stimulus by controlling the flow of information through descending pathways[33].

The identification of these neurophysiological processes involved in this disease allows for a multimodal diagnostic and therapeutic approach, in which a holistic view of the patient must be taken, which is in line with a more comprehensive bio-psycho-social model. Finally, in the present study, we can point out methodological difficulties related to the sample size and the representation of the female gender in the whole sample. This is partly explained by the higher prevalence of the disease in women than in men. As a recommendation for future research, it is important to take into account the influence of the time of evolution and the history of treatments that the patient has received, in the development of the symptoms of the disease, in order to be

Table 4 Estimation of the multiple linear regression model for Control Group and Fibromyalgia Group

		Control Group					Fibromyalgia Group						
	Model *	Unstandardized Coefficient		Standard Coefficients	T	P-value	Unstandardized Coefficient		Standard Coefficients	T	P-value	Collinearity statistics	
		B	Std. Error	Beta			B	Std. Error.	Beta			Tolerance	VIF
	Constant	-137.642	160.705		-0.856	0.406	10.011	15.114		0.662	0.518		
Mental status and attention	MMSE	0.512	2.44	0.069	0.21	0.837	1.322	0.514	0.492	2.57	0.021	0.206	4.864
	ACPT	4.379	7.069	0.262	0.619	0.546	0.764	0.303	0.461	2.523	0.023	0.226	4.43
Language	COWAT.SEM	0.25	0.425	0.261	0.588	0.566	-0.299	0.112	-0.496	-2.673	0.017	0.219	4.576
	COWAT.PHON	-0.05	0.137	-0.12	-0.366	0.72	0.245	0.071	0.691	3.428	0.004	0.186	5.386
Memory	RAVLT.A1	1.811	1.038	0.462	1.744	0.103	1.451	0.495	0.319	2.932	0.01	0.636	1.572
	RAVLT.A5	-1.654	1.218	-0.44	-1.359	0.196	0.622	0.197	0.369	3.155	0.007	0.552	1.813
	RAVLT REC	1.7	2.185	0.227	0.778	0.45	-1.36	0.215	-1.196	-6.335	0.000	0.212	4.728
	RAVLT FREC	1.333	3.135	0.177	0.425	0.677	-1.794	0.305	-0.658	-5.876	0.000	0.6	1.666
	ROCF EV	-0.303	0.36	-0.268	-0.843	0.413	-0.297	0.061	-0.599	-4.893	0.000	0.502	1.99
Executive Functions	MENTAL CON	0.663	0.927	0.208	0.715	0.486	-1.053	0.34	-0.679	-3.099	0.007	0.157	6.365
	WCST CAT	2.687	2.297	0.621	1.17	0.262	-1.962	0.506	-1.002	-3.877	0.001	0.113	8.859
	WCST PERSEV. ERR	0.226	0.237	0.492	0.952	0.357	-0.185	0.04	-1.138	-4.639	0.000	0.125	7.977
	TMT B	-0.001	0.045	-0.008	-0.023	0.982	-0.038	0.011	-0.648	-3.434	0.004	0.212	4.719
Depression	DEP BECK	0.316	0.257	0.429	1.231	0.238	0.136	0.048	0.387	2.865	0.012	0.414	2.417
Anxiety	ANS HAM	0.067	0.263	0.111	0.253	0.804	0.02	0.052	0.064	0.386	0.705	0.27	3.7

*Group control and Fibromyalgia, with dependent variable: Profile of Cortisol.
MMSE: Minimental State Examination; COWAT.SEM: Controlled Oral Word Association Test - Semantic Fluidity; COWAT.PHON: Controlled Oral Word Association Test - Phonologic Fluidity; RAVLT: Rey auditory-verbal test (A1 Trial, A5 Trial); REC Recognition; FREC False Recognition; ROCF EV: Rey-Osterrieth complex figure test - Evocation; WCST CAT: Test of Wisconsin Categories; WCSN PERSEV.ERR: Wisconsin card sorting - Perseverative errors; CONTROL MEN: Subscale of Wechsler of Mental Control. TMT-B: Trail Making part B; DEP BECK: Beck Depression Inventory; ANS HAM: Hamilton Anxiety Scale.

able to understand more accurately the relations of influence between each of the variables that affect the disorder.

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CONFLICT OF INTERESTS

The authors declare that there was no conflict of interests in the realization of the present study.

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