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Neuropsychological assessment of cognitive disorders in patients with fibromyalgia, rheumatoid arthritis, and systemic lupus erythematosus

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ABSTRACT

Introduction: This study assesses the possible existence of cognitive disorder associated with chronic diseases [fibromyalgia (FM), rheumatoid arthritis (RA) and lupus (SLE)], and the influence of the variables age, educational level and psychiatric symptoms on those disorders. **Materials and methods:** The patients were referred by the Rheumatology Outpatient Clinic of the Hospital Universitário de Brasília (HUB), with ages ranging from 30 to 80 years, and were divided into the following three groups: FM, 13 patients; RA, 13 patients; and SLE, 11 patients. Their performance in the neuropsychological tests of memory, language, executive functions and neuropsychiatric inventory was assessed considering their type of chronic disease, educational level and age. In addition, the cutoff points of cognitive normality of population samples were compared with the patients' performances. **Results:** The cognitive disorders were shown to be associated with the three diseases studied, but with significant differences between them. **Conclusion:** The variables studied (low educational level and advanced age) were associated with various degrees of impairment in the different cognitive functions in the three pathological groups. However, FM and SLE groups showed significantly higher means of the neuropsychiatric symptoms of anxiety, irritability and hallucinations than the RA group in the neuropsychiatric inventory.

Keywords: cognition, chronic disease, fibromyalgia, rheumatoid arthritis, systemic lupus erythematosus.

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CHRONIC PAIN DISEASES AND THEIR COGNITIVE ASPECTS

Fibromyalgia

Fibromyalgia (FM) is considered a musculoskeletal syndrome of chronic and diffuse pain, because of its large number of symptoms. It is diagnosed in the presence of generalized pain for three months, in combination with pain in at least 11 of 18 tender point sites on digital palpation, according to the American College of Rheumatology.[1]

Pain in FM is different from any other sensorial impression, because it is characterized not only by the sensory-discrimination dimension, but also by the important affective-emotional component, constituted by the affective-motivational dimension of pain.[2]

In FM, the central nervous system activity is modulated by psychological variables, which contribute to the establishment of an abnormal response to pain, such as cognitive distortions, excessive attention to noxious stimuli, inadequate attitudes for managing pain, and emotional instability when recalling painful experiences.[2] The sympathetic autonomic nervous system is hyperactive during all the time, especially during sleep, a phase when several neurotransmitters, hormones and antibodies, such as serotonin, substance P, growth hormone, and cortisol, are synthesized or regulated. Thus, some metabolic disorders originate in the transitions of the non-REM sleep stages, mainly in stage 4, which is the last stage preceding REM sleep, a phase with high cerebral activity, characterized by dreaming and memory consolidation. Patients with FM show no injury in the tissues affected by pain, but have metabolic

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changes, such as high concentrations of substance P in the cerebrospinal fluid and low concentrations of pain-inhibiting neurotransmitters, which cause high sensitivity.[3]

The chronicity of FM affects not only patients' quality of life, but also their social relations, habits and routines, causing an increase in the psychological abnormalities common to FM, especially depressive states and psychiatric disorders.[4]

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic, autoimmune, chronic inflammatory disease, which affects the joints and has systemic manifestations, such as morning stiffness, fatigue, and weight loss. The involvement of other organs reduces life expectancy by five to ten years. Disease progression makes the patients unable to perform their daily-life activities.[5,6]

Patients with RA can have cognitive disorders due to the disease itself or their chronic pain condition. Depression is a factor constantly present, influencing patients' quality of life. In the initial RA stages, symptoms of anxiety also occur.[7] However, the previous personality and social stress are the two most important aspects regarding the appearance of psychological disorders in RA.[8]

Psychological disorders also develop in association with physical impairment. However, the pharmacological treatment of RA does not affect the psychiatric findings, which require other resources.[8]

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic disease of unknown cause. It comprises autoimmune and inflammatory processes in a multisystem form, often affecting the central, peripheral and autonomic nervous system, generating neurological impairment, and neuropsychiatric and psychofunctional syndromes, such as convulsions, headache, organic cerebral syndrome, and psychosis. Neurological impairment can occur simultaneously with other symptoms, or after disease onset.[9–11]

SLE can result from immune damage, or from several systemic manifestations. The scientific community has reached consensus regarding the multifactorial etiology of the disease, suggesting the following causative factors: hormonal, genetic, infectious, environmental, and psychological.[9–12] However, several researchers have associated worsening of SLE primarily with psychological factors.[11–13]

The SLE diagnosis should be established based on at least four of the following 11 criteria: malar rash, discoid rash, photosensitivity, oral and nasal ulcers, arthritis, serositis, renal disorder, neurological disorder, hematologic disorder, immunologic disorder, and antinuclear antibodies.[14]

Researchers have reported a 75% incidence of cognitive disorders, anxiety and depression in SLE.[9] According to them, the cognitive disorders did not differ among the patients when comparing gender, race, disease duration, disease activity, or any clinical manifestation variables. In addition, no relation was identified between the cognitive disorders and the medications used by the patients.

This study aimed at assessing the existence of cognitive disorders associated with FM, SLE, and RA, by use of neuropsychological tests, having the cutoff points of clinical consensus as parameters of normality. Cognitive performance was assessed considering the influence of the variables age, educational level, and psychiatric symptoms.

MATERIALS AND METHODS

This was a pilot study approved by the Ethics Committee on Research with Human Beings of the Health Sciences School of the Universidade de Brasília (protocol #20/2010).

Data collection was performed at the Hospital Universitário de Brasília of the Universidade de Brasília (HUB/UnB), with patients referred by the Rheumatology Outpatient Clinics, who voluntarily submitted to the study, after being informed about the research and providing written informed consent.

This study assessed 37 patients divided into three groups, as follows: FM, 13 patients; RA, 13 patients; and SLE, 11 patients. Their ages ranged from 30 to 80 years, and only one patient was from the male gender. The educational level ranged from one to 12 years of schooling.

The following neuropsychological tests were used: Mini-Mental State Examination (MMSE);[15] digits forward (DF) and digits backwards (DB) subtests, and Logical Memory I (LM-I) and II (LM-II) of the Wechsler Memory Scale (WMS);[16] Similarities subtest (SIM) of the Wechsler Adult Intelligence Scale (WAIS-III);[17] Phonemic Verbal Fluency test (VFT-Pho) and Semantic Verbal Fluency test – Animals (VFT-SeAn) and Fruits (VFT-SeFr) categories;[18] clock drawing test (CDT);[19] Five-Points test (5PT);[20] and neuropsychiatric inventory (NPI).[21]

The possibility of association between chronic pain diseases (FM, RA, and SLE) and cognitive disorders was assessed by using the correlation between the patients' performance in the neuropsychological tests applied and the cutoff points considered normal in such tests, reported in the literature. The association of the cognitive disorders with the following variables were also assessed: age, educational level, psychiatric symptoms, and disease duration.

Statistical analysis

Data analysis was performed by use of robust statistics, which is the set of techniques used to attenuate the effect of the outliers and

that preserves the distribution form more adherent to empirical data. According to Wilcox,[22] means can be distorted by outliers, not reflecting the accuracy of the central value of the data. Thus, that author has recommended the use of the median, which is an extreme form of trimmed mean, in which any value 20% above or below the fixed point is ruled out, and the central value of the original data is more accurately obtained. Thus, our study used the Keselman technique,[23] in which, at first, the scores are ordered from the lowest to the highest, and 20% of the lowest and highest data are removed. Then the remaining scores replace those that were removed. These are the so-called trimmed scores. The analysis of variance of the trimmed scores was performed by using the following tests: a) Kruskal-Wallis test, a nonparametric method to test the equality of the medians of the population with more than two groups; in this study, it was aimed at assessing the existence of differences between the medians of the three groups of diseases (FM, SLE, and RA) regarding cognitive performance, in addition to assessing the influence of age and educational level on the presence of psychiatric symptoms; b) Mann-Whitney test, used to assess whether two independent samples originate from the same distribution. In this regard, all patients were organized in two groups according to the following variables: age (young adults, up to 49 years; and elderly, up to 80 years); educational level (low, up to five years of schooling; and medium-high, at least six years of schooling); and duration of disease (early discovery, up to three years when diagnosed; and late discovery, more than four years when diagnosed).

RESULTS

The nonparametric Kruskal-Wallis test showed significant differences between the groups of chronic diseases.

The group of patients with FM showed a lower performance as compared with those of the other groups in the following subtests: LM-I of the WMS [(K = 7.73) *P < 0.05]; SIM of the WAIS-III [(K = 22.94) *P < 0.05]; VFT-SeAn [(K = 5.98) *P < 0.05], and DB of the WMS [(K = 11.02) *P < 0.05]. In addition, patients with FM showed an increase in the perseverance error rate in the 5PT [K = 9.41 *P < 0.05] as compared with the other groups.

The group of patients with RA showed a lower performance as compared with those of the other groups in the following subtests: CDT [(K = 16.43) *P < 0.05], VFT-Pho [(K = 7.12) *P < 0.05], and 5PT [(K = 9.16) *P < 0,05]. FM and RA groups had performances below the cutoff point expected in the following subtests: LM-I of the WMS, VFT-Pho, VFT-SeAn, VFT-SeFr, and 5PT (Table 1).

Table 1
Neuropsychological performance of the groups of chronic rheumatological diseases according to the type of disease and significant differences between the groups according to the nonparametric Kruskal-Wallis test

Tests (cutoff points)[Ref.]	RA (n = 13)	FM (n = 13)	SLE (n = 11)	Statistics and P value
MMSE (< 24)[1]	23.07 (1.70)	23.07 (1.84)	23.45 (1.77)	(K = 4.05) P = 0.13
LM-I (< 7.5)[2]	6.80 (0.72)	6.11 (1.24)	7.77 (1.21)	(K = 7.73) *P < 0.05
LM-II (4.5)[2]	4.61 (0.84)	4.42 (1.09)	7.59 (3.35)	(K = 5.34) P = 0.94
SIM (< 10)[3]	11.15 (1.72)	10.61 (3.04)	18.18 (1.47)	(K = 22.94) *P < 0.05
CDT (< 6)[4]	7.61 (1.89)	7.84 (1.51)	9.63 (0.50)	(K = 16.43) *P < 0.05
VFT-Pho (< 30)[5]	19.38 (6.87)	22.15 (4.41)	26.45 (6.81)	(K = 7.12) *P < 0.05
VFT-SeAn (≤ 15)[5]	11.07 (2.39)	10.61 (2.18)	12.90 (1.81)	(K = 5.98) *P < 0.05
VFT-SeFr (≤ 15)[5]	11.61 (2.18)	11.53 (0.51)	12.72 (2.37)	(K = 2.00) P = 0.36
5PT (≤ 15)[6]	12.76 (3.60)	13.76 (3.56)	18.00 (2.79)	(K = 9.16) *P < 0.05
5PT-perseverance[6]	3.38 (3.47)	6.46 (4.19)	1.54 (1.43)	(K = 9.41) *P < 0.05
DF (< 6)[7]	9.76 (1.92)	10.15 (1.34)	8.90 (0.94)	(K = 4.09) P = 0.12
DB (< 4)[7]	11.15 (1.72)	10.61 (3.04)	18.18 (1.47)	(K = 11.02) *P < 0.05
NPI hallucinations	0.30 (0.75)	1.84 (1.67)	2.0 (1.94)	(K = 8.14) *P < 0.01
NPI irritability	0.53 (1.45)	1.84 (2.15)	2.81 (2.04)	(K = 7.36) *P < 0.02
NPI anxiety	2.46 (1.50)	3.30 (1.10)	3.45 (1.80)	(K = 6.04) *P < 0.05

Patients' performance in the neuropsychological tests. MMSE: Mini-Mental State Examination; LM-I: logical memory I subtest of the Wechsler Memory Scale; LM-II: logical memory II subtest of the Wechsler Memory Scale; SIM: similarities subtest of the Wechsler Adult Intelligence Scale; CDT: clock drawing test; VFT-Pho: phonemic verbal fluency test; VFT-SeAn: semantic verbal fluency test – animals category; VFT-SeFr: semantic verbal fluency test – fruits category; 5PT: Five-Points test; DF: digits forward subtest of the Wechsler Memory Scale; DB: digits backwards subtest of the Wechsler Memory Scale; NPI: neuropsychiatric inventory. Organized according to the types of pathologies (RA, FM, and SLE) with significant differences indicated by K in the Kruskal-Wallis test, and significance in *(P > 0.05). References of the cutoff points: 1) Bertolucci, Brucki, Campacci and Juliano (1994); 2) Hodges & Patterson (1995); 3) Nascimento (1998); 4) Sunderland *et al.* (1989); 5) Bayles, Kasniak (1987); 6) Bayles, Kasniak (1987); Andreas *et al.* (1992); 7) Regard, Strauss & Knapp (1982); 8) Nascimento (1998).

The SLE group showed the best performances in the LM-I and DB of the WMS, SIM of the WAIS-III, CDT, VFT-Pho, VFT-SeAn, VFT-SeFr, and 5PT subtests. However, regarding the cutoff points of the cognitive performance normality, such performances were below the expected range in the VFT-Pho, VFT-SeAn, and VFT-SeFr subtests. In addition, SLE and FM groups showed symptom frequency rates significantly greater than that of the RA group regarding hallucination [(K = 8.14) *P < 0.01] and irritability [(K = 7.36) *P < 0.02], as well as regarding symptom intensity, in which anxiety [(K = 6.04) *P < 0.05] was significantly elevated in both groups (Table 1).

The other psychiatric symptoms (disillusion, restlessness, dysphoria, euphoria, apathy, disinhibition, and aberrant motor activity) did not differ between the groups regarding intensity or frequency.

In addition, a nonparametric analysis was performed to assess whether the mean age and educational level differed in the diseases studied. The Kruskal-Wallis test revealed that RA, FM, and SLE did not differ regarding the educational level. Regarding age, however, the SLE group significantly differed from the others [(K = 20.28) *P < 0.05], possibly due to its lower mean age (Table 2).

The nonparametric Mann-Whitney test showed a significant difference in performance between the groups divided according to age in the following subtests: MMSE [(Z = -2.13) *P < 0.05], LM-I of the WMS [(Z = -2.14) *P < 0.05], LM-II of the WMS [(Z = -2.29) *P < 0.05], CDT [(Z = -3.24) *P < 0.05], VFT-Pho [(Z = -2.63) *P < 0.05], VFT-SeAn [(Z = -2.49) *P < 0.05], and 5PT [(Z = -2.51) *P < 0.05]. In all those subtests, younger patients performed better (Table 3).

Table 2
Age and years of schooling of patients in the chronic rheumatological diseases (RA, FM, and SLE) according to the nonparametric Kruskal-Wallis test

	Age	Years of schooling
RA (n = 13)	55.07 (8.33)	1.84 (0.68)
FM (n = 13)	53.30 (3.85)	2.07 (0.75)
SLE (n = 11)	37.54 (5.90)	2.27 (0.78)
Statistics and P value	(K = 20.28) *P < 0.05	(K = 2.03) P = 0.36

Mean, standard deviation, and differences between medians with significant differences indicated by K in the Kruskal-Wallis test and significance in *(P > 0.05).

Table 3
Neuropsychological performance of patients with chronic rheumatologic diseases organized according to their ages, and significant differences according to the nonparametric Mann-Whitney test

Tests (cutoff points)[Ref.]	Young adults (n = 19)	Elderly (n = 18)	Statistics and P value
MMSE (< 24)[1]	24.11 (1.60)	22.84 (1.74)	(Z = -2.13) *P < 0.05
LM-I (< 7.5)[2]	7.33 (1.29)	6.39 (1.03)	(Z = -2.14) *P < 0.05
LM-II (4.5)[2]	6.52 (2.96)	4.39 (0.96)	(Z = -2.29) *P < 0.05
SIM[3]	15.55 (3.86)	10.68 (2.45)	(Z = -3.65) P = 0.70
CDT (≤ 6)[4]	9.11 (1.07)	7.52 (1.80)	(Z = -3.24) *P < 0.05
VFT-Pho (≤ 30)[5]	25.11 (6.64)	19.94 (5.61)	(Z = -2.63) *P < 0.05
VFT-SeAn (≤ 15)[6]	12.44 (2.17)	10.52 (2.09)	(Z = -2.49) *P < 0.05
VFT-SeFr (< 15)[6]	12.55 (2.09)	11.31 (1.45)	(Z = -1.68) P = 0.09
5PT[7]	16.50 (3.41)	12.94 (3.73)	(Z = -2.51) *P < 0.05
5PT-perseverance	3.38 (3.48)	4.42 (4.15)	(Z = -0.66) P = 0.51
DF (< 6)[8]	9.55 (1.54)	9.73 (1.55)	(Z = -0.37) P = 0.07
DB (< 4)[8]	9.33 (1.57)	10.10 (1.62)	(Z = -1.54) P = 0.12

Patients' performance in the neuropsychological tests. MMSE: Mini-Mental State Examination; LM-I: logical memory I subtest of the Wechsler Memory Scale; LM-II: logical memory II subtest of the Wechsler Memory Scale; SIM: similarities subtest of the Wechsler Adult Intelligence Scale; CDT: clock drawing test; VFT-Pho: phonemic verbal fluency test; VFT-SeAn: semantic verbal fluency test – animals category; VFT-SeFr: semantic verbal fluency test – fruits category; 5PT: Five-Points test; DF: digits forward subtest of the Wechsler Memory Scale; DB: digits backwards subtest of the Wechsler Memory Scale. Organized according to age groups with significant differences indicated by Z in the Mann-Whitney test and significance in *(P > 0.05) between the groups of young and elderly adults. References of the cutoff points: 1) Bertolucci, Brucki, Campacci and Juliano (1994); 2) Hodges & Patterson (1995); 3) Nascimento (1998); 4) Sunderland *et al.* (1989); 5) Bayles, Kasniak (1987); 6) Bayles, Kasniak (1987); Andreas *et al.* (1992); 7) Regard, Strauss & Knapp (1982); 8) Nascimento (1998).

Table 4
Neuropsychological performance of patients with chronic rheumatologic diseases organized according to their educational levels, and significant differences according to the nonparametric Mann-Whitney test

Tests (cutoff points)[Ref.]	Low educational level (n = 22)	Medium-high educational level (n = 15)	Statistics and P value
MMSE (< 24)[1]	22.90 (1.60)	24.26 (1.75)	(Z = -2.36) *P < 0.05
LM-I (< 7.5)[2]	6.47 (0.99)	7.40 (1.40)	(Z = -1.99) *P < 0.05
LM-II (4.5)[2]	4.50 (0.93)	6.80 (3.19)	(Z = -2.03) *P < 0.05
SIM (≤ 10)[3]	11.86 (3.28)	14.80 (4.45)	(Z = -2.10) *P < 0.05
CDT (≤ 6)[4]	7.86 (1.80)	8.93 (1.27)	(Z = -2.13) *P < 0.05
VFT-Pho (≤ 30)[5]	20.40 (6.16)	25.46 (6.20)	(Z = -2.36) *P < 0.05
VFT-SeAn (≤ 15)[6]	10.81 (2.17)	12.40 (2.26)	(Z = -1.98) *P < 0.05
VFT-SeFr (≤ 15)[6]	11.36 (1.64)	12.73 (1.94)	(Z = 1.99) *P < 0.05
5PT (15)[7]	13.36 (3.65)	16.60 (3.69)	(Z = -2.26) *P < 0.05
5PT-perseverance	3.50 (3.97)	4.53 (3.64)	(Z = -1.34) P = 0.17
DF (< 6)[8]	9.50 (1.68)	9.86 (1.30)	(Z = -1.18) P = 0.23
DB (< 4)[8]	9.63 (1.76)	9.86 (1.45)	(Z = -0.83) P = 0.40

Patients' performance in the neuropsychological tests. MMSE: Mini-Mental State Examination; LM-I: logical memory I subtest of the Wechsler Memory Scale; LM-II: logical memory II subtest of the Wechsler Memory Scale; SIM: similarities subtest of the Wechsler Adult Intelligence Scale; CDT: clock drawing test; VFT-Pho: phonemic verbal fluency test; VFT-SeAn: semantic verbal fluency test – animals category; VFT-SeFr: semantic verbal fluency test – fruits category; 5PT: Five-Points test; DF: digits forward subtest of the Wechsler Memory Scale; DB: digits backwards subtest of the Wechsler Memory Scale. Organized into groups according to the educational level, with significant differences indicated by Z in the Mann-Whitney test and significance in *(P > 0.05) between the groups of low and medium-high educational level. References of the cutoff points: 1) Bertolucci, Brucki, Campacci and Juliano (1994); 2) Hodges & Patterson (1995); 3) Nascimento (1998); 4) Sunderland *et al.* (1989); 5) Bayles, Kasniak (1987); 6) Bayles, Kasniak (1987); Andreas *et al.* (1992); 7) Regard, Strauss & Knapp (1982); 8) Nascimento (1998).

The Mann-Whitney test showed significant differences between the low and medium-high educational level groups in the following subtests: MMSE [(Z = -2.36) *P < 0.05], LM-I of the WMS [(Z = -1.99) *P < 0.05], ML-II of the WMS [(Z = -2.03) *P < 0.05], SIM of the WAIS-III [(Z = -2.10) *P < 0.05], CDT [(Z = -2.13) *P < 0.05], VFT-Pho [(Z = -2.36) *P < 0.05], VFT-SeAn [(Z = -1.98) *P < 0.05], VFT-SeFr [(Z = 1.99) *P < 0.05], and 5PT [(Z = -2.26) *P < 0.05].

All the results of the subtests indicate a significantly lower performance in the low-educational-level group (Table 4).

Finally, regarding disease duration, the Mann-Whitney test showed no significant difference in the cognitive performances in the neuropsychological tests, when the patients were divided into the two groups of early and late discovery of chronic pain diseases (*P > 0.05).

DISCUSSION

The results confirm the existence of cognitive disorders associated with FM, SLE, and RA. Patients with RA showed a reduced performance in the tests assessing the cognitive spheres regarding visual-constructional apraxia (CDT and VFT-Pho), that is, the ability to draw a picture based on a visual memory reference and phonemic verbal fluency. We can conclude that those patients have apraxic cognitive disorders possibly due to physical and motor impairment of RA in addition to the cognitive deficits observed in that disease. The reduced phonemic fluency observed in such patients might be related to the social stress present in RA.[8]

Patients with FM, on the other hand, had deficits in the tests assessing operational memory (LM-I, VFT-SeAn, SIM, and DB), as well as perseverance errors in 5PT, which also refer to executive function disorders. A reduction in concentration and memory loss have already been shown in patients with FM,[24] and those cognitive changes in attention are directly related to deficits in operational memory and executive function.[25]

Patients with SLE had the best performances as compared with the other two groups. However, the performance of the SLE group was below the cutoff point of cognitive normality in the phonetic and semantic verbal fluency tests (VFT-Pho, VFT-SeAn, and VFT-SeFr). In addition, it showed a significantly higher rate of psychiatric disorders (anxiety, irritability, and hallucination). Studies with patients with SLE have shown that 75% of them have cognitive deterioration associated with psychiatric disorders, such as depression, anxiety, and irritability.[9,11]

Regarding the types of chronic diseases, no difference in the educational level was observed. However, regarding age, the SLE group differed significantly from the other groups due to its lower mean age. Healthy elderly when compared with youngsters regarding cognitive aspects, show a mild and generalized slowness, in addition to accuracy loss,[26,27] which might have influenced the results of this study, favoring the SLE group as compared with the RA and FM groups in that aspect.

When assessing the age groups without considering the types of chronic diseases, young adults performed better in all tests as compared with the elderly. The literature confirms the low cognitive performance of the elderly with no disease, suggesting that such decline results primarily from aging, characterizing a normal decline in the functioning of memory basic processes. When daily life activities of the elderly decline along with their cognitive performance, however, a nosological entity should be present.[26,27]

Regarding the data related to the influence of the educational level, this study showed a reduced cognitive performance mainly in the operational memory sphere of the low-educational-level group, suggesting that memory tests can dependent on the educational level.[25]

The coinciding performances below the cognitive normality cutoff points in the phonetic and semantic verbal fluency tests of the FM and SLE groups are likely to be associated with the high intensity and frequency rates of psychiatric disorders, such as hallucination, irritability and anxiety, found in the NPI of those two groups, especially in the SLE group, which had the greatest rates. Such data are in accordance with the findings of other studies indicating that patients with psychiatric disorders have difficulties strongly related to functional deficits that reflect on academic performance, productivity, work, and social, familial and affective relationships.[28] Such functional deficits associated with anxiety occur similarly in other diseases, such as dementia, potentiating the impaired participation or the engagement in essential activities of daily social life, leading to a reduction in performing tasks involving attention, psychomotricity, verbal and nonverbal memory, comprehension, executive functions, verbal fluency, and planning.[29]

According to some studies, the increase in cognitive dysfunctions of SLE is not related to the duration of the chronic rheumatologic disease,[30] confirming our results regarding disease duration and its influence on the patients' performance in cognitive tests.

In patients with FM, the increased release of substance P is influenced by the low levels of serotonin and the presence of non-restoring or superficial sleep. Those patients can have as much as a three-fold increase in substance P levels as compared with healthy individuals.[31] It is worth emphasizing that the ascending serotonergic pathways, coincidently those whose levels are reduced in patients with FM, project themselves to the raphe nuclei and from those to the thalamus and areas innervated by the medial forebrain bundle, with emphasis to the hippocampus – important areas for the storage of operational and long-term memories.[32]

Several studies have shown that substance P has different effects related to learning in rats[33] and fish,[34] ranging from a facilitating effect, when applied immediately or up to three days after the training for learning acquisition, to the lack of effect on memory consolidation, when applied from the fourth day of training onward.[35] Thus, the deficits in operational memory and executive functions found in patients with FM in this study can be somehow related to the reduced serotonin levels in that disease.

A consensus recently published has revealed the importance of rehabilitation programs that use the cognitive-behavioral therapy, aiming at improving chronic pain diseases such as FM and SLE.[36]

Neuropsychological studies on chronic pain diseases and their cognitive dysfunctions are very important, because the deep knowledge on the cognitive aspects of a certain disease provides effective clues for the construction of rehabilitation programs.[37,38] Cognitive stimulation is possible because of cerebral plasticity, and rehabilitation with cognitive exercises can modulate plastic processes in the brain, influencing positively the functional organization of neural connections involved in memory.[37,38] Finally, cognitive stimulation through rehabilitation programs can reduce the cognitive deficits found, thus promoting better quality of life or even preventing the aggravation of cognitive and emotional deficits, which have been identified in patients with RA, FM, and SLE.

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