Behavioural Neurology

An Integrative Neuropsychological Approach to Chronic Pain, Emotions and Clinical Symptoms

Lead Guest Editor: Carmen M Galvez-Sánchez
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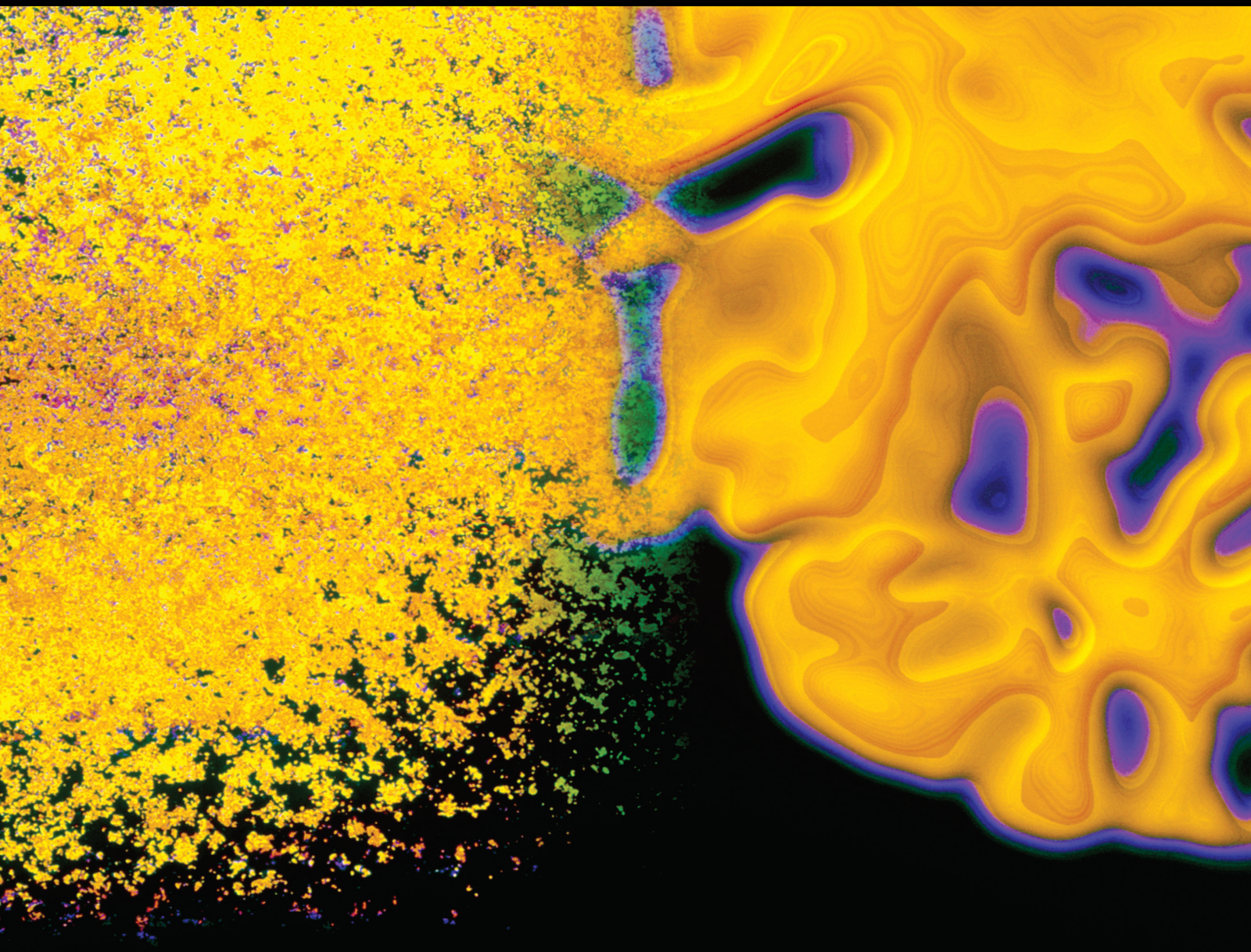

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Contents

Hindawi
Behavioural Neurology
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Editorial

An Integrative Neuropsychological Approach to Chronic Pain, Emotions, and Clinical Symptoms

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Chronic pain is a serious and increasing health problem, frequently accompanied by high comorbidity of anxiety, depression, insomnia, and cognitive disorders [1–4]. It is estimated that the prevalence of chronic pain in Europe is 19% [5, 6]. In 2006, Breivik et al. [4], prevented a prominent increase in chronic pain proportional to the population aging. Indeed, this prominent increase would entail higher socio-health costs and would require more effective strategies for its prevention, diagnosis, and treatment [4]. Nevertheless, chronic pain itself negatively affects the quality of life of patients and patients' relatives and generates high socio-sanitary expenses. The pain-related high socio-sanitary expenses are the result of the efforts on pain management and numerous indirect economic costs (e.g., by the labour productivity lessen and absenteeism and disability heighten) [4–6] Given the above-mentioned aspects, chronic pain has been recognized as a bioethical issue and different international organizations (e.g., World Health Organization and International Association for the Study of Pain) have declared the exigency of an adequate pain therapy as a human right [6]. To meet adequate pain therapy requirements, an integrated approach to neuropsychological, emotional, and clinical symptoms is essential. In this detail, the transdiagnostic and personalized perspectives have been scientifically and clinically supported [7, 8].

The special issue "An Integrative Neuropsychological Approach to Chronic Pain, Emotions and Clinical Symptoms" aimed at highlighting the latest progress on chronic pain's neuroscience and related symptoms to promote prevention and intervention-integrated strategies. This research topic includes five original research articles. The majority (three in total; [9–11]) examined fibromyalgia syndrome (FMS), one of the prototypical chronic pain conditions characterized by widespread chronic pain and symptoms, such as fatigue, unrefreshing sleep, cognitive deficits, and comorbid emotional alterations (i.e., anxiety and depression) [12, 13]. Concerning cognitive deficits, FMS patients tend to exhibit difficulties in verbal memory, organization and planning abilities, strategic planning, self-regulation, processing speed, attention, and cognitive flexibility [9–11]. The remaining studies explored chronic tension-type headache (CTTH) and rats with global cerebral ischemia [14, 15]. The last one, investigated the effect of voluntary wheel running on striatal dopamine levels and anxiety-like behaviour in rats with global cerebral ischemia. This study is not included in the present editorial as the results and methodology are difficult to be generalized and replicated in humans [15].

The first study [9], investigated executive functions in FMS patients compared with healthy controls via a Go/No-Go task. The variability of reaction time (RT)—by using traditional and ex-Gaussian parameters—was evaluated as a marker of executive function impairments. The study demonstrated that indices of RT variability, in particular those derived from the ex-Gaussian function, maybe a complement of speed and accuracy parameters in the assessment of executive function impairments in FMS and, therefore, facilitate the personalization of cognitive function therapies. In particular, compared with controls, FMS patients showed greater intraindividual RT variability along the task (indexed by the ex-Gaussian parameter tau) and a heightened decrease in

the Go/No-Go hit rate after the change of the task rule (i.e., No-Go stimuli response). No group differences were observed regarding the false alarm rate. Results suggested deficient cognitive flexibility (decline in hit rate after the task change) but intact inhibitory response (no false alarm differences) in FMS. Moreover, increased tau in FMS indicated greater fluctuations in executive control and more frequent temporary lapses of attention.

The second study [11] assessed the negative impact of FMS-associated symptoms on the functional capacity of the patients. The FMS functional capacity was measured by the Fibromyalgia Impact Questionnaire (FIQ). The FIQ scores were positively associated with the majority of patients "symptoms (i.e., pain, fatigue, insomnia, depression, and trait anxiety). Among these symptoms, depression, fatigue, and pain catastrophizing (in this order) were those with more predictable power of FMS functional capacity. Furthermore, the most relevant factors affecting the association between pain and FMS functional capacity were pain catastrophizing and depression. Both, pain catastrophizing and depression were key factors mediating the association between clinical pain (total and intensity) and FMS functional capacity. The authors discussed the relevance of targeting depression and pain catastrophizing as treatment goals to reduce the impact of pain in FMS patients" daily function. The third study [10] demonstrated the relevant impact of social support on the cognitive performance of FMS patients. All dimensions of the Social Support Behaviours Scale (i.e., emotional support, practical assistance, socializing, financial assistance, advice/guidance, family support, and friends support) exhibited a positive impact on verbal memory, organization and planning abilities, strategic planning, self-regulation, processing speed, attention, and cognitive flexibility of FMS patients. Social support dimensions not only positively impact the number of correct responses and processing speed of neuropsychological tests but also the number of errors.

The fourth study [14], explored descriptively the association between self-efficacy and headache impact, anxiety, and physical activity levels in patients with CTTH; a chronic pain pathology and the most prevalent primary headache disorder worldwide [16, 17]. In this study [14] physical activity levels showed positive moderate correlations with self-efficacy in the domain of physical function. Linear regression models determined that self-efficacy and anxiety sensitivity showed a significant association with the headache impact and the anxiety sensitivity index. In addition, no associations were reported between pain intensity, duration, or frequency and psychosocial factors or headache impact. This study showed a great disease's negative impact on daily tasks and physical activity in CTTH patients. The last factors were influenced by anxiety and self-efficacy.

To conclude, the future of chronic pain prevention, diagnosis, and treatment implies overcoming some relevant concerns and considering some recommendations, such as: (1) the screening for cognitive deficits as a part of the routine diagnostic of FMS, (2) the design of psychoeducation and intervention programs directed not only to FMS patients but also relatives, healthcare workers, and the general population, (3) the use of indices of RT variability, in particular those derived from the ex-Gaussian function, as a complement to assess cognitive function impairments in FMS patients, and (4) the relevance of targeting factors, such as the depression and pain catastrophizing in FMS patients' intervention, and physical activity and self-efficacy in the CTTH patients' intervention; in both conditions with the clinical goal of reducing the disease's impact. The special issue findings highlight the benefits that would entail the creation of personalized evaluation and treatment plans—embracing all the reported factors—in chronic pain patients [18, 19].

Conflicts of Interest

The author(s) declare(s) that they have no conflicts of interest.

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Research Article

Acceptance Factors and Psychological Investigation of Clinical Trials in Cancer Patients

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Aim. To understand the degree of oncology patients' awareness of drug clinical trials and oncology patients' willingness to participate in drug clinical trials and the factors influencing them. *Methods*. The differences in the relevant variables of patients' willingness to accept clinical trials were analyzed, and a descriptive analysis was done for the measurement data (mean and standard deviation). Pearson's correlation coefficient analysis was used to examine the correlation between willingness and the demographic variables. Stepwise regression analysis was used to explore the influencing factors of patients' willingness to accept clinical trials. *Results*. There were no statistical differences in age, gender, education level, marital status, place of residence, monthly income, medical payment method, and treatment time ($P > 0.05$). Patients' willingness to accept drug clinical trials differed in their cognitive degree of clinical drug trials ($P = 0.002$). Patients' willingness to accept drug clinical trials differed in their experience in clinical trials ($P < 0.001$). The correlation difference was statistically significant. The willingness to accept drug clinical trials was negatively correlated with treatment time ($R = -0.16$, $P < 0.05$) and positively correlated with awareness of clinical trials and whether they had been subjects ($R = 0.16$ and 0.43, $P < 0.05$). Multiple regression analysis showed that patients' willingness was directly influenced by age, treatment time, and whether they had been subjects ($F = 21.315$, $P < 0.001$). *Conclusion*. Age, treatment time, and whether they had been subjects were the direct influencing factors of patients' willingness. This study pointed out that hospitals should do a good job in the publicity of clinical trials of new drugs, expand publicity channels, increase publicity efforts, improve the awareness of clinical trials of the masses, and promote the enthusiasm of the masses to participate in clinical trials of drugs.

1. Introduction

In the 21st century, cancer has become the main killer that threatens human health and longevity. According to the latest global cancer statistics report published by the International Agency for Research on Cancer (IARC) in the Journal of Clinician Cancer in 2021, the estimated number of new cancer cases in the world in 2020 is 19 292 789. The age-standardized incidence rate by world standard population (ASIRW) was 2,010 per million, which was significantly higher than that in 2018 (1,979 per million) [1]. The trial of new cancer drugs is the key to the clinical application of new drugs, and it also provides opportunities and possibilities for cancer patients to improve their quality of life and prolong their lifespan.

1.1. Current Status of Cancer. According to statistics from the World Health Organization in 2019, cancer is currently

the first or second leading cause of death in 112 countries [2]. Cancer not only afflicts patients physically but also ravages their mental health. Zabora et al. investigated the psychological status of 4,496 cancer patients and found that the proportion of patients with depression and anxiety was as high as 35.1% [3]. The worse the prognosis and the heavier the burden of the disease, the higher the degree of depression and anxiety. On the other hand, cancer also brings a heavy burden to the society and economy. As far as China is concerned, China has a population of 1.4 billion. Even a slight increase in the incidence and mortality of a certain type of cancer will affect the life expectancy of a sufficient number of people and consume a large number of social medical resources [4]. Therefore, in this fierce war between all mankind and cancer, scientists must race against time to research therapeutic drugs and seek the well-being of human beings for a healthy life.

1.2. Comparison of Current Situation of Drug Clinical Trials at Home and Abroad. The research and development of new drugs is not easy. As a crucial step from laboratory research to clinical application, drug clinical trials naturally play a pivotal role. China once hindered drug innovation due to a long drug review process and strict clinical trial application policies [5]. In order to encourage drug innovation, in 2015, the State Council of the People's Republic of China issued a landmark policy—"Opinions on Reforming the Approval System for Drugs and Medical Devices" [6], which accelerated the new process of domestic anticancer drug research and development. As of April 2020, there were a total of 1,974 drug clinical trial institutions recognized by the State Drug Administration, including 888 antitumor drug clinical trial institutions [7]. However, the National Cancer Institute's Clinical Trials Collaborative Program includes 3,100 institutions and 14,000 investigators [8]. Based on the differences in the population base and national conditions of cancer between China and the United States, China's current drug clinical trial research and development is still far from meeting the needs of China's drug research and development. Recruiting a sufficient number of subjects for clinical data research and confirming the efficacy and safety of new drugs are the key to successful clinical trials of new drugs. However, in China, patients' cognition and participation in clinical trials are not high. Zhang investigated the acceptance of clinical trials in 678 cancer patients, and only 42.1% of patients expressed willingness to participate in clinical trials [9], which is much lower than that of foreign patients whose results are 50%-80% [10, 11]. In a comparative survey of urban and rural patients' attitudes toward clinical research in the United States and China, it was found that compared with Chinese patients, American patients may be less concerned about participating in research [12]. In order to increase the participation of domestic patients in clinical trials and accelerate the process of new drug research and development, we need to understand the willingness and motivation to participate in clinical trials of new drugs.

1.3. Factors Related to the Willingness of Patients to Participate in Clinical Trials. We noted that in the study by Cao et al. [13], people who know about drug clinical trials were more inclined to participate in the trial. Age, gender, financial income, and the level of concern of health care professionals were found to be relevant factors influencing oncology patients' participation in clinical trials in the study by Zhang [9], and the study by Huang et al. and Lang et al. showed that physicians' concern was also an important factor influencing patients' choices [14, 15]. In 2016, Igwe et al. used the Attitudes on Randomized Trials Questionnaire to study the attitudes and willingness of American patients to participate in clinical trials [16] and concluded that psychological stress is not an important factor affecting patients' participation in clinical trials. However, considering the differences in public cognition between China and the United States, we designed a questionnaire and added new variables that might affect the willingness of patients to accept clinical trials on the basis of previous studies to carry out investigations and studies.

Based on the research literature and findings of previous researchers, we propose the following hypotheses:

Hypothesis 1. There are demographic differences in patients' willingness to participate in drug clinical trials.

Hypothesis 2. There is a correlation between patients' willingness to participate in drug clinical trials and their experience in clinical trials.

Hypothesis 3. Patients' willingness to participate in drug clinical trials is related to their mental health factors.

From June to December 2021, this study conducted a survey on the willingness and psychological factors of cancer patients to accept clinical trials in the Department of Oncology, the First Affiliated Hospital of Anhui Medical University, and collected a total of 211 survey results from oncology patients.

2. Method

2.1. Data Collection. The First Affiliated Hospital of Anhui Medical University is located in Hefei, the capital city of Anhui Province, with a superior geographical position, and its hospital has been shortlisted in the list of China's top 100 hospitals for many consecutive years and ranks first in Anhui Province, with strong comprehensive strength. In addition, the Department of Oncology, as a key department of the First Affiliated Hospital of Anhui Medical University, receives and treats cancer patients from all over the province, with a rich sample size. Therefore, the Department of Oncology of the First Affiliated Hospital of Anhui Medical University is a very suitable place for this questionnaire survey.

A total of 220 questionnaires were distributed, and 211 were recovered, with an effective rate of 95.9%. Of the valid responses, 109 were from men, and 102 were from women. There were 4 cases aged 30 years and younger, 58 cases aged 31 to 50 years old, 106 cases aged 51 to 70 years old, and 43 cases over 70 years old. Other demographic characteristics are detailed in Table 1.

Table 1: Demographic characteristic variables and sample distribution.

Variables	Total ($N = 211$)	Likely ($N = 73$)	Not likely ($N = 54$)	Undecided ($N = 84$)	χ^2	P
Age					5.343	0.254
≤50	62 (29.4%)	22 (30.1%)	20 (37.1%)	20 (23.8%)		
51-70	106 (50.2%)	34 (46.6%)	28 (51.9%)	44 (52.4%)		
>70	43 (20.4%)	17 (23.3%)	6 (11.1%)	20 (23.8%)		
Gender					2.494	0.287
Male	109 (51.7%)	41 (56.2%)	23 (42.6%)	45 (53.6%)		
Female	102 (48.3%)	32 (43.8%)	31 (57.4%)	39 (46.4%)		
Education					5.827	0.437
Uneducated	61 (28.9%)	18 (24.7%)	12 (22.2%)	31 (36.9%)		
Junior high school and below	114 (54.0%)	40 (54.8%)	34 (63.0%)	40 (47.6%)		
High school and junior college	30 (14.2%)	13 (17.8%)	7 (13.0%)	10 (11.9%)		
Undergraduate and above	6 (2.8%)	2 (2.7%)	1 (1.9%)	3 (3.6%)		
Marital status					2.640	0.640
Married	188 (89.1%)	68 (93.2%)	48 (88.9%)	72 (85.7%)		
Divorced & Unmarried	10 (4.7%)	2 (2.8%)	2 (3.7%)	6 (7.2%)		
Widowed	13 (6.2%)	3 (4.1%)	4 (7.4%)	6 (7.1%)		
Residence					2.786	0.594
Urban	40 (19.0%)	10 (13.7%)	13 (24.1%)	17 (20.2%)		
Town	49 (23.2%)	19 (26.0%)	10 (18.5%)	20 (23.8%)		
Countryside	122 (57.8%)	44 (60.3%)	31 (57.4%)	47 (56.0%)		
Monthly income					3.956	0.413
<1000	89 (42.2%)	27 (37.0%)	27 (50.0%)	35 (41.7%)		
1000-5000	107 (50.7%)	38 (52.1%)	24 (44.4%)	45 (53.6%)		
>5000	15 (6.2%)	8 (10.9%)	3 (5.6%)	4 (4.8%)		
Medical payment					0.352	0.838
Medical insurance	200 (94.8%)	69 (94.5%)	52 (96.3%)	79 (94.0%)		
At own expense	11 (5.2%)	4 (5.5%)	2 (3.7%)	5 (6.0%)		
Treatment time					12.501	0.052
<3 months	46(21.8%)	8(11.0%)	15(27.8%)	23 (27.4%)		
Three months to one year	79 (37.4%)	26 (35.6%)	24 (44.4%)	29 (34.5%)		
One to three years	57 (27.0%)	26 (35.6%)	9 (16.7%)	22 (26.2%)		
>3 years	29 (13.7%)	13 (17.8%)	6 (11.1%)	10 (11.9%)		
Awareness					12.339	0.002
Yes	64 (30.3%)	33 (45.2%)	10 (18.5%)	21 (25.0%)		
No	147 (68.7%)	40 (54.8%)	44 (81.5%)	63 (75.0%)		
Subject					53.321	<0.001
Yes	30 (14.2%)	28 (38.4%)	0 (0.0%)	2 (2.4%)		
No	181 (85.8%)	45 (61.6%)	54 (100.0%)	82 (97.6%)		

Notes: education, level of education received; marriage, marital status; residence, place of residence; medical payment, medical payment method; treatment time, the duration of the patient's treatment; awareness, patient's awareness of the clinical trial; subjects, patient's historical experience in clinical trials (the results were obtained through appropriate statistical processing herein).

The survey was conducted by clinical medical undergraduates trained by medical professionals. Before the survey, the reference answer points were stipulated, the scoring criteria were unified, and the possible answers were predicted. If the patient has doubts, the investigator could help him explain the meaning of the question but must not inspire, induce, or add subjective will, and the answer truly reflected the situation of the respondent; the questionnaire was withdrawn on the spot after answering the questionnaire.

Due to the large number of respondents, the authors of this study signed a document promising to obtain the oral informed consent of all respondents to the survey. This was approved by the Ethics Committee of Anhui Medical University.

2.2. Research Tools. The self-compiled questionnaire was divided into three parts; the first part was to collect demographic data of the respondents, mainly including the

patient's gender, age, educational level, marital status, place of residence, monthly income, medical payment methods, medical information, satisfaction with treatment, and treatment time.

The second part was to investigate the patient's awareness of clinical trials, willingness, and the reasons for their participation or rejection. A total of 7 small problems in 3 aspects were designed, and some problem options were also assigned to deal with. These are as follows: The first survey was to investigate whether patients were aware of the trial and related knowledge (yes (=1) and no (=2)), and if patients chose yes, they were further asked how they learned about it: doctor, relative or friend, or media such as books or the internet. The second survey investigated whether respondents had participated in drug clinical trials as subjects (yes (=1) and no (=2)). The third item asked the respondents about their willingness after the researchers informed the basic operation of the clinical trial in detail (willing to participate (=1), undecided (=2), and unwilling to participate (=3)). We further asked why they had joined or refused, and who they were turning to for help. The results of the analysis are shown below.

The third part was to use the self-rating anxiety and depression scale to understand the mental health of patients. The self-rating anxiety scale is a tool for measuring anxiety developed by Zung in 1971 [17]. The test is a short-distance self-assessment scale, easy to operate, time-consuming, and not affected by factors such as age, gender, and economic status; the scope of application is quite wide, and it is also one of the common tools used in psychiatric clinics. Tian et al. used the self-rating anxiety scale for clinical verification, which proved that it has good reliability and validity and can be used for clinical application (Cronbach's coefficient is 0.897, $P < 0.001$) [18]. Therefore, SAS was used in this study as a tool to assess the degree of anxiety in cancer patients. The self-rating depression scale is a tool developed by Zung in 1965 to measure depression [19, 20]. Li et al. used the self-rating depression scale for clinical validation, demonstrating that it has good reliability and validity and can be used for clinical application (Cronbach's coefficient 0.92, $P < 0.001$) [21].

2.3. Statistical Methods. Two members of the research team reviewed all the questionnaire data and used EpiData 3.1 to enter the data. Descriptive analysis of the measured data was performed using SPSS 19.0 [22]. This article conducted a difference analysis of relevant variables related to patients' willingness to accept clinical trials; a descriptive analysis was done for the measurement data (mean and standard deviation). Pearson's correlation coefficient analysis was used to examine the correlation between willingness and the demographic variables. Stepwise regression analysis was used to explore the influencing factors of patients' willingness to accept clinical trials. When $P < 0.05$, it was considered statistically significant.

3. Results

3.1. Differences in General Demographic Information. Based on the preliminary statistics of demographic variables and cognitive status, the results of comparing differences are shown in Table 1. 54.0% of the respondents had a junior high school education or less, 89.1% of the respondents were married, 57.8% lived in rural areas, and 42.2% had a monthly income of less than 1,000 yuan. Those between 1,000 and 5,000 yuan accounted for 50.7%, and nearly all (94.8%) of the patients were covered by medical insurance. The stratified proportion of treatment time was evenly distributed, accounting for 21.8% less than three months, 37.4% from three months to one year, 27.0% from one year to three years, and 13.7% for more than three years. 70.2% of the respondents did not pay attention to medical information. Of the 211 patients, based on their completed SAS and SDS scale scores, 112 had no anxiety, 61 had mild anxiety, 33 had moderate anxiety, and 5 had severe anxiety. 120 had no depression, 73 had mild depression, 10 had moderate depression, and 8 had severe depression; details are shown in Table 1.

We compared the basic information of patients in the three groups who chose to participate in the clinical trial with those who were unwilling to participate and those who could not make up their minds. The results showed that there was no statistical difference in age, gender, education level, marital status, place of residence, monthly income, medical payment method, and treatment time ($P > 0.05$), which denied Hypothesis 1; There were differences in patients' willingness to accept drug clinical trials with respect to their awareness of clinical drug trials ($P = 0.002$) and differences in patients' willingness to accept drug clinical trials with respect to their historical experience in clinical trials ($P < 0.001$), and the relevant differences were statistically significant, which laid the foundation for the study of factors influencing patients' willingness to accept drug clinical trials.

Based on sample data of patients' willingness, SAS, SDS, and demographic variables, we create a binary variable correlation matrix (Table 2).

It can be concluded from Table 2 that the patients' willingness to accept drug clinical trials was negatively correlated with treatment time and positively correlated with their awareness of clinical trials and whether they had been subjects, which verified Hypothesis 2. There was no statistically significant correlation between patient' s willingness to accept drug clinical trials and SAS and SDS scores, which initially denied Hypothesis 3. Treatment time was negatively correlated with patients' age. Awareness of clinical trials was negatively correlated with education level and treatment time; whether they had been subjects was negatively correlated with payment method and positively correlated with awareness. SAS score was positively correlated with age. SDS score was positively correlated with the SAS score and negatively correlated with gender, and marital status was positively correlated with age. Place of residence was negatively correlated with education level, monthly income was positively correlated with education level, and monthly income was negatively correlated with place of residence. The ways to know the knowledge of clinical trials were negatively correlated with the place of residence and positively correlated with whether they had been subjects.

According to the analysis results in Table 2, variables directly and indirectly related to patients' willingness were

Table 2: Correlation matrix of willingness and demographics and SAS and SDS scoring variables.

	Mean	SD	1	2	3	4	5	6	7	8	9	10	11	12	13	14
(1) Age	58.60	12.95	1													
(2) Gender	1.48	0.50	**-0.33**	1												
(3) Education	1.91	0.73	**-0.18**	-0.11	1											
(4) Marriage	2.10	0.53	**0.14**	-0.07	-0.06	1										
(5) Residence	2.39	0.79	-0.03	0.11	**-0.39**	-0.01	1									
(6) Monthly income	1.66	0.64	-0.08	-0.12	**0.42**	0.02	**-0.27**	1								
(7) Payment method	1.05	0.22	-0.02	-0.06	-0.06	0.07	0.10	-0.01	1							
(8) Treatment time	2.33	0.97	**-0.14**	0.04	0.10	-0.05	0.01	0.00	0.01	1						
(9) Awareness	1.71	0.47	0.05	-0.02	**-0.18**	0.01	0.07	-0.05	-0.13	**-0.18**	1					
(10) Subject	1.86	0.35	-0.05	0.07	0.06	0.05	-0.13	0.04	**-0.15**	-0.13	**0.53**	1				
(11) Ways	1.58	0.81	0.05	-0.23	0.24	-0.09	**-0.35**	0.06	-0.03	-0.16	0.07	**0.46**	1			
(12) SAS	45.33	13.01	**0.15**	0.07	-0.07	-0.09	0.02	0.01	0.00	-0.06	**0.16**	0.05	0.17	1		
(13) SDS	50.69	11.80	0.04	**0.19**	-0.07	-0.06	0.04	-0.08	-0.04	-0.02	**0.26**	**0.25**	0.20	**0.62**	1	
(14) Willingness	2.05	0.86	0.00	0.02	-0.10	0.03	-0.06	-0.09	0.01	**-0.16**	**0.16**	**0.43**	0.24	0.01	0.10	1

Note: The correlations marked in bold in the table are statistically significant. Ways are patients' access to clinical trials. The connotation of other variables is shown in Table 1.

selected for stepwise multiple regression analysis [23, 24], and the results are shown in Table 3.

The results of multiple regression analysis showed that age, treatment time, and whether they had been subjects were the direct influencing factors of patients' willingness, while the remaining related variables may be the indirect influencing factors.

4. Discussion

There were no statistical differences in patients' willingness to accept drug clinical trials with respect to age, gender, education level, marital status, place of residence, monthly income, and medical payment method as well as treatment time. The possible reasons for this were due to insufficient access to information on clinical trials, and as shown by the information of 211 oncology patients in this survey, only 64 patients were aware of clinical trial programs and related knowledge. A survey of 64 patients found that 40 (62.5%) were referred by their doctors, 11 (5.2%) by friends and relatives, and 13 (6.2%) through media channels such as books and the Internet. The second reason may be patients' lack of trust in doctors. For example, according to the survey results, the top three reasons for unwillingness to participate in clinical trials were fear of adverse reactions of new drugs (61.9%), fear of delaying the routine treatment (44.0%), and unwillingness to be treated as experimental subjects (32.1%). This was consistent with Sun et al.'s findings that doctor-patient trust is low [22]. This was also the reason why patients' willingness to accept drug clinical trials had significant differences in their cognitive degree of clinical drug trials. Of course, other reasons cannot be ruled out. The reasons for the differences in patients' willingness to accept drug clinical trials with respect to their historical experience in clinical trials were that historical experience increased patients' knowledge of clinical trials, their experience of free treatment in clinical trials, or their trust in doctors due to their better experience in previous clinical trials, which was consistent with the results of this study that "the top three reasons for willingness to participate was to try new treatment drugs (68.5%), trust in doctors and team (65.8%) and to get free treatment (47.9%)".

Patients' willingness to accept clinical trials of drugs was negatively correlated with treatment time and positively correlated with awareness of clinical trials and whether they had been subjects. One of the possible reasons for this is that patients who have been cured for too long have lost confidence in their own health and trust in their doctors, leading to a decrease in willingness to accept clinical trials. Patients with higher cognitive level and more clinical trial historical experience had a higher understanding of patient drug clinical trials, so it is understandable that they had a higher level of support for clinical trials. This further reflects the low awareness rate and lack of publicity of clinical trials in China, which is consistent with the results of this survey. Out of 211 cancer patients surveyed, only 64 (30.3 percent) said they had heard of and understood the concept of clinical trials, much lower than the 76.5% of Korean cancer patients [18]. At the same time, we also conducted a survey on patients who knew clinical trial knowledge and found that 62.5% of them obtained information from doctors' introduction, while only 6.2% of them learned information from books, the Internet, and other media. However, the situation in South Korea was different from ours [21]. 37.5% of patients in South Korea collected information from doctors or nurses, and 34.3% got information from mass media including TV, newspapers, and the Internet. It can be seen that the lack of appeal and publicity of the domestic medical media for clinical trials fails to let the general public get relevant information and makes it difficult to recruit volunteers for clinical trials in China. If only relying on doctors and other staff to spread the trial information, it is quite difficult; therefore, both medical websites and medical newspapers and magazines should make efforts to promote drug clinical

Table 3: Prediction of willingness.

Predictor	Step 1		Step 2		Step 3	
	B/Coef	SE	B/Coef	SE	B/Coef	SE
Willingness						
Age	-.002	.006	-.008*	.004	-.008*	.004
Gender	.029	.165				
Education	.038	.131	-.084	.067		
Marriage	-.010	.149				
Residence	-.024	.108				
Monthly income	-.152	.124				
Payment method	.126	.277	.089	.214		
Treatment time	-.255**	.077	-.134**	.050	-.133**	.049
Awareness	-.205	.323	-.128	.123		
Subject	1.085***	.184	1.030***	.162	.921***	.136
Ways	.080	.106				
SAS	-.005	.007				
SDS	-.002	.009				
Adjust R^2	.491		.223		.225	
F	5.676***		11.042***		21.315***	

Notes: *, **, and *** indicate $P < 0.05$, $P < 0.01$, and $P < 0.001$.

trial projects. If only everyone knows, anyone will participate. The second reason is that the more knowledgeable one is about clinical trials, the more likely one is to choose to participate in a trial study. Those who had done the trial were more willing to participate in the trial than those who had not done it, which may be related to the fact that those who had experienced the trial process were more knowledgeable about it and its operation and trusted drug clinical trials more. This is consistent with the findings of Huang et al. and Lang et al. [14, 15]. Therefore, it is not only the responsibility of medical staff but also the obligation of the whole society to popularize the relevant knowledge of drug clinical trials for patients. Only by promoting the popularization of knowledge related to clinical trials can we improve the enthusiasm of patients to participate in the development of new drugs in China and benefit more cancer patients. However, there is a lack of attention to clinical trial knowledge and volunteer recruitment in China. Just relying on a small board in front of the hospital or a small corner of the publicity board is not enough to achieve the purpose of publicity. Although recruitment information in the Internet era will be published on the official website of the hospital or commercial recruitment website, this information is fragmentary, and the website itself lacks attention. Therefore, it is imperative to establish authoritative and popular clinical trial recruitment websites.

The possible reason for the negative correlation between treatment time and age of patients is that the older the patients are, the weaker their physical function is, the more difficult it is to recover, and the longer the treatment time is. Awareness of clinical trials was negatively correlated with education level and treatment time, which may be because the higher the education level, the stronger the ability to accept new knowledge, and the more likely to worry. The longer the treatment time, the greater the family economic expenditure, the weaker their own health confidence, and the worse the trust between doctors and patients, so there was a negative correlation. This may also be the reason why subjects' experience was negatively correlated with payment method and positively correlated with awareness of clinical trials. The results of the current survey show the reason for the low degree of willingness of patients to participate. The results of this survey showed that only 34.6% of the patients were willing to participate in clinical trials, which is a relatively low willingness to participate compared to both domestic (40.9%-93.3%) and foreign (56.7%-88.0%) studies [13–15, 25–28]. The reasons for this may be as follows: First, in this study, unlike the previous scale design, we added the option of "uncertainty" to the choice of whether the patients were willing to participate in the clinical trial. Secondly, the respondents were not well informed about the clinical trial, and although the author has explained it in detail, the patients could not accept the new and unfamiliar thing in a short period of time. Through further analysis, it was found that 68.5% of the patients wanted to try new drugs, and 47.9% of the patients wanted to get free treatment, which were the main driving forces for the patients to participate in the trial, while only 16.4% of the patients wanted to make contributions to the medical cause. Different from the Chinese who take self-interest as the motivation for participation, altruism and promoting scientific development are more important motivations in American patients [12]. The main reasons for Chinese patients' unwillingness to participate were fear of adverse drug reactions (61.9%) and fear of the impact of interruption of routine treatment (44.0%). Chinese patients pay more attention to safety, while American patients have greater concerns about the privacy of participating in clinical

research, which is also the main reason for their reluctance to participate in clinical research [12]. In the question "Who would you turn to if you couldn't make up your mind?" 68.5% of the patients chose to ask the doctor's opinion, which was consistent with 65.8% of the patients who chose "trust to the doctor" as the reason for participating in the experiment. Therefore, physicians play an important role in promoting patient participation in clinical trials. Different from previous studies on factors affecting the willingness of patients to participate in clinical trials, we took the psychological status of patients into consideration, but the results showed that the mental health status of patients did not affect the willingness of patients to participate in clinical trials. This result was consistent with the results of Igwe et al.'s study in the United States [16]. Meanwhile, we found that patients with clinical trial experience had higher levels of depression, which may be worthy of further attention, and lest depression affect patients' decision of clinical trial intention.

The results of regression analysis showed that age, treatment time, and whether they had been subjects were the direct influencing factors of patients' willingness. The possible reasons for this are that age is directly related to patients' physical function, which determines patients' recovery and healing time, which in turn affects patients' level of trust in physicians and directly influences patients' willingness to conduct clinical trials; patients' clinical trial experience determines patients' sense of clinical trial experience and directly determines patients' decision to conduct clinical trials again.

5. Conclusion

The results of this study indicate that age, treatment time, and whether they had been subjects are the direct influencing factors of willingness. Domestic drug clinical trial centers should reasonably analyze the age characteristics of patients, timely carry out the knowledge propaganda of new drug clinical trials for patients, play the value of advocacy of patients with clinical trial historical experience, address the low degree of understanding of clinical trials and the limitation of knowledge channels for tumor patients, actively do a good job of propaganda, expand propaganda channels, and increase propaganda efforts, which not only help to improve the public's knowledge of clinical trials but also promote the enthusiasm of the public to participate in clinical trials. It will not only promote the enthusiasm of people to participate in drug clinical trials but also accelerate the development of tumor-related drug therapy in China.

6. Limitations

There are few survey samples. Compared with more than 500 samples investigated in other studies, this study is slightly insufficient. According to the criteria proposed by Comrey, the size of 100 samples is too small, while 200 are qualified, 300 are excellent, 500 are good, and 1000 are very good [29, 30]. For the general analysis of the following 40 project factors, 200 samples are sufficient in most cases. The investigation unit is limited to the oncology department of the First Affiliated Hospital of Anhui Medical University, which lacks national representation. In the next step, we can expand the scope of the research area and the number of research samples. Due to the limitation of the actual survey environment, this study adopts convenient sampling rather than random sampling. Besides, we do not take into consideration other factors (e.g., stage and severity of disease and personality traits) that may influence participants' choice to join clinical trials.

Data Availability

The data used to support the findings of this study are included in the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

JJS designed this study (substantial contributions to the conception). JYF, CCZ, NNJ, WMZ, JJG, and YYH collected the data. JYF, CCZ, and JJS extracted and analyzed the data and interpreted the data for the work. JJS, JQH, and LPZ provided guidance for statistical analysis and provided financial support. They agreed to be accountable for all aspects of the work in ensuring that questions are related to the accuracy. JYF and JJS wrote the manuscript. JJS, JYF, CCZ, and LPZ reviewed the manuscript. JYF, CCZ, and JJS contributed equally to this work.

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Research Article

Exercise on Striatal Dopamine Level and Anxiety-Like Behavior in Male Rats after 2-VO Cerebral Ischemia

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The purpose of this study was to discuss the effect of voluntary wheel running on striatal dopamine levels and anxiety-like behavior in rats with global cerebral ischemia. The male Sprague-Dawley rats were signed on in this study and randomly divided into following 4 groups: Control group (C group), Sham group (S group), ischemia group (I group), and 3 weeks physical exercise before ischemia group (3RI group). The rats in the 3RI group were placed in a voluntary running wheel for three weeks to exercise. Then, the rats in I and 3RI groups received bilateral carotid artery ligation (2-VO) operation. The C and S group did not perform voluntary running exercise and the bilateral common carotid arteries of S group were exposed without ligation. In vivo microdialysis was used in conjunction with high performance liquid chromatography (HPLC) and electrochemical detection to ascertain the level of dopamine in the striatum. Elevated plus maze (EPM) and open field (OF) were used to test anxiety status at 24 hours and 7days after 2-VO cerebral ischemia. Meanwhile, gait and motor coordination evaluations were carried out to eliminate the influence of non-specific motor problems. The results indicated that cerebral ischemia instigate the increase of striatal dopamine in I group rats during acute cerebral ischemia. A 3-week voluntary wheel running significantly enhances the striatal dopamine before ischemia and obstructs a further increase of dopamine during acute cerebral ischemia in 3RI group rats. At 24 hours after ischemia, striatal dopamine returned to pre-ischemic levels in 3RI group. Striatal dopamine in I group were less than pre-ischemic levels at 7 days. Behavioral data indicated that 3-week voluntary wheel running promoted recovery of anxiety-like behavior and gait were not affected by 2-VO cerebral ischemia at 24 hours post-ischemia rats. Therefore, it can be concluded that 3-week physical exercise significantly increased the striatal dopamine and improved anxiety-like behavior by inhibiting the increase of dopamine during acute cerebral ischemia and suppressing the decrease of dopamine after 24 hours and 7 days cerebral ischemia.

1. Introduction

Cerebral ischemia is considered among one of the most fatal diseases, which exhibits attributes of higher morbidity, mortality, and disability [1, 2]. Global cerebral ischemia, which normally occurs after a cardiac arrest, can cause selective neuronal cell death, and, as a result, it causes disability and dementia [3, 4]. 2-VO vascular block (2-VO), an animal model made by permanently ligating the bilateral common carotid arteries in rats, can cause a chronic state of cerebral hypoperfusion after ligation, thus producing ischemic and hypoxic damage to brain tissue, which can better simulate human cerebrovascular disease and dementia in the acute ischemic and chronic hypoperfusion periods [5, 6]. At the same time, the 2-VO method produced a whole brain ischemia model in rats without apparent motor system damage, with high survival rate, good repeatability and stability, simple operation, less trauma to the animals, easy recovery, and easy to eliminate the influence of other factors on anxiety-like behavioral experiments in rats [7, 8]. Meanwhile, it has

been demonstrated that the functional symptoms of neural damage occur from several hours to days after cerebral ischemia [9]. Furthermore, it can also lead to cognitive and emotional deficits in patients or in experimental animals [10, 11].

Previous reports suggested that cerebral ischemia rats showed increased anxiety-like behavior, activity level, and habituation shortfall [12]. Dopamine levels in specific brain regions have been found to be positively correlated with increased anxiety-like behavior [13]. Several reports support this concept. For example, in vitro study it has been appeared that the slice in the nucleus accumbens of social isolation rearing rats after electrical stimulation resulted in lasting increased anxiety-like behavior, dopamine released, and dopamine transporter activity [9]. While selective dopamine depletion within the prefrontal cortex has been done by 6-hydroxydopamine injection, it could remarkably increase anxiety-like behavior in rats [14]. Dopamine is a well-known catecholaminergic neurotransmitter in the brain that plays an important role in memory processes and emotional aspects [15], particularly through the interconnection of the striatum and the prefrontal cortex [16]. The striatum is one of the most important nuclei of the basal ganglia; its function is vital for motor control, cognition, stimulus-response learning, action selection, and emotional reconciliation [17]. Furthermore, the striatum is known to be one of the core regions susceptible to ischemic insult [18]. Numerous studies have shown that cerebral ischemia can cause dopamine release in the striatum [19, 20]. In addition, in vivo imaging studies have been observed that striatal dopamine is a key player in anxiety disorders [21, 22]. Pharmacological research has shown that medicine therapy could alleviate symptoms of anxiety by decreasing excessive dopamine accumulation during the acute cerebral ischemia/reperfusion [14]. However, early efforts have been made to understand regulation of anxiety that are closely related to striatal dopamine synthesis capacity [9, 12]. Further studies have shown that moderate treadmill exercise before cerebral ischemia can prevent oxidative stress-prompted anxiety-like behavior in rats [23]. When compared to treadmill exercise, the advantage of voluntary exercise is that it is an active and spontaneous exercise that can significantly stimulate the autonomic activity of the rat and significantly increased the level of neurotrophic factor in rat brain and enhanced neuroplasticity [24]. Although it has been well documented that striatal dopamine released induced by ischemic brain injury has a closely related anxiety-like behavior, whether pre-ischemia wheel running has anxiolytic effects by regulating level of the dopamine in the striatum is currently unknown.

As a result, the purpose of this study was to investigate the effect of voluntary wheel running on striatal dopamine levels and anxiety-like behavior in rats following cerebral ischemia.

2. Materials and Methods

2.1. Animals and Training. Male Sprague-Dawley rats (3 months old, weighting 300 ± 10 g) were procured from Peking University's Experimental Animal Center and randomly divided into following 4 groups: Control group (C group), sham group (S group), ischemia group (I group), and 3 weeks voluntary wheel running before ischemia group (3RI group). The rats in the 3RI groups were placed in a voluntary running wheel (wheel circumference, 100 cm, Harvard Apparatus) for three weeks to exercise. The groups C, S, and I were also assigned to the reorganized voluntary running wheel (running wheel were fixed). The running wheel was equipped with a magnetic counter to track wheel revolutions [25]. The distance was calculated by multiplying the number of wheel revolutions by the circumference of the wheel. In accordance with previous research, the rats primarily exercised at night from 19 : 00 to 7 : 00, covering approximately 5000 meters per week [26]. According to our experiments, the distance of animals exercised autonomously were about 1250 m in the first three days, and the average exercise distance were about 400 m per day. These rats that exercise distance less than 200 m per day were excluded. Throughout the experiment, there were 3 animals that were not able to keep up with the mentioned conditions. It was decided not to collect the data of these three rats, and it was chosen to select new rats to replace them. Then, the rats in 3RI and I group were received bilateral carotid artery ligation (2-VO) operation. In the S group, only the bilateral common carotid arteries were exposed without ligation. All rats were housed in 12-hour light/dark cycles with plenty of food and water. All procedures and protocols were approved by the institutional animal ethical committee of the Capital University of Physical Education and Sports (2020A53). The experiment was carried out in accordance with approved guidelines of Good Treatment of Laboratory Animals issued by the Ministry of Science and Technology of China.

2.2. Surgical Procedure. The stereotaxic surgery method was based on previous research [27]. The rats were placed in a stereotaxic frame with the incisor-bar set at 3.3 mm below the interaural line for the flat skull position after being anesthetized with 8% emulsified isoflurane (0.55 ml/kg, intraperitoneal injection). According to standard stereotaxic procedures, a guide cannula was lowered into the right striatum (anteroposterior = 0 mm, mediolateral = 3.0 mm, dorsoventral = 4 mm, relative to bregma) [28]. Three screws were inserted into the skull around the cannula and secured with dental acrylic.

The bilateral common carotid arteries (BCCAs) were ligated in the two-vessel occlusion (2-VO) ischemia models using the methods previously described [29, 30]. In brief, the rats were anesthetized intraperitoneally with 10% chloral hydrate (350 mg/kg i.p.), fixed supine, disinfected with anterior cervical debridement, incised along the middle of the neck, and the double common carotid arteries were isolated and double ligated with No.1 surgical wire. At the same time, the cervical sympathetic nerve and vagus nerve were avoided, and the rats' anal temperature was kept at 37 ± 0.5°C during the operation, as was spontaneous respiration.

2.3. In Vivo Microdialysis and High Performance Liquid Chromatography. In vivo microdialysis was carried out by

inserting a microdialysis probe (CMA/12, CMA/microdialysis AB, membrane length = 4 mm, Stockholm, Sweden) through the guide cannula and continuously perfusing with artificial cerebrospinal fluid (126 mM NaCl, 2.4 mM KCl, 1.1 mM $CaCl_2$, 0.85 mM $MgCl_2$, 27.5 mM $NaHCO_3$, 0.5 mM Na_2SO_4, 0.5 mM KH_2PO_4, pH = 7.0) at a flow rate of 2 L/min driven by a microinjection pump (CMA/100, CMA Microdialysis AB, Stockholm, Sweden).

After 90 minutes, samples were collected in a 0.2 ml vial, and microdialysis was performed in the striatum at a flow rate of 2 μL/min for a continuous 60 minutes. Samples were taken at two different times, one before and one after ligation. In addition, we used an animal awake activity device to collect 120 μL of striatal dopamine of rats 24 hours after cerebral ischemia. The samples were analyzed for DA content in an HPLC system equipped with an isocratic pump (Waters Corporation, Milford, MA, USA, Waters 515, flow 1 ml/min), an RP-18 column (Waters Corporation, Milford, MA, USA, Xterra, 5 μM particle size, 2.1 × 100 mm, Waters), and an amperometric detector (BAS Inc., West Lafayette, IN, USA, LC-4B, oxidation potential 0.5 V). The DA elutions were completed in all of these conditions in 4.5 minutes.

2.4. Behavioral Testing. The elevated plus maze (EPM) was used to analyze anxiety-like behavior by determining animals' emotional response to external stressful stimuli [31]. The EPM was made of black polypropylene and had two opposing open arms (25 × 8 cm), two opposing closed arms (25 × 8 × 20 cm), and a central platform (8 × 8 × 8 cm) shaped like a cross. The maze was 50 cm above the ground. Individual rats were placed in the center, their heads pointing toward one of the closed arms and given 5 minutes to explore the arena. All four paws entering an arm were defined as an open or closed arms entry. The open-field test (OF) was used to determine animals' spontaneous locomotor activity [32]. The OF test was conducted after EPM test. The interval between the two experiments was 1 hour. In standard room lighting conditions, the OF was performed in a 50 × 50 cm open field surrounded by 50 cm high walled Plexiglas chambers. Individual rats were placed in the center and given 5 minutes to explore the arena. Both experiments were tested at 24 hours and 7 days after cerebral ischemia.

To avoid external distractions, the behavioral tests were conducted in an isolated behavioral testing room within the animal facility. Animal behavior was observed by investigators via a video monitor in another room. Shanghai Mobile Datum Information Technology Co., Ltd. provided the apparatus and analysis software used in the behavioral tests. Rats were housed in the testing room for at least 1 hour before the experiments to facilitate adaptation to the experimental environment. The animals were uninformed about the test situation and were only used once [33]. Alike the other behavior test, the EPM and OF were cleaned with a solution of 75% ethyl alcohol after testing.

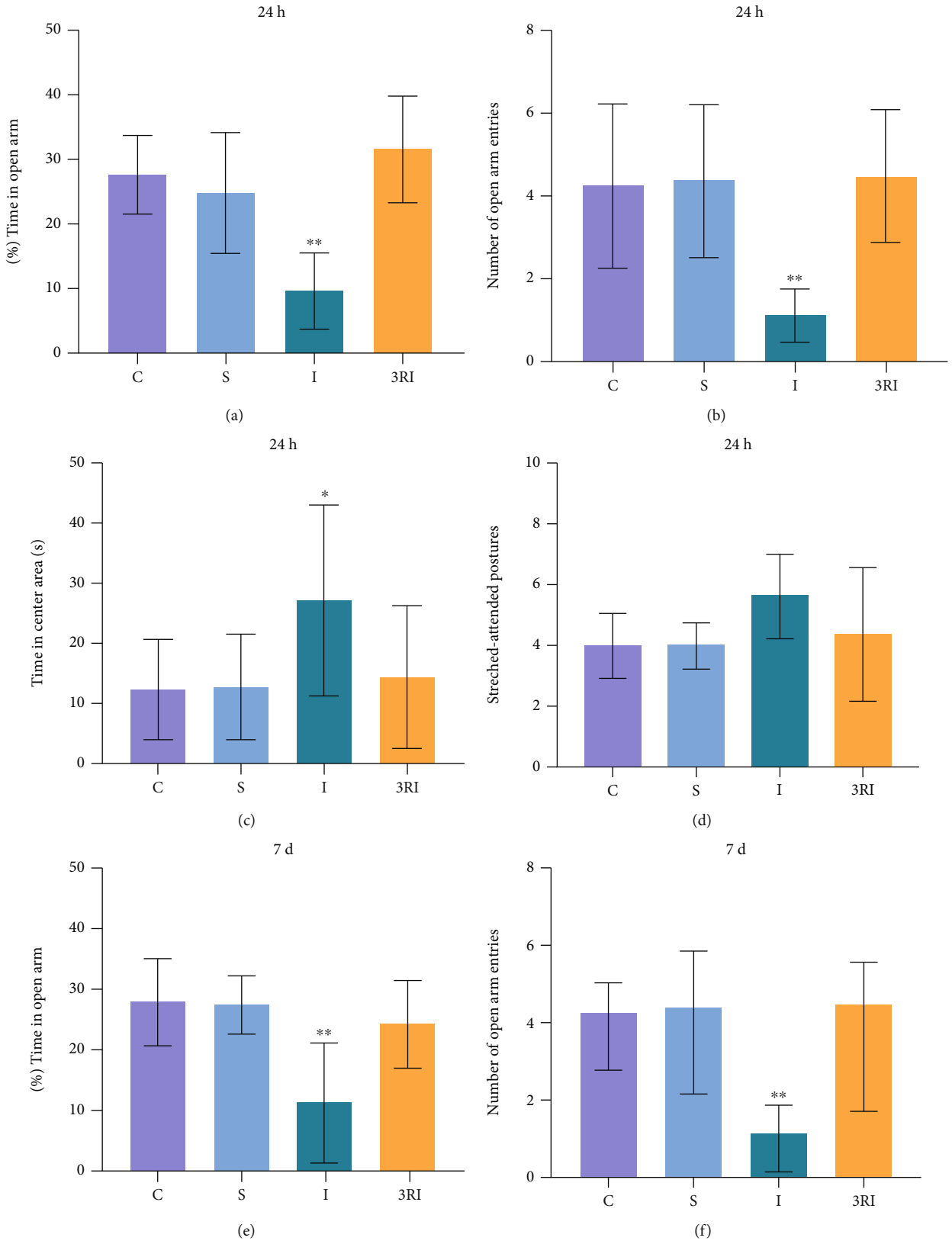
2.5. Gait Analysis in Rats. In order to eliminate the effect of changes in the locomotor ability of rats before and after cerebral ischemia on subsequent behavioral experiments, the present experiment was conducted to evaluate the locomotor ability of experimental rats using a previously reported method. The gait parameters were measured before and after the experiment by applying different color dyes to the front and hind paws of the rats when they were freely moving [34]. The gait angle of right foreleg (GARF), the vertical distance between the anterior and posterior step lines on both sides of the foreleg (track width of foreleg (TWF), the horizontal distance between the midpoint of the horizontal line of two consecutive steps of the right foreleg and the midpoint of the horizontal line of two consecutive steps of the hind limb (foot base of right foreleg, FBRF), and the horizontal distance of the line of the right foreleg (right foot base, RFB) were measured three times consecutively. The above parameters were statistically analyzed.

2.6. Statistical Analysis. Data were analyzed by SPSS25.0 (SPSS Inc., Chicago, IL, USA), and the results were expressed as means ± standard deviation (SD), and all data showed normal distribution. Repeated measures ANOVA was used to compare dopamine in different groups at various time points. Differences in the behavior and gait data were analyzed using one-way ANOVA, followed by the Bonferroni test for intergroup comparisons. A P value < 0.05 was considered statistically significant.

3. Results

3.1. Elevated plus Maze. Figure 1(a) shows that the percent time of open arms in each group after ischemia. The percent time in the 4 groups had significant difference ($F(3, 28) = 12.941$, $P = 0.000017$). Bonferroni multiple comparison post hoc test showed that the percent time of C, S and 3RI group was significantly longer when compared with I group ($P < 0.01$). There was no significant difference among C, S and 3RI group ($P > 0.05$). Figure 1(b) showed the entrance numbers of open arms in each group after ischemia. The entrance numbers in the 4 groups had significant difference ($F(3, 28) = 8.219$, $P = 0.000444$). Bonferroni multiple comparison post hoc test showed that the entrance numbers of C, S, and 3RI group were significantly greater when compared with I group ($P < 0.01$). There was no significant difference among C, S, and 3RI group ($P > 0.05$). Figure 1(c) showed that the time in center area of each group after ischemia. The time in center area in the 4 groups had significant difference ($F(3, 28) = 3.359$, $P = 0.033$). Bonferroni multiple comparison post hoc test showed that the entrance numbers of C, S, and 3RI group were significantly shorter when compared with I group ($P < 0.05$). There was no significant difference among C, S, and 3RI group ($P > 0.05$). Figure 1(d) shows that stretched-attended postures of each group after ischemia. The stretched-attended postures had no significant difference in the 4 groups ($F(3, 28) = 2.226$, $P = 0.107$). Although the stretched-attended postures of I group were increased, there were no significant difference when compared with C, S, and 3RI group ($P > 0.05$).

Figure 1(e) shows that the percent time of open arms in each group after ischemia. The percent time in the 4 groups had significant difference ($F(3, 28) = 9.157$, $P = 0.00022$).



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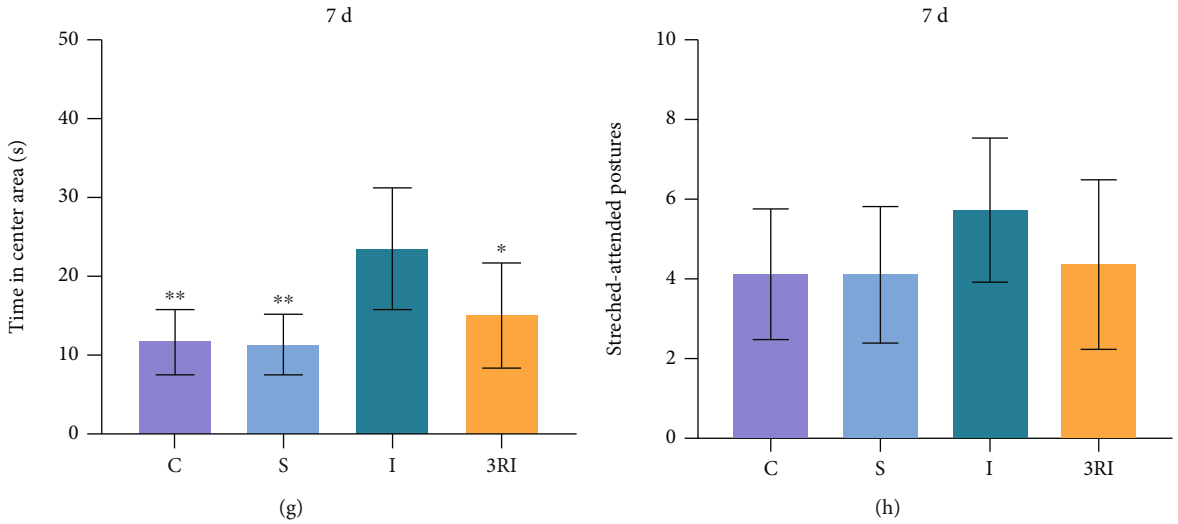


Figure 1: (a) The percent time of open arms in each group at 24 hours after ischemia. $^{**}P < 0.01$ compared with I group; (b) the entrance numbers of open arms in each group. $^{**}P < 0.01$ compared with I group; (c) the time in center area in each group. $^{*}P < 0.05$ compared with I group; (d) the stretched-attended postures of 4 groups after ischemia. (e) the percent time of open arms in each group at 7 days after ischemia. $^{**}P < 0.01$ compared with I group; (f) the entrance numbers of open arms in each group. $^{**}P < 0.01$ compared with I group; (g) the time in center area in each group. $^{*}P < 0.05$ compared with I group; (h) the stretched-attended postures of 4 groups after ischemia.

Bonferroni multiple comparison post hoc test showed that the percent time of C, S, and 3RI group were significantly longer when compare with I group ($P < 0.01$). There was no significant difference among C, S, and 3RI group ($P > 0.05$). Figure 1(f) showed the entrance numbers of open arms in each group after ischemia. The entrance numbers in the 4 groups had significant difference ($F(3, 28) = 7.551$, $P = 0.00075$). Bonferroni multiple comparison post hoc test showed that the entrance numbers of C, S, and 3RI group were significantly greater when compare with I group ($P < 0.01$). There was no significant difference among C, S, and 3RI group ($P > 0.05$). Figure 1(g) showed the time in center area of each group after ischemia. The time in center area in the 4 groups had significant difference ($F(3, 28) = 7.192$, $P = 0.0011$). Bonferroni multiple comparison post hoc test showed that the entrance numbers of C, S and 3RI group were significantly shorter when compare with I group ($P < 0.05$). There was no significant difference among C, S, and 3RI group ($P > 0.05$). Figure 1(h) shows that stretched-attended postures of each group after ischemia. The stretched-attended postures were no significant difference in the 4 groups ($F(3, 28) = 1.432$, $P = 0.254$). Although the stretched-attended postures of I group were increased, there were no significant difference when compared with C, S, and 3RI group ($P > 0.05$).

3.2. Open Field Test. Figure 2(a) shows that the total distance of each rat groups in open field test. The total distance in the 4 groups had significant difference ($F(3, 28) = 11.851$, $P = 0.000035$). Bonferroni multiple comparison post hoc test showed that the total distance of C, S, and 3RI group were significantly longer when compared with I group ($P < 0.01$). There were no significant differences among C, S, and 3RI group ($P > 0.05$).

Figure 2(b) shows the average speed of each group in open field test. The average speed in the 4 groups had a significant difference ($F(3, 28) = 11.851$, $P = 0.000035$). Bonferroni multiple comparison post hoc test showed that the average speeds of C, S, and 3RI group were significantly faster when compared with I group ($P < 0.01$). There were no significant differences among C, S, and 3RI group ($P > 0.05$).

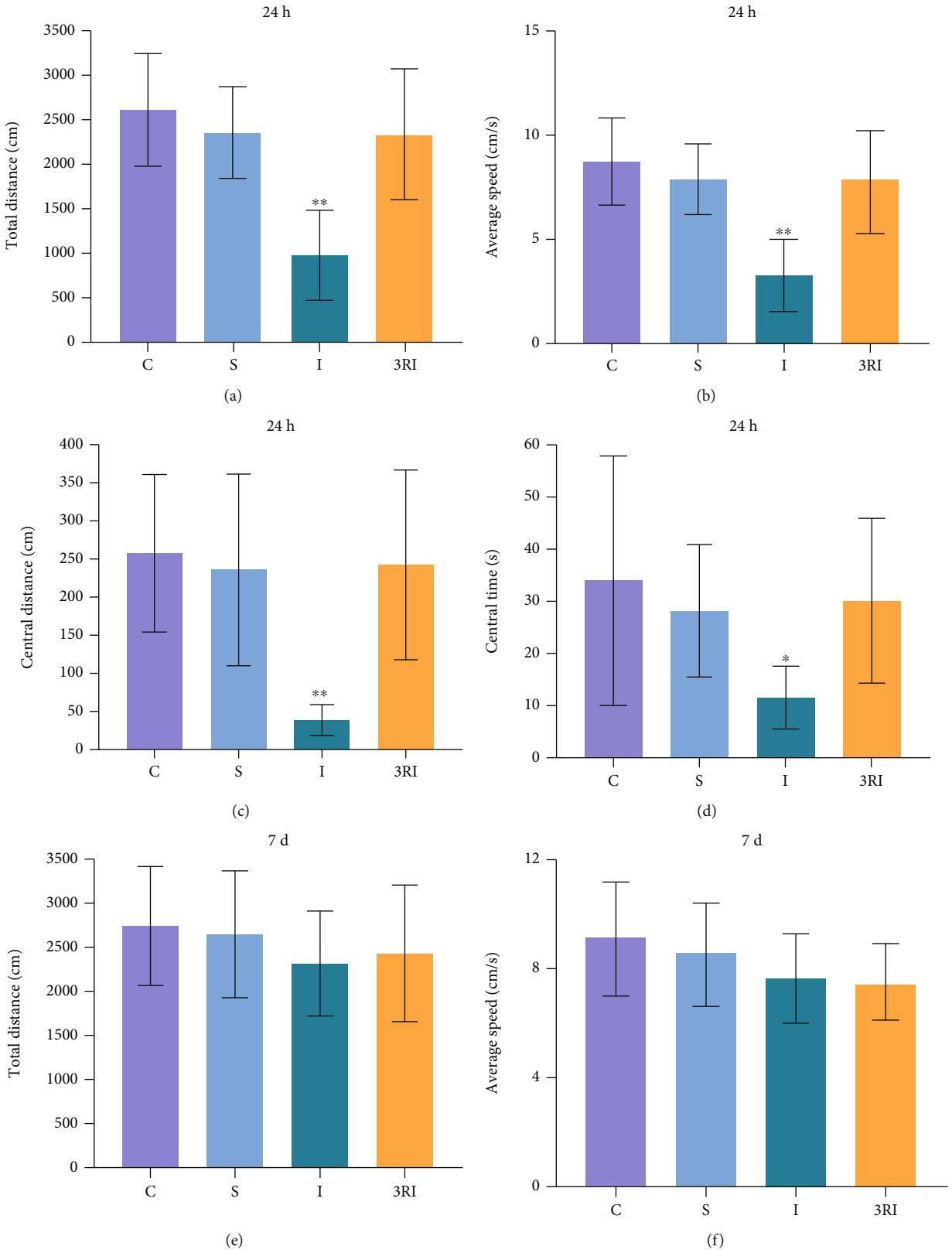
Figure 2(c) shows that the central distance of 4 groups in open field test. The central distance in the 4 groups had significant difference ($F(3, 28) = 6.774$, $P = 0.001$). Bonferroni multiple comparison post hoc test showed that the central distances of C, S, and 3RI group were significantly longer when compared with I group ($P < 0.01$). There were no significant differences among C, S, and 3RI group ($P > 0.05$).

Figure 2(d) shows the central time of 4 groups in open field test. The central time in the 4 groups had significant difference ($F(3, 28) = 3.132$, $P = 0.041$).Bonferroni multiple comparison post hoc test showed that the central time of C, S, and 3RI group was significantly longer when compared with I group ($P < 0.05$). There were no significant differences among C, S, and 3RI group ($P > 0.05$).

Figure 2(e) shows the total distance of each rat groups in open field test. The total distance in the 4 groups had significant difference ($F(3, 28) = 0.629$, $P = 0.603$). Bonferroni multiple comparison post hoc test showed that the total distance of C, S, I, and 3RI group had no significant difference ($P > 0.05$).

Figure 2(f) shows the average speed of each group in open field test. The average speed in the 4 groups had significant difference ($F(3, 28) = 1.513$, $P = 0.233$). Bonferroni multiple comparison post hoc test showed that the average speed of C, S, I, and 3RI group were no significant difference ($P > 0.05$).

Figure 2(g) shows the central distance of 4 groups in open field test. The central distance in the 4 groups had significant difference ($F(3, 28) = 4.511$, $P = 0.011$). Bonferroni multiple comparison post hoc test showed that the central



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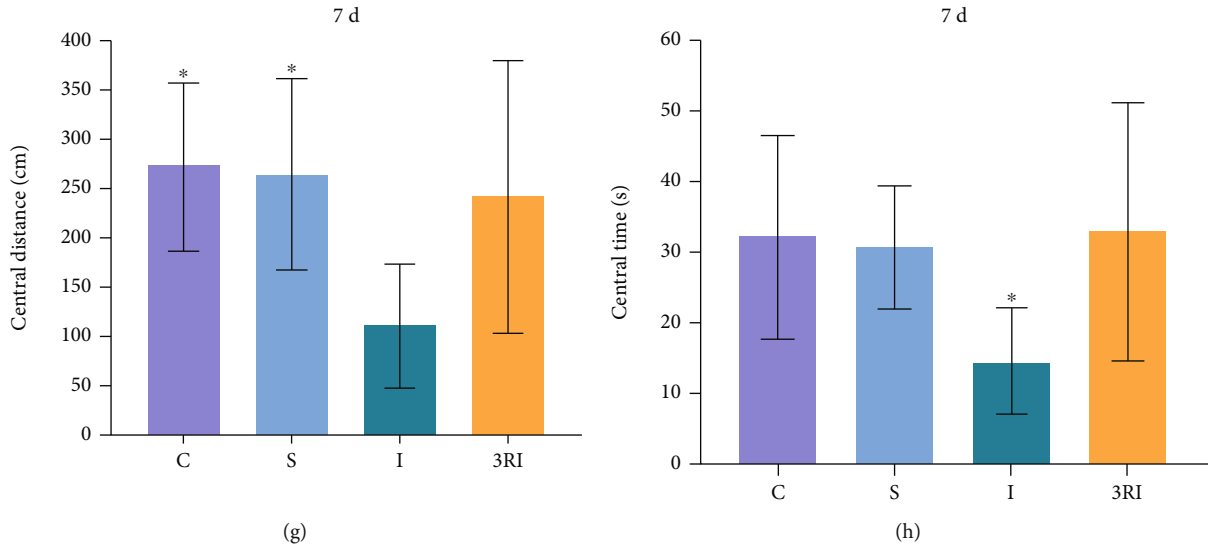

Figure 2: (a) The total distance of 4 groups in open field test at 24 hours after ischemia. $^{**}P < 0.01$ compared with I group. (b) The average speed of 4 groups in open field test. $^{**}P < 0.01$ compared with I group. (c) The central distance of 4 groups in open field test. $^{*}P < 0.05$ compared with I group. (d) The central time of 4 groups in open field test. $^{**}P < 0.05$ compared with I group. (e) The total distance of 4 groups in open field test. (f) The average speed of 4 groups in open field test. (g) The central distance of 4 groups in open field test. $^{*}P < 0.05$ compared with I group. (h) The central time of 4 groups in open field test. $^{*}P < 0.05$ compared with I group.

distances of C and S group were significantly longer when compared with I group ($P < 0.01$). There were no significant differences among C, S, and 3RI group ($P > 0.05$).

Figure 2(h) shows the central time of 4 groups in open field test. The central time in the 4 groups had significant difference ($F(3, 28) = 3.559$, $P = 0.027$). Bonferroni multiple comparison post hoc test showed that the central time of C, S, and 3RI group were significantly longer when compare with I group ($P < 0.05$). There were no significant differences among C, S, and 3RI group ($P > 0.05$).

3.3. Gait Analysis in Rats. Figures 3(a)–3(d) show gait parameters of each rat groups. The GARF ($F(3, 28) = 0.165$, $P = 0.919$), TWF ($F(3, 28) = 0.197$, $P = 0.897$), FBRF ($F(3, 28) = 0.228$, $P = 0.876$), and RFB ($F(3, 28) = 0.039$, $P = 0.99$) had no significant difference among 4 groups.

3.4. The Striatal Dopamine Level in each Group. Figure 4 shows the changes in striatal dopamine in each group before ischemia, during the acute phase of ischemia, and 24 hours after ischemia. A 4×4 repeated measures ANOVA was performed on dopamine, with ischemia as a between-group factor and time (before, acute phase, 24 hours, 7 days) as a within-group factor. These results showed a significant main effect of ischemia ($F(3, 28) = 104.599$, $P = 0.000023$, $\eta^2 = 0.918$) and a significant main effect of time (Greenhouse-Geisser adjusted $F(1.771, 49.6) = 103.714$, $P = 0.00004$, $\eta^2 = 0.787$), for dopamine, which was significantly higher in the ischemia than non-ischemia group. There was also a significant ischemia × time interaction effect (Greenhouse-Geisser adjusted $F(5.314, 49.6) = 77.153$, $P = 0.00012$, $\eta^2 = 0.892$). When compared with C and S group, the extracellular dopamine level had no significantly difference at the four time points ($P > 0.05$). When compared with dopamine of I group, the dopamine of 3RI group has significant difference before ischemia ($P < 0.001$). The extracellular dopamine of I group has significantly increased ($P < 0.05$), and the extracellular dopamine of 3RI group has no significant difference during the acute phase of ischemia when comparing pre-ischemia ($P > 0.05$). At 24 hours after ischemia, striatal dopamine returned to pre-ischemic levels in 3RI group ($P > 0.05$). Striatal dopamine in I group was smaller than pre-ischemic levels at 7 days ($P < 0.05$).

3.5. Voluntary Exercise Behavior. Average running distance of rats in this experiment was 679 m each night. The distance increased rapidly over the first week and reached the maximum mean distance of 885 m on 7th night and then remained around 726 m. The mean distance of the rats in the 3 weeks was about 14265 m.

4. Discussion

Cerebral ischemia in humans is a common and frequently-occurring disease, which leads to limb movement disorders, cognitive dysfunction, and emotional disorders of ischemia patients [35]. New studies revealed that cerebral ischemia can give rise to emotional impairment resulted by increased anxiety-like behavior [36, 37]. Studies in the past have revealed that high-anxiety animals were less exploration behavior in the open arms of elevated plus maze and central zone of open field test [38]. Thus, elevated plus maze and open field test are used in evaluation of anxiety-like behavior [39, 40]. As shown in Figures 1 and 2, the percent time and entrance number of open arms in I group were significant less than C, S, and 3RI group. Besides, the time in center area in I group were significant more than C, S, and 3RI group.

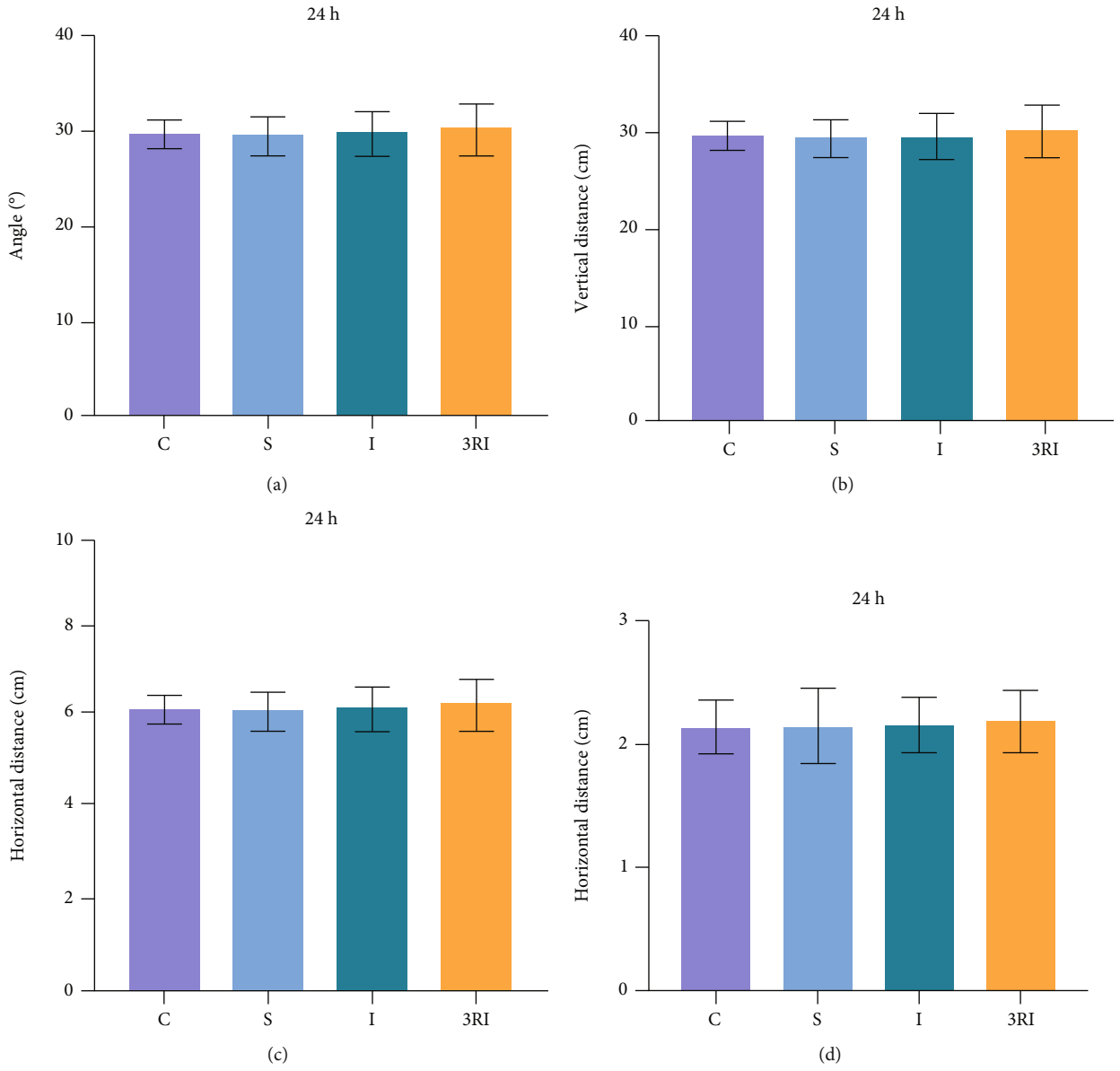

Figure 3: The gait analysis of 4 groups.

And the central time and central distance of open field in I group were significant less than C, S, and 3RI group, either. This result indicated that 24 hours cerebral ischemia can lead to anxiety-like behavior in rats. These findings are in accordance with the previous study. The findings of the previous studies have revealed that the rats could develop anxiety-like behavior after global cerebral ischemia [41]. Therefore, this experiment successfully established model of anxiety in rat after global cerebral ischemia. In addition, this study also found that the average speed and total distance of open field in I group were significant less than S and 3RI group. It was believed that the animals may develop depression-like behavior, which is not in accordance with previous studies and may be due to the different modelling methods used, as the previous study only ligated the common carotid arteries bilaterally for 10 minutes [42], whereas this experiment used a permanent arterial ligation. Therefore, whether depression-like behavior occurs in rats after permanent ligation of the bilateral common carotid artery and whether exercise obstructs this behavior requires further study. Besides, our study found that rats also showed significant anxiety-like behavior on day 7 after cerebral ischemia, and this study is consistent with previous studies. Previous study found that rats exhibited significant anxiety-like behavior after 1 week of cerebral ischemia [43]. Furthermore, in order to eliminate the influence of non-specific motor problems on the findings of this experiment, gait and motor coordination evaluation was carried out on each group of animals, and the findings revealed that there were no significant differences among the four groups (Figure 3).

The findings of this experiment also revealed that the content of striatal dopamine was notably increased after ischemia; there was significant difference between before and acute ischemia in I group (Figure 4). The results were

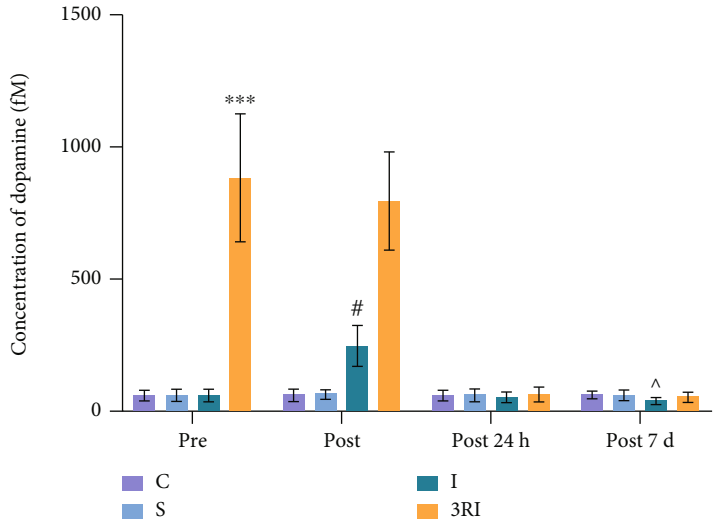

Figure 4: The changes of striatal dopamine in each group at 4 points in time. $^{***}P < 0.001$ compared with I and S group before ischemia. $^{\#}P < 0.05$ compared with I group before ischemia. $^{\wedge}P < 0.05$ compared with S group at 7 days after ischemia.

in accordance with previous research. It has been found that the striatal dopamine content increased significantly, rising to 150% of the baseline level at 20 minutes, and the dopamine level in the striatum at 120 minutes after ischemia was significantly higher than that before ischemia [44]. The findings of the previous studies have shown that cerebral ischemia instigates a neurotoxic cascade resulting in various biochemical and metabolic disturbances such as excessive dopamine accumulation in striatum. A substantial body of evidence has progressively researched the mechanism of deleterious effect of excessive dopamine on neurons. First, oxidation of large amounts of dopamine promotes the generation of free radicals, in particular, in regions of the brain such as the striatum [45]. Second, the oxidized dopamine can form covalent bonds, which may lead to modification of protein structure and function and cause further tissue damage [46]. Third, excessive dopamine can also react with hydroxyl radicals to generate the more dopaminergic neurotoxin 6-hydroxydopamine [47]. These results suggest that dopamine accumulation may be closely related to acute cerebral ischemic damage. Therefore, attenuation or prevention of striatal dopamine accumulation during the acute cerebral ischemia may reduce ischemia-induced impairments in anxiety-like behavior.

In addition, our study found that rats had significantly lower striatal dopamine levels than controls on day 7 after cerebral ischemia. Consistent with our findings, recent studies have suggested that the depletion of dopamine in the striatum can induce anxiety-like behavior in low exploratory rats [48]. Our preliminary experimental study also found that anxiety-like behavior instigated by molar loss was strongly associated with a decrease in striatal dopamine levels [49]. Furthermore, quetiapine effectively attenuated anxiety-like behavior and neurotoxicity in dopaminergic terminals [50]. Thus, it is reasonable to suggest that the decrease of striatal dopamine level in chronic cerebral ischemia can be one of the important reasons of anxiety-like behavior in cerebral ischemia rats.

In recent years, many researches have committed on the treatment methods and mechanisms of cerebral ischemia [51, 52], However, therapeutic strategies for the anxiety caused by cerebral ischemia have not been well researched. Studies showed that aerobic exercise attenuates ischemia-induced memory impairment by enhancing cell proliferation and suppressing neuronal apoptosis [53]. Besides, some research showed that exercise training had antidepressant and anxiolytic effects and protected against harmful consequences of stress [54, 55]. The exercise methods of involuntary, forced, and voluntary exercise were extensively used in animals in this research [56]. Further studies indicated that voluntary wheel running can be one of the best ways to promote cognition and emotion [57, 58]. Meanwhile, some researches showed that 3 weeks prerequisite exercise improves behavioral functions following transient cerebral ischemia in rats [59]. Thus, the present study selected 3 weeks voluntary wheel running as preventative approach. As shown in Figure 5, we found that the rats in this experiment exhibited the similar exercise tendency by recording the daily running distance of the rats; therefore, the exercise protocol used in this experiment was proved effective [60]. Researchers have shown that exercise can enhance blood flow [61], oxygenation [62], and levels of neurotrophic factor [63] and vascular endothelial growth factor [64] in the brain that provided neuroprotection to the brain under ischemic conditions. Further, our research demonstrate that 3 weeks voluntary wheel running can inhibit dopamine levels during acute cerebral ischemia. Thus, it is viable to suggest that maintaining stable dopamine levels during acute cerebral ischemia can be the reasons to induce that voluntary wheel running improve anxiety-like behavior after cerebral ischemia in rats.

It is worth to mention that 3 weeks voluntary wheel running not only remarkably improved the anxiety of cerebral ischemia rats, but also notably increased the dopamine level in striatum. The experimental study found that the striatal dopamine in 3RI group was crucially higher than I and S

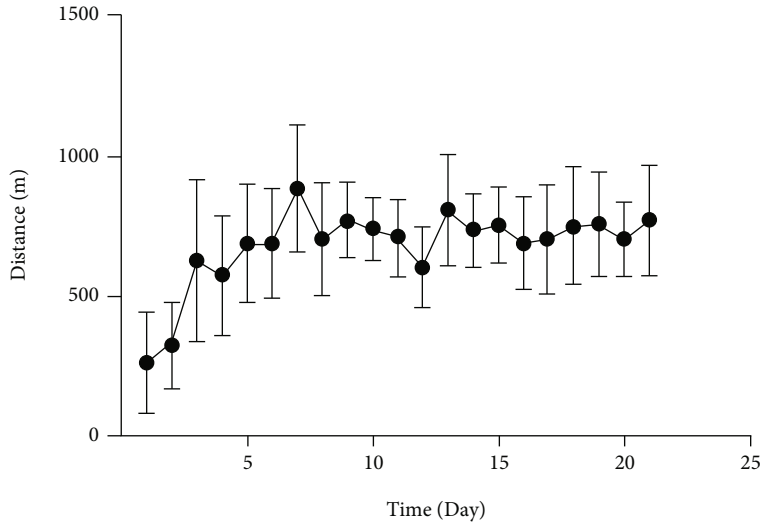

Figure 5: Average wheel running distance over 21 days.

group before and after ischemia; its maximum value reached about 15 and 12 times of I and S group before and after ischemia. Reference to the literature on exercise-induced changes in striatal dopamine levels is scarce. Some past studies observed that striatal dopamine content of endurance training and sham group were significantly increased and remained at a basic level about 150% in the 60-minute training course and about 3 hours after the training [65, 66]. This study revealed that striatal dopamine levels of rats increased significantly after voluntary running wheel exercise and returned to basal levels 24 h after cessation of exercise. These findings suggested that exercise stimulated the release of dopamine in striatum and the increase of striatal dopamine will return to the base level over a period of time, which was consistent with the results of this study.

Although we found that 3 weeks voluntary wheel running has the tendency to improve the anxiety-like behavior induced by cerebral ischemia and increased the striatal dopamine, it is unsured whether this releaving of anxiety after exercise is directly induced by the dopamine releasing or by other exercise-related neurochemical modification. It is required to further study addressing at correlation between dopaminergic neural circuit effected by exercise and anxiety-related changes of dopamine level by neuropsychopharmacology experiments.

5. Conclusions

3 weeks exercise can outstandingly increase the striatal dopamine level before ischemia and improve the anxiety-like behavior in rats of cerebral ischemia by inhibiting the increase the striatal dopamine level during acute cerebral ischemia and suppressing the decrease of dopamine after 24 hours cerebral ischemia.

Data Availability

Data are available by contacting the corresponding author.

Conflicts of Interest

The authors proclaim that there is no conflict of interests.

Acknowledgments

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Research Article

Relationship between Self-Efficacy and Headache Impact, Anxiety, and Physical Activity Levels in Patients with Chronic Tension-Type Headache: An Observational Study

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Background. Chronic tension-type headache is the primary headache with the highest prevalence. The present study is aimed at analyzing the associations between patient self-efficacy and headache impact with pain characteristics, kinesiophobia, anxiety sensitivity, and physical activity levels in subjects with chronic tension-type headache. *Materials and Methods*. An observational descriptive study was carried out. A total sample of 42 participants was recruited at university environment with diagnosis of tension-type headache. Headache characteristics (frequency, intensity, and duration), physical activity levels, pain related-self-efficacy, kinesiophobia, anxiety sensitivity, and headache impact were measured. *Results*. The HIT-6 (61.05 ± 6.38) score showed significant moderate positive correlations with the ASI-3 score (17.64 ± 16.22; $r = 0.47$) and moderate negative correlations with the self-efficacy in the domains of pain management (31.9 ± 10.28; $r = -0.43$) and coping with symptoms (53.81 ± 14.19; $r = -0.47$). ASI-3 score had a negative large correlation with self-efficacy in the domains of pain management ($r = -0.59$), physical function (53.36 ± 7.99; $r = -0.55$), and coping with symptoms ($r = -0.68$). Physical activity levels showed positive moderate correlations with the self-efficacy in the domain of physical function ($r = 0.41$). Linear regression models determined that the self-efficacy and anxiety sensitivity with showed a significant relationship with the HIT-6 score ($R^2 = 0.262$; $p = 0.008$) and with the ASI-3 score ($R^2 = 0.565$; $p < 0.001$). In addition, no correlations were found between pain intensity, duration or frecuency with psychosocial factors, or headache impact. *Conclusions*. The present study showed that patients with chronic tension-type headache had a great negative impact on daily tasks and physical activity levels, which were associated with higher anxiety levels and lower self-efficacy.

1. Introduction

Headache is considered the second cause of disability worldwide in people between 10 and 24 years old and ranks fifth between 25 and 54 years, according to the 2019 Global Burden of Disease Study. Besides, this report shows how depression is ranked fourth and fifth, and anxiety sixth and fourteenth for both ranges of age, respectively [1].

According to the International Headache Society (IHS) classification (third edition), Tension-Type Headache (TTH) is considered the most common primary headache [2]. TTH lifetime prevalence rate was about 26.1% to 45% [1]. TTH affects people's daily life activities in a large number of areas, which implies an increase in stress levels, impaired cognitive capacity, and a negative impact on sleep quality [3]. People with chronic daily headaches have an extremely low quality of life in all domains except for purely physical or motor functioning, which is less affected [4]. Similarly, TTH is associated with an increased number of sick leave days, as well as with lower efficiency in working

tasks [5], and a lower quality of social and family relationships [6]. These consequences seem to be directly proportional to the duration, frequency, and intensity of pain [3].

Main comorbidities linked with TTH are stress, anxiety, and depression [7]. Prevalence values of anxiety and depression in subjects with TTH are 64-90% [8]. An observational study reports that headache episode frequency has been associated with anxiety, with a significant increase in anxiety when headache frequency raises [9]. Indeed, anxiety levels have been found to be significantly higher in patients with TTH than in healthy controls [10].

Some studies evaluated kinesophobia as a factor associated with TTH, although no clear data has been drawn regarding this issue [11–13]. Kinesiophobia refers to excessive, irrational, and debilitating fear a person may suffer from physical movement and/or activity due to a vulnerability perception to experience a painful injury or reinjury [14]. This fact often leads to physical inactivity as well as an increase in pain intensity in subjects with musculoskeletal pain conditions [15]. However, no significant associations between pain intensity and decreased physical activity have been reported in patients with TTH [11–13].

In regard to physical activity levels, self-efficacy seems to have a relevant role. Self-efficacy is defined as an individual's belief in his/her capacity to produce an adequate yield in daily life activities. Self-efficacy has a direct connection with headache, and it refers to the confidence level a subject has to prevent and/or control pain episodes [16]. This feature could explain why subjects with the same pain intensity levels have different levels of disability in their daily lives, since population groups with lower self-perceived ability feel they are unable to prevent or control headache attacks [17]. In fact, self-efficacy helps to improve adherence to behavioral interventions [16], and consequently, this factor should be addressed in therapeutic interventions [17].

A number of neuroimaging studies have demonstrated that morphological changes in corticolimbic structures and emotional systems are associated with persistent pain. Patients with chronic pain conditions show reductions in gray matter volume in the hippocampus and amygdala. Given the functions of these two regions, this reduction suggests that the development of chronic pain may be correlated with emotional and cognitive changes [18].

In summary, functional and structural changes in the corticolimbic system and corticolimbic interactions in patients with chronic pain can contribute to emotional and cognitive problems [19].

To date, few studies have been conducted with patients with TTH that report a broad analysis of the associated psychosocial aspects, analyzing their impact on the severity of this pathology [20–22]. In addition, TTH is common among people who spend much sitting time at work, like university employees [23, 24], and the World Health Organization global action plan on workers' health establishes that lifestyle interventions should be carried out within the workplace [25].

The present study is aimed at analyzing the associations between patient self-efficacy and headache impact with pain characteristics, kinesiophobia, anxiety, and physical activity level in subjects with TTH.

2. Methods

An observational study following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [26] was conducted in patients with chronic TTH. The study protocol adhered to the principles of the 1964 Declaration of Helsinki and its subsequent clarifications and was approved by the Research Ethics Committee of the Rey Juan Carlos University of Madrid (reference number: 1802202105721).

2.1. Participants. The participants were university employees recruited through the occupational health unit, when they fulfilled the following criteria: (1) adults aged 18-65 years and (2) diagnosed with chronic TTH (duration > six months) by their neurologist, following the criteria of the International Headache Society classification of headaches, in its third edition [2].

2.2. Variables. Anthropometric variables were age in years, height in centimeters (cm), and weight in kilograms (kg). Height was measured with a measuring rod (Ano Sayol SL, Barcelona, Spain) and weight with a mechanical scale (Asimed T2, Barcelona, Spain). Body mass index (BMI) was calculated as weight (kg)/height (m^2) following Shephard's protocol [27].

2.2.1. Physical Activity Levels. The level of physical activity was measured using the exercise habits registered with the IPAQ short-form questionnaire (International Physical Activity Questionnaire) of 7 days was used, validated, and adapted to Spanish [28, 29]. The questionnaire provides information on the estimated energy expenditure in 24 hours, by calculating the metabolic equivalents per task per minute per week (METs/minute/week), establishing a classification based on the standard values (Hagströmer et al., [30]). The questionnaire also evaluates sports experience and weekly training time, as well as physical activity in different areas of daily life such as activities at home or sedentary time [30, 31].

2.2.2. Headache Characteristics. Headache duration (hours/day), intensity (from 0 (no pain at all) to 10 (the worst pain ever possible), and frequency (episodes per month) were measured following previous research [32].

2.2.3. Headache Impact Test (HIT-6). The Headache Impact Test (HIT-6) measures the impact that headaches have on daily activity tasks. Regarding the severity of the impact, ≥60 means very severe impact; 56-59, significant impact; 50-55, moderate impact; and ≤49, little impact [33].

2.2.4. Tampa Scale for Kinesiophobia (TSK-11):. The Tampa Scale for Kinesiophobia (TSK) is one of the most widely used measures to assess pain-related fear in patients with pain. Factor analysis reveals a 2-factor model of 11 elements replicated in both samples, called TSK-11. The instrument shows good reliability (consistency and internal stability) and validity (convergent and predictive), with the advantage of brevity. Evidence is provided on the discriminant validity

between both TSK factors (called Activity and Harm Avoidance). TSK-11 was validated by Gómez-Pérez et al. [34]. Items on the TSK-11 are scored from 1 (strongly disagree) to 4 (strongly agree). Therefore, total TSK-11 scores range from 11 to 44 points, with higher scores indicating greater fear of pain, movement, and injury. A score ≤ 28 is considered low kinesophobia; 29-35, moderate kinesophobia; and ≥36, high kinesophobia.

2.2.5. Anxiety Sensitivity Index-3 (ASI-3):. The Anxiety Sensitivity Index-3 (ASI-3) measures the dispositional tendency to fear the somatic and cognitive symptoms of anxiety due to a belief that these symptoms may be dangerous or harmful. ASI-3 is a new 18-item self-report scale designed to assess the three most replicated facets of anxiety sensitivity, the physical, cognitive, and social dimensions. For ASI-3, the study by Beghi et al. [35] was followed; the responses are scored from 0 (very little) to 4 (a lot). A higher total score indicates greater anxiety [35]. A score ≤ 10 is considered low anxiety; 11-16, moderate anxiety; and ≥17, high anxiety.

2.2.6. Chronic Pain Self-Efficacy Questionnaire:. The Chronic Pain Self-Efficacy Questionnaire, which assesses the patient's belief about their ability to perform certain activities, was originally developed by Anderson [36] and validated and translated into Spanish by Martín-Aragón [37]. This validation has been established as a reliable and valid instrument to assess self-efficacy expectations regarding the control of chronic benign pain, in which 19 questions were asked regarding three domains of self-efficacy: pain management, physical functioning, and coping with symptoms. Each item is answered on a scale of 0 to 10 under, where 0 means "not completely confident" and 10 "completely confident." Higher scores indicate greater levels of confidence in dealing with pain.

2.3. Statistical Analysis. The Shapiro-Wilk test was employed to assess the normality [38]. A descriptive analysis was developed for all the subjects using the mean ± standard deviation (SD). In addition, to analyze the relationship between continuous variables, Spearman's correlation test and Pearson's correlation test were performed for the nonparametric and parametric variables, respectively. The magnitudes of correlation (positive and negative) between continuous variables were qualitatively interpreted using the following criteria: trivial ($r \leq 0.1$), small ($r = 0.1$–0.3), moderate ($r = 0.3$–0.5), large ($r = 0.5$–0.7), very large ($r = 0.7$–0.9), and almost perfect ($r \geq 0.9$) [39]. After Bonferroni's correction was applied, the statistical significance was set at an alpha level of <0.0056, as 9 comparisons were made. A multiple linear regression was performed using the force-entry method and the R^2 change coefficient to state the quality adjustment. HIT-6 and ASI-3 were considered dependent variables, and self-efficacy was considered an independent variable. Graphs of standardized predicted value against standardized residuals were analyzed to assess linearity and homoscedasticity. The multicollinearity was assessed by VIF and tolerance statistics. Finally, a multiple linear regression was performed among variables that already showed significant correlations. The statistical significance was set at an alpha level of <0.05. All analyses were conducted using IBM SPSS for Windows (version 25, IBM Corporation, Armonk, New York).

3. Results

Adults ($N = 42$) with chronic tension-type headache were analyzed. Most of the participants were female (76%) and had a healthy body weight and low-moderate physical activity levels.

Most of the participants had long-lasting high intensity headaches.

Concerning the impact that headaches have on daily activity tasks, 83% of the participants reported a very severe or significant impact, while most of the participants reported a low kinesophobia. However, most of the participants had high (36%) or moderate (24%) anxiety levels. Regarding self-efficacy, the participants showed a high score in the physical function domain, but moderate scores in pain management and coping with symptoms.

Table 1 shows the mean scores and standard deviation of the headache's characteristics and the scores of the TSK-11, Chronic Pain Self-Efficacy Questionnaire, ASI-3, and HIT-6.

3.1. Correlations between the Continuous Variables. The HIT-6 score showed moderate positive correlations with the ASI-3 score ($r = 0.47$; $p = 0.002$) and moderate negative correlations with the self-efficacy in the domains of pain management ($r = -0.43$; $p = 0.002$) and coping with symptoms ($r = -0.47$; $p = 0.005$) (Table 2).

In addition, the ASI-3 score had a negative large correlation with self-efficacy in the domains of pain management ($r = -0.59$; $p < 0.001$), physical function ($r = -0.55$; $p < 0.001$), and coping with symptoms ($r = -0.68$; $p < 0.001$) (Table 2).

Physical activity levels showed positive moderate correlations with the self-efficacy in the domain of physical function ($r = 0.41$; $p = 0.005$) (Table 2). Finally, no associations were found between psychosocial factors and headache impact with pain duration, intensity, or frequency (Table 2).

3.2. Multivariate Predictive Analysis of Headache Impact and Anxiety. Regarding the multivariate regression analysis, the linear regression model determined significant differences ($p < 0.05$) for headache impact and anxiety sensitivity. Furthermore, self-efficacy and anxiety sensitivity (predictors) showed a significant relationship with the HIT-6 score ($R^2 = 0.262$; $p = 0.008$) and self-efficacy with the ASI-3 score ($R^2 = 0.565$; $p < 0.001$) (Table 3).

4. Discussion

The present study was aimed at examining the associations between patient self-efficacy and headache impact with pain characteristics, kinesiophobia, anxiety, and physical activity level in middle-aged individuals with TTH. Our hypothesis, based on the belief that larger anxiety or kinesiophobia levels, lower physical activity level, and lower self-efficacy,

Table 1: Descriptive analysis of the variables analyzed in 42 patients with chronic tension-type headache.

Variables		Mean ± SD
Sociodemographic characteristics	Age (years)	36.69 ± 13.26
	Body mass index (kg/m^2)	20.38 ± 3.29
Headache characteristics	Headache intensity (0 to 10)	7.14 ± 1.32
	Headaches episodes duration (hours/day)	16.18 ± 9.47
	Headaches episode frequency (times per month)	11.05 ± 9.47
QUESTIONNAIRES	TSK-11 total score ≤28 low kinesiophobia 29-35 moderate kinesiophobia ≥26 high kinesiophobia	9.00 ± 5.12 (91% low kinesophobia)
	Self-efficacy total score Range 0-190	139.07 ± 29.45
	Self-efficacy pain management Range 0-50	31.90 ± 10.28
	Self-efficacy physical functioning Range 0-60	53.36 ± 7.99
	Self-efficacy coping with symptoms Range 0-80	53.81 ± 14.19
	ASI-3 total score 0-10 low anxiety 11-16 moderate anxiety ≥17 high anxiety	17.64 ± 16.22 (36% high anxiety; 24% moderate)
	HIT-6 total score ≥60 very severe impact 56-59 significant impact 50-55 moderate impact ≤49 little impact	61.05 ± 6.38 (83% very severe or significant impact)

TSK-11: Tampa Scale for Kinesiophobia; ASI-3: Anxiety Sensitivity Index-3; HIT-6: Headache Impact Test-6.

Table 2: Correlations between the continuous variables.

	Headaches duration	Headache intensity	Physical activity levels	Self-efficacy coping with symptoms	Self-efficacy physical function	Self-efficacy pain management	TSK-11	ASI-3	HIT-6
Headaches frequency	-0.264	-0.234	0.277	-0.001	0.008	0.197	0.091	-0.016	0.141
Headaches duration†		-0.342	-0.255	0.089	-0.148	-0.027	-0.108	-0.041	-0.007
Headache intensity†			-0.172	0.291	-0.171	0.030	-0.278	-0.211	-0.105
Physical activity levels†				0.080	0.412*	0.264	0.204	-0.052	0.047
Self-efficacy copying with symptoms					0.678	0.536	-0.210	-0.688*	-0.471*
Self-efficacy physical function†						0.734	-0.037	-0.554*	-0.290
Self-efficacy pain management							-0.208	-0.668*	-0.425*
TSK-11†								0.095	0.048
ASI-3†									0.493*

*Significance level was set at $p < 0.0056$; †Spearman's correlation was realized.

Table 3: Multivariate predictive analysis of headache impact and anxiety sensitivity.

Parameter (Dependent variables)	Model (Independent variables)	R^2 change	Beta value	P value
HIT-6	Self-efficacy coping with symptoms	—	-0.246	0.304
	Self-efficacy pain management		-0.065	0.780
	ASI-3		0.254	0.214
		0.262		0.008
ASI-3	Self-efficacy coping with symptoms	—	-0.352	0.049
	Self-efficacy pain management		-0.160	0.407
	Self-efficacy physical function		-0.322	0.053
		0.565		<0.001

would be related to greater pain, and higher headache impact was partially supported. Lower self-efficacy and higher anxiety were associated with higher headache impact. In addition, this study identified that higher physical activity levels were related with higher self-efficacy.

Pain is complex and can rarely be explained purely by a single variable. However, the present study demonstrated the importance of considering self-efficacy when evaluating pain in patients with TTH. In fact, both lower self-efficacy and higher anxiety were related to higher headache impact in participants with TTH. Indeed, HIT-6 questionnaire score was >60, which is considered a severe impact of headaches on patients' quality of life. This finding matched with other research groups with wider study populations and similar aged-based features [40, 41].

Self-efficacy is considered a core component in self-management, yet there is a lack of knowledge about the association between self-efficacy and health-related outcomes in patients with TTH. Low self-efficacy is related to a variety of poor outcomes in both nonsurgical management and postoperative rehabilitation of musculoskeletal conditions [42–44]. Several studies have shown that evidence-based interventions can improve self-efficacy and self-management [45–47]. In this line, physical activity is a potential self-management treatment and has a positive impact on physical function and disease-related symptoms such as pain [48]. Additionally, according to Varkey et al. [49], physical inactivity is a risk factor associated with a higher prevalence of migraine. In accordance with our results, self-efficacy has been linked with physical activity [50, 51]. As noted, in previous studies, poorer pain self-efficacy predicted higher levels of anxiety [52, 53], which was associated with higher headache-related disability and frequency of episodes [9, 11, 54]. The results of the current study were consistent with these previous findings. In addition, the authors have found clinically relevant anxiety levels, according to the ASI-3 score. As previously mentioned, physical self-efficacy is associated with anxiety and it may play a role in the chronicity of headaches.

We hypothesize that pain responses such as resting and guarding the craneocervical region have been described as passive coping and viewed as reflecting patient-perceived helplessness in controlling pain or reliance on others for pain management. Resting and guarding consistently have been found to be associated with worse outcomes and thus have been considered maladaptive for chronic pain [55]. Even though findings from the present study cannot be extrapolated to treatment outcomes in patients with TTH, the characterizations of poor psychosocial health provide guidance to health professionals and should consider screening for self-efficacy and kinesiophobia in patients not responding to conservative therapeutic management.

Kinesiophobia has been studied as a clinically relevant factor linked to several extracranial pathologies such as isolated neck or shoulder pain [56]. Several studies in head-referred symptoms like migraine [57], temporomandibular disorders [58], and TTH [59] are inconsistent with our findings. Recently, one study reported that patients with chronic TTH and chronic migraine showed similar kinesiophobia scores but were significantly worse when compared to controls [13]. However, findings from the present study did not support that patients' perception and their fear of movement influence their pain experience or headache impact. Therefore, our findings disagree with the fear-avoidance model [60], which suggests that kinesiophobia is a potential psychological factor that could favor pain chronicity.

Contradicting our hypothesis, headache characteristics were not related to psychosocial factors or headache impact in people with chronic TTH. A possible explanation for this finding in that evidence regarding pain intensity, duration, or frequency in people with chronic TTH compared to asymptomatic controls is limited and conflicting [61], suggesting that resiliency factors and other potential behavioral targets such as pain acceptance can promote positive pain-related outcomes.

The present study has several limitations. Its observational nature does not allow causation, and results should be interpreted with caution. Another limitation of the study is that 76% of the sample are women and future research should determine if these results would be similar in men population. Moreover, the sample size was small, complicating output of regression models. The lack of a control group makes the results to be taken with caution. All data were self-reported and may be subject to information bias. In addition, outcomes related to depression and pain catastrophizing may be interesting, as well as other physical variables such as somatosensory, motor control, or cervical range of motion. Further studies should consider these variables to strengthen this study.

5. Conclusions

In summary, the present study showed that chronic TTH patients had a great negative impact on daily tasks, which was associated with higher anxiety and lower self-efficacy. In contrast, higher physical levels could enhance self-efficacy and attenuate the headache impact of this type of patients. Therefore, physical activity management and improved self-efficacy should be taken into account in chronic TTH patients.

Data Availability

The data presented in this study are available on request from the corresponding author.

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Supplementary Materials

The questionnaires used in the present study were the TSK-11 to assess the kinesiophobia, HIT-6 for headache impact, chronic pain self-efficacy scale, ASI-3 Index to assess anxiety sensitivity, and IPAQ to evaluate the physical activity levels of the participants. *(Supplementary Materials)*

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Research Article

Revealing the Role of Social Support on Cognitive Deficits in Fibromyalgia Syndrome

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Despite the relevance of cognitive deficits in fibromyalgia syndrome (FMS) and the attempts to elucidate the influence of the disorder symptoms in the cognitive decline reported by patients, no studies have explored the specific role of social support on cognition in FMS. Social support has been shown to be an essential modulator factor on cognitive performance in other diseases. Sixty-four women with FMS and 32 healthy women participated in the study and completed questionnaires pertaining to anxiety, depression, fatigue, insomnia, clinical pain, and social support, along with a neuropsychological battery assessing verbal memory, organization, strategic and planning abilities, self-regulation, processing speed, attention, and cognitive flexibility. Results showed that FMS patients exhibited lower values in all social support dimensions in comparison with healthy individuals, especially in the socializing dimension. Despite the lower social support observed in FMS, all social support dimensions showed a positive impact on verbal memory, organization and planning abilities, strategic planning, self-regulation, processing speed, attention, and cognitive flexibility in these patients. In fact, social support was associated with greater correct responses and processing speed and minor number of errors in all the neuropsychological battery tests. Socializing was the main predictor of organization and planning abilities, strategic planning, and self-regulation. In sum, results suggest that social support may be a key factor in buffering the cognitive decline observed in FMS. Designing psychoeducation programs and intervention programs directed not only to FMS patients but also relatives, health care workers, and the general population might be essential to improve the social support of FMS patients and positively impact on patient's cognitive status.

1. Introduction

Fibromyalgia syndrome (FMS) is a chronic pain disorder with a prevalence around 2-4% in the general population, being more frequent in women than in men [1]. FMS may be conceptualized as a widespread and persistent musculoskeletal pain, accompanied by several symptoms such as fatigue, insomnia, morning stiffness, depression, anxiety, and cognitive problems [1–3]. Cognitive impairments, which negatively impact on patient's life, frequently comprise problems in memory, attention, concentration, language, cognitive flexibility, and processing speed, along with reduced organization and planning abilities, among others, and are considered between the most disabling and worrisome symptoms of the disease [3–8].

Emotional aspects also play a relevant role in FMS. FMS has been associated with high negative affectivity [9–11], pain catastrophizing [12–16], alexithymia [17–19], self-esteem, and self-efficacy deficits [3, 20–23]. Negative affectivity (e.g., anxiety, depression, pain catastrophizing, and alexithymia) increases the intensity and severity of symptoms in FMS, worsening the quality of life of these patients [10, 12, 24, 25]. In addition, these emotional aspects have been associated with lessen cognitive performance in FMS [3, 5, 7, 18, 26–30], indicating the relevance of emotional aspects in cognitive deficit in FMS. In the same line, emotional factors are increasing its relevance due to the transdiagnostic perspective, which is showing greater scientific support and playing a crucial role in clinical management [3, 11, 31, 32]. Moreover, the transdiagnostic perspective

seems to be also crucial for personalized behaviour management, which has shown to be essential for mood regulation as an alternative to medications [33].

Furthermore, other factor that can influence FMS symptoms is social support [34]. Social support may be conceptualized as resources provided to people in need by their social network and may be measured through the individual's perception of the degree to which interpersonal relationships can fulfil certain social support functions [35]. Social support is part of the social network function of each individual, generally related to the number and/or frequency of contacts with family members, relatives, friends, and colleagues [36]. Social support generally comprises several dimensions such as emotional, instrumental, appraisal (which implies information relevant to self-evaluation), and information, among others [34].

At this regard, some studies have reported a lack of social support in FMS patients [37, 38]. Although studies exploring the social support role in FMS symptoms are scarce, social support seems to contribute to improve mental and physical health in FMS patients [34]. In fact, the positive social interaction subcategory of social support has showed a negative association with the Fibromyalgia Impact (measured with the Fibromyalgia Impact Questionnaire) [34], depression state [34, 39], and alexithymia [40]. Besides, social support has been strongly related to anxiety, burnout, and severity of pain in FMS patients [39]. Similarly, Montoya et al. [41] reported that FMS patients perceived less general pain and thermal pain sensitivity as well as diminished brain activity elicited upon tactile stimulation of a tender point when the significant other was present in comparison with when the patients were alone, confirming the notion of social support as a factor explaining pain processing not only at the subjective behavioural level but also at the central nervous system level [41]. Similarly, a recent study confirmed the analgesic effects of social support, which was even observed without verbal or physical contact [42]. Partner empathy seems to reduce affective distress during pain exposure, decreasing pain sensitivity and promoting pain coping [42]. This is congruent with the proposed contribution of poor psychosocial functioning and unsatisfactory relationships in the genesis and maintenance of chronic pain [40].

However, the role of social support on FMS patient's cognition has not been studied until now. Previous studies in other populations confirm that the social support plays an important role involving in the maintenance or enhancement of mental health and cognitive functioning in elderly people [43–49], caregivers [50], and academic performance [51–53]. Therefore, based on these results, it might be hypothesized a similar effect of social support on cognitive performance in FMS patients.

Although the multifactorial nature of FMS has been stablished, research regarding family, work, and social support needs to be increased [54]. Considering the above-reviewed literature, the main objective of this research is to analyse, for the first time, the effect of social support on cognitive performance in FMS (specifically verbal memory, organization, strategic and planning abilities, self-regulation, processing speed, attention, and cognitive flexibility). Studies as the present one can contribute to development prevention and intervention programs aimed at improving the quality of life of FMS patients. To the best of our knowledge, this is the first study which assess the impact of social support in cognitive performance in FMS.

2. Materials and Methods

2.1. Participants. In total, 64 women with FMS, recruited from the AFIXA (Fibromyalgia Association of Jaén, Spain), participated in the study. All of them were examined by a rheumatologist and met the 1990 and 2010 American College of Rheumatology criteria for FMS [1, 2]. The control group comprised 32 healthy women. Given the main research objective of the study, analyses were restricted to the FMS group. The control group was only used for comparative purposes. Exclusion criteria for both study groups included the presence of metabolic abnormalities, neurological disorders, drug abuse, and severe somatic (e.g., cancer) or psychiatric (e.g., psychotic) diseases. Healthy individuals were further required not to suffer from any kind of acute or chronic pain. All participants were right handed.

2.2. Instruments and Measures

2.2.1. Psychological Assessment. A semistructured interview was performed to obtain the patients' clinical history and sociodemographic data. The Structured Clinical Interview for Axis I Disorders of the Diagnostic and Statistical Manual for Mental Disorders (SCID) [55] was applied to assess the presence of possible mental disorders. Furthermore, the following self-report questionnaires were administered (values of Cronbach's α are reported from the available literature):

(i) State-Trait Anxiety Inventory (STAI) [56, 57]. This 20-item 4-point Likert scale's instrument allows for the assessment of current and habitual anxiety (e.g., state anxiety and trait anxiety, respectively; score range: 0-60). Cronbach's $\alpha = .93$ for the state anxiety and .87 for trait anxiety [57]

(ii) Beck Depression Inventory (BDI) [58, 59]. This 21-item scale was applied to assess depression (4-point Likert scales, scores range: 0-63). Cronbach's $\alpha = .95$ [59]

(iii) Fatigue Severity Scale (FSS) [60, 61]. This scale allows assessment of fatigue based on 9 items (7-point Likert scales, score range: 9-63). Cronbach's $\alpha = .88$ [61]

(iv) Oviedo Quality of Sleep Questionnaire (OQSQ) [62]. The insomnia subscale of this instrument, comprising of 9 items (5-point Likert scales, score range: 9-45), was used in the study. Cronbach's α of insomnia = .88 [62]

(v) McGill Pain Questionnaire (MPQ) [63, 64]. This 73-item instrument evaluates the different dimensions of pain. In the current research, the total pain

experience (score range: 0-167) and current pain intensity (MPQ) were used. Cronbach's α of total pain = .74 [64]

(vi) SS-B Social Support Scale [65, 66] is a 45-item (4-point Likert scales) questionnaire which allow to obtain information of five modes of supportive behaviours: emotional support, socializing, practical assistance, financial assistance, and advice/guidance. Moreover, this questionnaire is typically completed with respect to family and friends separately (family support and friends' support, respectively), providing information about the supportive behaviour available from relatives and friends. Cronbach's α = .82 [65]

2.2.2. Cognitive Assessment

(i) Zoo Map Task (ZMT) from the Behavioural Assessment of the Dysexecutive Syndrome [67, 68] was used to evaluate the planning and organizational abilities. In this test, the participant has to plan a route to visit 6 of 12 possible locations in a zoo. The ZMT has two parts: (1) a more demanding open situation, in which little information is provided that would help to generate an appropriate plan, and (2) a situation that implies simply following a concrete, externally imposed strategy. Execution time and number of errors in each part in addition to the total number of correct responses were used as performance indices

(ii) Verbal Learning Test (TAVEC) [69] assesses verbal memory function. At the beginning of the test, a list of 16 words (shopping list) is read to the participant five times (list A); the participant has to reproduce as many words as possible directly after each trial (immediate free recall). Immediately after, another list is read once (list B) and then has to be reproduced (interference control condition). Following a 20 min break, the words of list A have to be reproduced again (long-delay recall). Thereafter, a list of 44 words is read, which includes all words of list A, some words of list B, and further distractor words included in neither list A nor list B. The participant has to decide whether or not each of these words is part of list A (recognition). In the analysis, list A (immediate free recall), list B (interference control), short-term free memory, short-term guided memory or with semantic keys, long-term free memory, long-term guided memory or with semantic keys, and recognition correct responses were used as performance parameters. Guided memory refers to the trials in which words are reproduced according to semantic categories (e.g., fruits, clothes or tools).

(iii) Revised Strategy Application Test (R-SAT) contains three paper-and-pencil activities, all of which include visual, motor, and linguistic abilities, specifically, figure tracing, sentence, assigned a weighted value, summed, divided by the total possible score for each category, and multiplied by 100. R-SAT allows to measure the strategic planning and self-regulation [70]. The task includes three simple activities, e.g., figure tracing, sentence copying, and object numbering. Activities are presented in two different stacks of 120 items each one. Items differ in terms of their size (large, small) and time requirements (brief, medium, long). A large item scores 0 points, and a small item scores 100 points, where participants are instructed to get as many points as possible. In addition, items in which a face is displayed have to be avoided. The items are intermixed; nevertheless, the number of brief items decreases progressively within both stacks. As the execution time of the task is restricted to 10 min, the most efficient strategy is to complete brief items instead of longer ones. Therefore, the predisposition to complete items in the presented sequence has to be overcome. R-SAT further provokes an unstructured environment in the laboratory in which environmental cues and internal habits oppose the most efficient strategy, thus reproducing the real-life situations. At the end of the task, participants are asked about the strategy which, according to their appraisal, was optimal to get the maximal number of points [70]. Participants also have to mark in a separate sheet when they think a minute has been spent (control marks) without using any watch. Performance was indexed by the number of correct answers (brief items), errors (long items and faces), and control marks

(iv) Trail Making Test (TMT) [71, 72] evaluates processing speed, attention, and cognitive flexibility. The test, in which visual targets (numbers, letters) are presented on sheets of paper, includes the following tasks, all of which have to be executed as fast as possible: (1) visual scanning (cross out all number 3s on a page with different numbers), (2) number sequence (connect the numbers 1 to 16 in sequential order), (3) letter sequence (connect the letters A to P in alphabetic order), (4) switching (connect numbers and letters in alternating order, e.g., 1, A, 2, and B), and (5) motor speed (trace a predefined path). In addition to execution time, the following kinds of errors were recorded: For condition 1: (1) omissions (when the participant fails to mark any 3) and (2) commissions (when the person marks a letter or a number other than 3); for the rest of conditions (2, 3, and 4): (3) sequence (connection of correct item with an incorrect one), (4) set loss (connection of items of different categories) and (5) time out (exceeding the time limit of 250 s).

2.3. Procedure. The study was conducted in one session, divided in two parts conducted on the same day. During the first part, a clinical psychologist took the patients' clinical

history, recorded sociodemographic data and medication use, and verified the inclusion and the exclusion criteria. Later, SCID interviews were carried out, and the questionnaires were fulfilled. In the second part, the neuropsychological battery was administered in the following order: ZMT, R-SAT, TAVEC (free recall), TMT, and TAVEC (second part). The tests were presented in this order to avoid the possible interference effect of the different cognitive domains, especially in verbal memory. Five breaking minutes was provided between each test. The study protocol was approved by the Ethics Committee for Human Research of the University of Jaén, and all participants provided written informed consent.

2.4. Statistical Analysis. In order to determine the optimal sample size based on expected effect sizes, the G∗Power 3.1.7 program was used [73]. Assuming an effect size of .75 and an alpha level of .05 and a beta error of 20% as a basis, a sample size from 21 participants per group appeared optimal. Comparisons between FMS patients and healthy individuals in clinical and demographic variables were performed using F-tests and χ^2-tests. Group differences in cognitive performance were analysed by means of multivariate analysis of variance (MANOVA). Age, years of education, and body mass index were entered as covariates in this analysis (MANCOVA). A second MANCOVA was performed with the purpose to determine the possible role of emotional (i.e., state and trait anxiety and depression) and clinical variables (i.e., insomnia and fatigue) in cognitive performance. Effect sizes are indicated by adjusted eta squared (n_p^2). Associations between social support questionnaire dimension scores and neuropsychological test performance were evaluated in two steps, both restricted to the FMS group ($N = 64$). Firstly, at an exploratory level, Pearson correlations were computed. Secondly, multiple regression analyses were performed. Two blocks of variables were used as predictors in the analyses: (1) to control for the effects of age, body mass index, and years of education, these variables were entered simultaneously (enter method); (2) to determine social support predictive power for cognitive performance, the dimensions of the social support scales that showed significant correlations with the different neuropsychological parameters, in the exploratory analysis, were included (stepwise method) together with total and intensity of clinical pain (MPQ). The inclusion of clinical pain as a possible predictor lies in its relevance as one of the main explanatory mechanisms of cognitive deficits in FMS [7, 8, 26, 74, 75]. The SPSS software (version 22.0) was employed for data analysis (IBM Corporation, Armonk, NY).

3. Results and Discussion

Table 1 displays the sociodemographic and clinical data of both study groups. FMS patients displayed higher values for all clinical and emotional variables in comparison with healthy individuals (all ps < .0001). In addition, FMS patients displayed lower values for all social support variables compared to healthy individuals (all ps < .05, except financial assistance (SSB) ($p = .050$) and friends' support (SSB) ($p = .363$)).

3.1. Group Differences in Cognitive Performance. Table 2 shows neuropsychological test scores of FMS patients and healthy individuals and statistics of the univariate group comparisons. The MANOVA for the neuropsychological battery scores showed a multivariate group effect ($F\,[26, 69] = 3.39$, $p < .0001$, $n_p^2 = .56$). Moreover, this multivariate group effect ($F\,[26, 66] = 2.96$, $p < .0001$, $n_p^2 = .54$) remains significant in the MANCOVA (using as covariables the age, BMI, and years of education). Additionally, the second MANCOVA (including as covariable state and trait anxiety, depression, fatigue, and insomnia) showed that the multivariate group effect ($F\,[26, 64] = 1.71$, $p = .042$, $n_p^2 = .41$) remains significant. On purpose, also at the multivariate level, state anxiety ($F\,[26, 64] = 1.41$, $p = .132$, $n_p^2 = .37$) and insomnia ($F\,[26, 64] = .91$, $p = .599$, $n_p^2 = .27$) did not show any significant effect. By contrast, trait anxiety ($F\,[26, 64] = 2.18$, $p = .006$, $n_p^2 = .47$), depression ($F\,[26, 64] = 3.77$, $p < .0001$, $n_p^2 = 61$), and fatigue ($F\,[26, 64] = 1.90$, $p = .020$, $n_p^2 = .44$) exhibited a significant multivariate effect.

3.2. Correlations between Social Support and Cognitive Performance in FMS Patients. Table 3 displays correlations between social support dimensions and cognitive performance in FMS patients.

All SSB dimensions were positively associated with organization and planning abilities and strategic planning and self-regulation (total correct responses of ZMT and correct responses: short items of R-SAT). In addition, emotional support (SSB) and friends' support (SSB) were positively associated with verbal memory (list A: immediate free recall of TAVEC). Emotional support (SSB) was also positively associated with verbal memory (short-term guided memory of TAVEC). Practical assistance (SSB), socializing (SSB), and friends' support (SSB) were positively associated with strategic planning and self-regulation (control marks of R-SAT).

All SSB dimensions were also negatively associated with errors in organization and planning abilities and strategic planning and self-regulation tasks (error versions 1 and 2 of ZMT and error long items of R-SAT). Moreover, emotional support (SSB), practical assistance (SSB), socializing (SSB), financial assistance (SSB), and advice/guidance (SSB) were negatively associated with errors in strategic planning and self-regulation (error face items of R-SAT). Emotional support (SSB) was also negatively associated with processing time, attention, and cognitive flexibility (execution time 2: number sequence of TMT). Family support (SSB) was negatively associated with the time spending in organization and planning abilities (execution time version 2: ZMT). Practical assistance (SSB), socializing (SSB), financial assistance (SSB), and family support (SSB) were negatively associated with processing speed, attention, and cognitive flexibility (omission errors of TMT). All dimensions, except for family support (SSB), were negatively associated with processing speed, attention, and cognitive flexibility (sequence errors of TMT).

3.3. Results of Multiple Regression Analysis. Table 4 shows the significant results of the multiple regression analyses

Table 1: Sociodemographic and clinical variables and questionnaire scores in FMS patients ($N = 64$) and healthy individuals ($N = 32$) groups (M ± SD or number and %). Statistics of group comparisons are also included (F-test or χ^2-test).

	FMS patients	Healthy individuals	F or χ^2	p	η_p^2
Age	52.73 ± 7.89	51.13 ± 6.61	.99	.323	.01
Body mass index (BMI)	28.00 ± 5.03	26.06 ± 3.05	3.39	.069	.04
Education (years)	10.28 ± 4.30	12.00 ± 4.34	4.02	.050	.04
Antidepressant use (%)	53 (%)	5 (%)	40.27	<.0001	.65
Anxiolytic use (%)	50 (%)	5 (%)	34.06	<.0001	.60
Analgesic use (%)	53 (%)	3 (%)	47.34	<.0001	.70
Opiate use (%)	33 (%)	0 (0%)	25.14	<.0001	.51
Trait anxiety (STAI)	50.67 ± 10.61	26.13 ± 15.95	80.66	<.0001	.46
State anxiety (STAI)	23.20 ± 4.25	15.56 ± 11.65	21.91	<.0001	.19
Depression (BDI)	43.52 ± 13.56	14.28 ± 17.36	81.92	<.0001	.47
Fatigue (FSS)	52.45 ± 9.99	25.66 ± 16.10	100.51	<.0001	.52
Insomnia (OQSQ)	39.09 ± 11.10	14.16 ± 9.62	117.34	<.0001	.56
Total pain (MPQ)	79.23 ± 36.18	19.03 ± 25.23	71.11	<.0001	.43
Current pain intensity (MPQ)	3.64 ± 1.20	1.28 ± .73	104.13	<.0001	.53
Emotional support (SSB)	44.44 ± 36.00	64.47 ± 53.02	4.77	.031	.05
Practical assistance (SSB)	35.14 ± 22.50	49.19 ± 39.38	4.95	.029	.05
Socializing (SSB)	30.80 ± 18.70	43.03 ± 34.11	5.17	.025	.05
Financial assistance (SSB)	36.16 ± 24.74	49.38 ± 39.67	4.01	.050	.04
Advice/guidance (SSB)	50.34 ± 32.00	73.72 ± 58.52	6.42	.013	.06
Family support (SSB)	102.61 ± 61.95	174.59 ± 161.81	9.86	.002	.10
Friends' support (SSB)	78.16 ± 72.00	94.06 ± 95.22	.84	.363	.01

Note: STAI: State-Trait Anxiety Inventory; BDI: Beck Depression Inventory; FSS: Fatigue Severity Scale; OQSQ: Oviedo Quality of Sleep Questionnaire; MPQ: McGill Pain Questionnaire; SSB: SS-B Social Support Scale.

for the prediction of performance parameters, after controlling for the effects of age, years of education, and BMI. At this regard, related to the first model, socializing (SSB) was the main predictor of organization and planning abilities and strategic planning and self-regulation (total correct responses of ZMT and R-SAT and errors of both versions in the ZMT test). In addition, current pain intensity (MPQ) was the main predictor of organization and planning abilities; processing speed, attention, and cognitive flexibility; and verbal memory (execution time in the version 2 of ZMT, execution time 2: number sequence of TMT, and short-term guided memory of TAVEC). Moreover, financial assistance (SSB) was the main predictor of strategic planning and self-regulation (error long items and face items of R-SAT), whereas friends' support (SSB) was the principal predictor of strategic planning and self-regulation, verbal memory, and processing speed, attention, and cognitive flexibility (control marks of R-SAT, list A: immediate free recall of TAVEC and sequence errors of TMT). And family support (SSB) was the main predictor of processing speed, attention, and cognitive flexibility (omission errors of TMT).

Regarding the second models, current pain intensity (MPQ) was the main predictor of organization and planning abilities (total correct responses of ZMT and error version 2 of ZMT). Furthermore, advice/guidance (SSB) was the main predictor of errors in organization and planning abilities (error version 2 ZMT). Besides, practical assistance (SSB) was the main predictor of strategic planning and self-regulation and verbal memory (correct responses: short items of R-SAT, error face items of R-SAT, and list A: immediate free recall of TAVEC). Emotional support (SSB) was the main predictor of processing speed, attention, and cognitive flexibility (execution time 2: number sequence of TMT).

4. Discussion

The main objective of the current research was to analyse the effect of social support on the cognitive performance in FMS (including verbal memory, organization, strategic and planning abilities, self-regulation, processing speed, attention, and cognitive flexibility). The present results reaffirm the higher values of clinical and emotional symptoms (e.g., clinical pain, insomnia, fatigue, depression, and anxiety) in FMS compared to healthy individuals [3, 4, 6–8, 18]. Furthermore, the cognitive impairments in FMS (especially in verbal memory, organization and planning abilities, strategic planning, self-regulation, processing speed, attention, and cognitive flexibility) are confirmed in line with the available scientific evidence [3–8].

Table 2: Mean (±SD) of neuropsychological test scores of FMS patients ($N = 64$) and healthy individuals ($N = 32$) and statistics of the univariate group comparisons.

		FMS patients	Healthy individuals	F [4, 66]	p	n_p^2
ZMT	Total correct responses	12.13 ± 2.84	13.38 ± 2.49	3.43	.067	.04
	Execution time version 1	239.33 ± 127.90	179.06 ± 82.45	3.87	.052	.04
	Execution time version 2	159.34 ± 107.42	90.13 ± 50.32	7.91	.006	.08
	Error version 1	2.89 ± 1.96	1.94 ± 1.16	4.90	.029	.05
	Error version 2	.88 ± 1.06	2.22 ± 10.56	.80	.373	.01
TAVEC	List A (immediate free recall)	37.50 ± 9.98	46.31 ± 10.52	11.85	.001	.12
	List B (interference control)	3.53 ± 1.89	4.53 ± 2.00	3.82	.054	.04
	Short-term free memory	7.91 ± 3.43	10.44 ± 2.97	9.25	.003	.09
	Short-term guided memory	9.59 ± 2.73	10.84 ± 3.03	2.30	.133	.03
	Long-term free memory	8.80 ± 2.82	10.53 ± 3.20	4.96	.028	.05
	Long-term guided memory	9.19 ± 2.86	11.28 ± 2.84	8.10	.005	.08
	Recognition correct responses	9.28 ± 6.06	15.16 ± 1.51	24.95	<.0001	.22
R-SAT	Correct responses (short items)	44.22 ± 9.11	50.34 ± 7.50	13.52	<.0001	.13
	Error long items	4.95 ± 7.41	2.03 ± 2.40	4.97	.028	.05
	Error face items	1.61 ± 2.10	.44 ± .91	8.31	.005	.08
	Control marks	4.84 ± 2.26	6.41 ± 2.28	10.00	.002	.10
TMT	Execution time 1 (visual scanning)	80.03 ± 108.79	41.88 ± 13.31	3.42	.068	.04
	Execution time 2 (number sequence)	98.55 ± 63.96	60.31 ± 25.71	7.42	.008	.08
	Execution time 3 (letter sequence)	105.34 ± 70.65	66.91 ± 30.18	5.61	.020	.06
	Execution time 4 (switching)	231.05 ± 130.98	119.16 ± 51.34	18.24	<.0001	.17
	Execution time 5 (motor speed)	140.91 ± 58.38	98.09 ± 49.73	7.77	.006	.08
	Omission errors	.22 ± .68	.06 ± .25	1.50	.224	.02
	Commission errors	.03 ± .18	.00 ± .00	1.76	.188	.02
	Sequence errors	2.28 ± 3.09	.91 ± 1.51	4.25	.042	.05
	Set loss errors	3.05 ± 5.65	.31 ± .69	6.53	.012	.07
	Time out errors	10.91 ± 10.80	.78 ± 2.06	22.05	<.0001	.20

Note: ZMT: Zoo Map Test; TAVEC: Verbal Learning Test; R-SAT: Revised Strategy Application Test; TMT: Trail Making Test. All execution times are indicated in s. $^{*}p < .05$. $^{**}p < .01$.

Results of the second MANCOVA further reveal that group differences in cognitive performance seem to be independent of emotional and clinical symptoms [76, 77]. At this regard, Roldán-Tapia et al. [76] pointed out that cognitive impairment in FMS patients could not be explained by the collateral effects of such pathologies, because cognitive profiles were different and appeared from the onset of the disease notion also supported by the research of Simos et al. [77].

Refer to social support, FMS patients displayed lower values for all social support variables compared to healthy individuals [37, 38], especially in the socializing area. Nevertheless, there was no any significant difference in financial assistance and friends' support between both groups. Although more studies are required to firm clear conclusions, some research has suggested that FMS patients seem to be more likely to include their physicians as intimate members of their social networks and less willing to take initiative in meeting new people than patients with rheumatoid arthritis (RA) [78]. This may explain the lower observed social support values associated with the socializing sphere in FMS patients. This finding also reinforces the significant role of health professionals in FMS [79]. Another explanation might relapse in the fact that FMS patients usually perceive little social support at work due to the lack of social knowledge and awareness on the disease [80]. This lack of social support reduces personal relationships at work. This is influenced by the misunderstanding about the lower effectiveness of FMS patients at work [80]. At the same time, the problems in the professional field and the need to stop working in some cases because of the illness symptoms might worsen the social isolation. It is well known that staying in the workplace prevents FMS patients from social isolation and reduces the negative impact of the disease on their quality of life [81]. Therefore, it is necessary to design programs

Table 3: Correlations between social support measured by SSB and cognitive performance in FMS patients ($N = 64$).

		Emotional support (SSB)	Practical assistance (SSB)	Socializing (SSB)	Financial assistance (SSB)	Advice/guidance (SSB)	Family support (SSB)	Friends' support (SSB)
ZMT	Total correct responses	.367**	.387**	.421**	.396**	.368**	.360**	.282*
	Execution time version 1	.050	-.009	.046	.039	.063	.012	.118
	Execution time version 2	-.124	-.203	-.192	-.181	-.157	-.257*	-.047
	Error version 1	-.385**	-.419**	-.438**	-.434**	-.371**	-.326**	-.364**
	Error version 2	-.373**	-.385**	-.425**	-.395**	-.377**	-.331**	-.299*
TAVEC	List A (immediate free recall)	.274*	.101	.143	.129	.158	-.023	.269*
	List B (interference control)	.138	.079	.068	.087	.083	.045	.071
	Short-term free memory	.223	.138	.163	.162	.131	.094	.203
	Short-term guided memory	.247*	.150	.155	.181	.107	.016	.163
	Long-term free memory	.186	.189	.197	.194	.136	.049	.232
	Long-term guided memory	.162	.068	.111	.090	.027	-.064	.124
	Recognition correct responses	.134	.118	.094	.137	.159	.202	.095
R-SAT	Correct responses (short items)	.401**	.404**	.460**	.411**	.419**	.312*	.370**
	Error long items	-.362**	-.343**	-.376**	-.391**	-.366**	-.312*	-.307*
	Error face items	-.348**	-.318*	-.344**	-.384**	-.338**	-.241	-.235
	Control marks	.094	.249*	.252*	.237	.225	.139	.258*
TMT	Execution time 1 (visual scanning)	.003	.190	.217	.149	.072	.023	.124
	Execution time 2 (number sequence)	-.257*	-.217	-.224	-.223	-.189	-.188	-.131
	Execution time 3 (letter sequence)	-.230	-.165	-.171	-.182	-.153	-.110	-.141
	Execution time 4 (switching)	-.220	-.226	-.233	-.200	-.204	-.156	-.139
	Execution time 5 (motor speed)	-.067	-.166	-.130	-.113	-.126	-.166	-.066
	Omission errors	-.190	-.262*	-.251*	-.252*	-.204	-.356**	-.120
	Commission errors	-.098	-.122	-.129	-.118	-.115	.029	-.197
	Sequence errors	-.254*	-.262*	-.306*	-.293*	-.270*	-.116	-.308*
	Set loss errors	-.174	-.175	-.201	-.217	-.186	-.169	-.122
	Time out errors	-.134	-.227	-.232	-.169	-.177	-.194	-.104

Note: ZMT: Zoo Map Test; TAVEC: Verbal Learning Test; R-SAT: Revised Strategy Application Test; TMT: Trail Making Test. *$p < .05$. **$p < .01$.

Table 4: Significant results of the second block (step-wise method) of the multiple regression analysis for the prediction of neuropsychological test scores by clinical pain and social support variables in FMS patients ($N = 64$).

		M	Predictors	β	Δr^2	t	p
ZMT	Total correct responses	1	Socializing (SSB)	.43	.18	4.20	<.001
		2	Socializing (SSB)	.43	.08	4.52	<.001
			Current pain intensity (MPQ)	-.30		-3.06	.003
	Execution time version 2	1	Current pain intensity (MPQ)	.30	.09	2.65	.010
	Error version 1	1	Socializing (SSB)	-.40	.15	-3.77	<.001
		2	Socializing (SSB)	-1.37	.05	-3.07	.003
			Advice/guidance (SSB)	1.00		2.24	.029
	Error version 2	1	Socializing (SSB)	-.39	.15	-3.50	.001
		2	Socializing (SSB)	-.39	.07	-3.68	.001
			Current pain intensity (MPQ)	.28		2.49	.015
TAVEC	List A (immediate free recall)	1	Friends' support (SSB)	.29	.08	2.53	.014
		2	Friends' support (SSB)	.74	.09	3.79	<.001
			Practical assistance (SSB)	-.55		-2.79	.007
	Short-term guided memory	1	Current pain intensity (MPQ)	-.34	.11	-2.89	.005
R-SAT	Correct responses (short items)	1	Socializing (SSB)	.47	.22	4.38	<.001
		2	Socializing (SSB)	1.44	.05	2.97	.004
			Practical assistance (SSB)	-.99		-2.05	.045
	Errors (long items)	1	Financial assistance (SSB)	-.38	.14	-3.15	.003
	Errors (face items)	1	Financial assistance (SSB)	-.39	.15	-3.21	.002
		2	Financial assistance (SSB)	-1.67	.08	-3.10	.003
			Practical assistance (SSB)	1.31		2.43	.018
	Control marks	1	Friends' support (SSB)	.26	.07	2.09	.041
TMT	Execution time 2 (number sequence)	1	Current pain intensity (MPQ)	.34	.10	3.21	.002
		2	Current pain intensity (MPQ)	.36	.05	3.53	.001
			Emotional support (SSB)	-.23		-2.23	.030
	Sequence errors	1	Friends' support (SSB)	-.31	.10	-2.57	.013
	Omissions errors	1	Family support (SSB)	-.36	.12	-2.89	.005

Note: Model (M), standardized β, change in r^2 (Δr^2), t, and p are indicated. Results of the first block, which served to control for the effects of age, education, and BMI, are not reported. ZMT: Zoo Map Test; TAVEC: Verbal Learning Test; R-SAT: Revised Strategy Application Test; TMT: Trail Making Test.

to increase the training and sensitization of relatives and friends of FMS patients, as well as of health providers and general population [79].

Related to social support and cognitive performance in FMS patients, all studied SBB dimensions (e.g., emotional support, practical assistance, socializing, financial assistance, advice/guidance, family support, and friends' support) were positively related to a better cognitive performance (higher levels of correct responses) in the organization and planning abilities (ZMT) and strategic planning and self-regulation tasks (R-SAT). Similarly, practical assistance, socializing, and friends' support (SSB) were positively linked to higher strategic planning and self-regulation performance (R-SAT). Moreover, emotional support and friends' support were positively associated with a better performance in the verbal memory domain (TAVEC).

In addition, the social support was not only positively related with the number of correct responses of neuropsychological test but also was associated with a reduction of the processing speed. In fact, family support was negatively associated with execution time version 2 of ZMT, which measures organization and planning abilities, whereas emotional support was also negatively linked to execution time 2 (number sequence) of TMT which assesses processing speed, attention, and cognitive flexibility.

Regarding the number of errors, social support also might be involved in the reduction of these one. In this sense, practical assistance, socializing, financial assistance, advice/guidance, family support, and friends' support were negatively associated with errors in organization and planning abilities tasks and strategic planning and self-regulation tasks (errors of both versions in ZMT and error long items of R-SAT, respectively). Additionally, emotional support, practical assistance, socializing, financial assistance, and advice/guidance were negatively related to error face items of R-SAT, which measure strategic planning and self-regulation performance. And all dimensions of the social support scale were negatively associated with different errors of TMT, which assesses processing speed, attention, and cognitive flexibility.

Moreover, socializing was the main predictor of organization and planning abilities and strategic planning and self-regulation (total correct responses of ZMT and R-SAT and errors of both versions in the ZMT test). One possible explanation can be the positive effect of social support in pain processing at the subjective behavioural level and at the central nervous system level of FMS patients [41]. In addition, an analgesic effect of social support has been reported in healthy population, even without verbal or physical contact [42]. Similarly, it is possible that socializing might have an analgesic effect on pain (one of the main explanatory factors of cognitive impairments in FMS [8, 74], which indirectly improve the cognitive performance of patients). Otherwise, this analgesic effect of social support in pain processing might be also favouring the cognitive processing areas. It is well known that pain is an attention-demanding stimulus that recruits brain areas also relevant for cognitive processing [8, 74, 82]. It would be interesting to assess the possible mediating role of social support in the relation between pain and cognitive performance in FMS.

Our research reveals the positive effect of social support especially in verbal memory, organization and planning abilities, strategic planning, self-regulation, processing speed, attention, and cognitive flexibility. Results are in line with previous studies suggesting a positive association between social support and health outcomes in FMS patients [34, 39–41].

Additionally, emotional support showed to be the social support's variable that account for the majority of associations with the cognitive parameters, suggesting, among all SBB dimensions, a special role of it in FMS cognition. This finding is according to previous studies that pointed out that social support, and particularly emotional support, was associated with decreases in health care use within a primary care setting [83]. Unfortunately, although the previous mentioned research is very meaningful, no cognitive aspects were evaluated, being this study the first one on this issue. Therefore, the role of social support on cognitive performance in FMS can be considered a research gap that needs to be overcome to better understand the disease and provide FMS patients a more holistic and personalized treatment. In addition, emotional support would need also to be promoted based on the transdiagnostic perspective which insist on the relevance of emotional and social aspect of the illnesses apart from treat on the disease symptoms [31, 32]. Furthermore, based on previous findings [33], it might be hypothesized the relevance of improving social support, especially emotional support, in order to personalized FMS treatment.

Nonetheless, despite the role of social support in FMS needs to continue being studied, our results may be explained based on previous research in other populations, which point out that social support is a significant factor involved in the maintenance or enhancement of mental health and cognitive functioning in general (e.g., elderly people [43–49], caregivers [50], and academic performance [51–53, 84]). In this regard, it has been noted that social relationships, especially social activities and networks, have a protective effect against greater cognitive decline in older adults [85, 86]. Cotton et al. [87] explored the neural correlates of social support in older adults and reported the existence of a gray matter network related to social support (including prefrontal, hippocampal, amygdala, cingulate, and thalamic regions), which was in turn associated with memory and executive function. Cacioppo and Hawkley [88] further showed that this gray matter network associated with tangible social support was composed by regions previously linked to memory, executive function, aging, and dementia. Authors concluded that more longitudinal research of the interrelationships between social support, brain structure, and cognition was needed and advised of the importance of strengthen social support as a new path toward improving cognition in aging [88]. Moreover, research and interventions in this field would help to better understand the contribution of poor psychosocial functioning (e.g., social support) and unsatisfactory relationships in the origin and maintenance of chronic pain [40], especially in FMS.

Likewise, social isolation (e.g., loneliness) has been proposed as a risk factor for and may contribute to poorer overall cognitive performance, faster cognitive decline, poorer executive functioning, and higher negativity and depressive cognition [88]. Loneliness has exhibited a mediating role between social isolation and subjective cognitive impairment in older people [89–92], including older immigrants [89]. The association between loneliness and subjective cognitive deficits has been well-stablished [93, 94]. On purpose, social support, indeed, is known to play a critical role in the detection and treatment of mild cognitive impairment [95–97].

Loneliness has been proposed as a risk factor of dementias, especially Alzheimer disease [96–99]. In general, higher levels of social engagement have been related to greater levels of cognition across the lifespan, association that seems to be more significant in populations at risk of cognitive impairment [100]. The research in other populations confirmed the protective role of social support in cognitive performance, although the exact nature of this association remains unclear [46, 85, 86, 89, 93, 94, 100]. Previous research also highlights the need of promoting psychosocial interventions and related public health strategies to enhance neurocognitive health, increasing specific forms of social support [94, 100–102], such as supportive listening [102]. In fact, social support group interventions in people with dementia and mild cognitive impairment exhibited psychological benefits, specifically, a reduction of depression and an improvement of the quality of life and the self-esteem [103]. Considering the prevalence and negative impact of cognitive deficits in FMS, it is worth keep exploring the effect of social support at this regard.

The main limitation of our study was its cross-sectional design, which does not allow for the establishment of causal associations. Longitudinal studies are required to better understand the association between social support and cognitive impairment in FMS. It also would be interesting to compare FMS patients with other clinical samples (e.g., RA patients), to determine if the observed association between social support and better cognitive performance is or not specific of FMS but can be extended to other pain conditions. Strengths of the study included the novelty and clinical relevance of the results, the statistical control of

sociodemographic variables, and the determination of the sample through the G∗Power program to ensure the statistical power of the analysis. Moreover, social support in FMS has been evaluated conforming the recommendation of not only to consider the amount of support reported by the patients but also the type of support they received [40].

Due to the relevance of cognitive deficits in FMS [3–8, 104], a routine screening for cognitive impairments in these patients should be included in both diagnosis and treatment [105]. Moreover, taking the biopsychosocial perspective into account, it must be also mandatory to explore and promote the social support network of these patients in order to prevent the worsening of cognitive performance and subsequent health-related quality of life. It is necessary to continue researching the mechanism through the social support benefit the cognitive performance in chronic pain patients, including FMS, and confirming the protective role of social support in this kind of disorders. It might be a promising future line of research and clinical practice to improve the quality of life of these patients.

Furthermore, the design of psychoeducation programs and intervention programs to improve the social support of FMS cannot only positively influence on patient's status but also in the health system as proposed by previous studies [106, 107]. In fact, some researches showed that one's social network was positively linked to health status and negatively related to health care use, reducing prescriptions, laboratory tests, and visits to a nurse, nurse practitioner, and/or physicians' assistant [107]. Nonetheless, it is important to highlight that for stablishing an effective social support network for FMS patients, it is necesary to provide relatives and friends with diseasse information for a better understanding. Therefore, it is important to also involve them in the psychoeducation programs [108]. At this regard, Kool et al. [109] analysed if social support and invalidation (lack of understanding and discounting by others) were differently related to physical and mental health. They studied 1455 patients with different chronic pain diseases, such as FMS, RA, ankylosing spondylitis, and osteoarthritis [109]. Their results confirmed that both invalidation and social support were linked to patients' mental health, but only invalidation was significantly related to patients' physical health, suggesting the relevance to include social support and invalidation in programs to improve health of patients with rheumatic diseases [109]. Besides, the therapeutic adherence in some FMS programs seems to be associated with some factors such as lack of motivation and lack of social support, among others [110]; therefore, enhancing the social support of these patients might have a positive impact in their treatments.

5. Conclusions

This is the first study exploring the influence of social support in cognitive performance of FMS patients. FMS displayed lower values in all social support variables compared to healthy individuals, especially in the socializing area, which was the main predictor of organization and planning abilities, and strategic planning and self-regulation of these patients (total correct responses of ZMT and R-SAT and errors of both versions in the ZMT test). All dimensions of social support exhibited a positive impact on verbal memory, organization and planning abilities, strategic planning, self-regulation, processing speed, attention, and cognitive flexibility. Social support dimensions not only positively impact on the number of correct responses and processing speed of neuropsychological test but also seem to reduce the number of errors. Improving the social networks of FMS patients might help to ameliorate their health status and cognitive performance while simultaneously reducing health care utilization. It is vital to involve not only FMS patients but also their relatives and friends along with health care workers and general population, in order to improve the FMS knowledge and sensitize people to the importance of social support in this disease.

Data Availability

The data presented in this study are available on request from the corresponding author.

Ethical Approval

The procedure followed the general criterion of the local ethics committee, based on the Helsinki Declaration principles, and was approved by the Bioethics Committee of the University of Jaén.

Conflicts of Interest

All the authors declare that they have no conflict of interest derived from the outcomes of this study.

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Research Article

The Mediating Role of Depression and Pain Catastrophizing in the Relationship between Functional Capacity and Pain Intensity in Patients with Fibromyalgia

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Background. Fibromyalgia syndrome (FMS) is a chronic musculoskeletal pain condition characterized by widespread pain, sleep problems (i.e., insomnia and unrefreshing sleep), fatigue, cognitive, and emotional difficulties. Although pain has been proposed the factor mostly impacting in the FMS patients' function, emotional and psychological FMS-associated factors are also known to exert a negative impact in quality of life and functional capacity. Nonetheless, the relationship between these factors and functional limitations in FMS patients is considered to be complex and not clearly defined. Therefore, the present study is aimed at assessing the associations between FMS functional capacity, FMS symptoms (pain, fatigue, insomnia, depression, and state and trait anxiety), and associated psychological factors such as pain catastrophizing, as well as the possible mediating role of these latter in the relationship between pain and FMS functional capacity. *Method*. 115 women diagnoses with FMS completed a set of self-administered questionnaires to evaluate the clinical and psychological variables of the study. *Results*. FMS functional capacity was positively associated with the majority of FMS symptoms except state anxiety. Regression analyses confirmed a greater prediction for FMS functional capacity by depression, fatigue, and pain catastrophizing, in this sequence. Both, pain catastrophizing and depression were important factors mediating the association between clinical pain (total and intensity) and FMS functional capacity. *Conclusions*. Findings support a key role of pain catastrophizing and depression in the disability associated to pain in FMS. Treatment goals directed to lessen depression and pain catastrophizing levels should be promoted to reduce the impact of pain in FMS patients' daily function.

1. Introduction

Fibromyalgia syndrome (FMS) is a chronic musculoskeletal pain condition characterized by widespread pain, sleep problems (i.e., insomnia and unrefreshing sleep), fatigue, cognitive, and emotional difficulties [1]. The current diagnosis is based on the 2010 American Rheumatology Criteria (ARC). The 2010 ARC criteria, unlike the former criteria, have excluded the tender point count, being more focused on patient-reported somatic symptoms and cognitive difficulties such as memory and attentional impairments [2]. FMS affects between 2.5 and 5% of the worldwide population [1]. The prevalence is 10 times higher in women than in men [1], partially due to a gender bias in the diagnosis [3, 4]. Apart from its high prevalence, FMS entails a high cost for the social and health system, since patients with FMS attend more consultations—both at the level of general medicine and specialized cohort in pain medicine and psychology—and are subjected to more prescriptions and neuroimaging and laboratory tests than the rest of the population [5–9].

FMS is much better understood now than ever before. However, the aetiology remains undetermined. No tissue inflammation or damage explains pain in FMS, but central nervous system (CNS) pain amplification, at least in part, is proposed to be responsible for FMS symptoms [10–12], not only the somatic but also the emotional and cognitive [13–16].

Positive affect disturbances in the context of negative affect [17, 18], aversive emotions [19] and pain catastrophizing [20], also common in FMS, have been associated to the pain modulation impairments [16, 20, 21]. In this context, FMS patients with greater pain catastrophizing levels tend to be less able to distract themselves from pain [20]. Depression and pain catastrophizing have been demonstrated to modulate alterations in central nervous pain processing in FMS [16]. In fact, it has been suggested that FMS patients, in general, tend to selectively attend to information regarding the body and the environment in relation to pain; this phenomenon has been called "cognitive-emotional sensitization" and increase the perception of that pain [22].

Although disabling pain is the hallmark of FMS and the most examined and explanatory factor in relation to functional capacity in FMS patients [23–25], emotional disturbances are also known to reduce functioning in physical, psychological, and social spheres of daily living in FMS patients [26]. For instance, rumination component of pain catastrophizing and depression has been factors directly associated with functional limitations in FMS [23, 27]. Altogether, the aforementioned factors increase the intensity and severity of pain symptoms and cause a great negative impact in functional capacity and quality of life [17, 28–32]. Furthermore, between the clinical FMS symptoms, fatigue has been thought to be one of the most concerning affecting functional's impact of FMS disease [33, 34], even producing intense sedentary behaviours by limiting the ability to carry out daily routines [34, 35].

Despite the last, the relationship between psychological cognitive processes, FMS symptomatology, and functional limitations is considered to be complex [27]. Furthermore, although numerous treatments are available for managing FMS symptoms, the conventional medical therapies that target this pathology produce limited benefits [36]. Regardless the empirical support of the relevance of the emotional and psychological factors in FMS, intervention protocols remain largely pharmacological [36]. Therefore, more comprehensive research analysing the factors mediating the association between pain and FMS functional limitations might be especially important for formulating shared and realistic FMS treatment goals.

Given the aforementioned close relationship between pain and FMS functional capacity as well as between psychological cognitive processes such as pain catastrophizing, affect disturbances (e.g., depression), fatigue and FMS functional capacity, and the necessity of a more comprehensive research in this regards, the present study is aimed at (1) exploring and analysing the association between FMS functional capacity, clinical variables (fatigue, pain, and insomnia), emotional symptoms (depression and anxiety), and psychological cognitive processes (pain catastrophizing); and (2) studying the possible mediating role of these clinical, emotional, and psychological factors on the relationship between pain and FMS functional capacity.

2. Materials and Methods

2.1. Participants. In total, 115 women with FMS, recruited from the Fibromyalgia Association of Jaén (AFIXA; Spain), participated in this cross-sectional study. All participants were examined by a rheumatologist and met the 2010 American College of Rheumatology criteria for FMS [1]. Exclusion criteria included the presence of metabolic abnormalities, neurological disorders, drug abuse, and severe somatic (e.g., cancer) or psychiatric (e.g., psychotic) diseases.

2.2. Instruments and Measures. A semistructured interview was used for obtaining the patients' clinical history and demographic data. The diagnosis of possible mental disorders was assessed by the Structured Clinical Interview for Axis I Disorders of the Diagnostic and Statistical Manual for Mental Disorders (SCID, [37]). In addition, the following self-report questionnaires were administered.

2.2.1. Fibromyalgia Impact Questionnaire (FIQ). Developed by Burckhardt et al. [38], FIQ is a self-administered questionnaire composed of 10 items that evaluates functional domains affected in FMS patients (e.g., problems with muscle tasks, problems with work, pain, fatigue, stiffness, depression, anxiety, and morning tiredness). The first item of the FIQ (i.e., the physical impairment subscale) is further divided into several sub-items. The maximum possible score of each item is 10. The final score ranges in a continuum between 0 and 100. The lower score indicates greater functional capacity and lower quality of life. In the present study, the Spanish adaptation by Esteve-Vives et al. [39] was used. The internal consistency measured by Cronbach's α of the overall FIQ score is 0.82 [39].

2.2.2. McGill Pain Questionnaire (MPQ). Developed by Melzack [40], MPQ is a 73-item questionnaire that allows for quantification of the pain multidimensional experience. MPQ consists of a ranking of pain descriptors (on an ascending intensity scale) corresponding to the following categories: sensory, miscellanea, affective, and evaluative pain. In the current study, the global MPQ score or total pain (i.e., the sum of the different pain categories and total score between 0 and 167) and the current pain intensity assessed via a 10 cm visual analogue scale (VAS) were used from the Spanish adaptation by Lázaro et al. [41]. Higher score indicates higher levels of pain. The Cronbach's α value for total pain is 0.74 [41].

2.2.3. State-Trait Anxiety Inventory (STAI). Original version is developed by Spielberger et al. [42]. This inventory assesses anxiety in adults differentiating between state anxiety (temporary levels of anxiety) and trait anxiety (longstanding anxiety levels; considered a personality trait). Each condition (i.e., state anxiety and trait anxiety) is measured by 20 items in a 4-point Likert scales. The score ranges between 0 and 60. Higher scores indicate higher levels of anxiety. The Spanish adaptation by Spielberger et al. [43] was applied in the present study. The Cronbach's α values are 0.93 for the state anxiety and 0.87 for the trait anxiety scales [43].

2.2.4. Beck Depression Inventory (BDI). Developed by Beck et al. [44], this 21-item self-reporting scale is applied for assessing the severity of depression symptoms in psychiatric and general populations. Each of the 21 items scores in a 4-point Likert scales ranging from absence of symptoms and

severe symptoms. Total score ranges from 0-63. Scores of 20–28 refer to moderate depression. Severe depression is diagnosed with scores of 29-63. Higher score indicates higher severity form of depression. The Spanish adaptation by Vázquez and Sanz [45] was applied. The Cronbach's α is 0.95 [45].

2.2.5. Fatigue Severity Scale (FSS). Developed by Krupp et al. [46], this unidimensional scale measures the impact and severity of fatigue (lack of mental and/or physical energy). FSS is composed by 9 items. Each of the 9 items rates in a 7-point Likert scales. Item-related questions are based on the previous week. Total score ranges between 9 and 63. Higher score indicates higher severity of fatigue. Spanish adaptation by Bulbena et al. [47] was used. The Cronbach's α is 0.88 [47].

2.2.6. Oviedo Quality of Sleep Questionnaire (COS). Developed by Bobes et al. [48], the COS measures the quality of sleep. COS comprises 15 items. Three subscales can be obtained from COS: subjective sleep satisfaction (scoring in a 7-point Likert scales), insomnia, and hypersomnia (both scoring in a 5-point Likert scales). Insomnia subscale of the COS, comprising of 9 items, was used in the study. The insomnia score ranges between 4 and 45. Higher score is indicative of higher insomnia levels. The Cronbach's α is 0.88 [48].

2.2.7. Coping Strategies Questionnaire (CSQ). Original version is developed by Rosenstiel and Keefe [49]. CSQ is a self-administered instrument that includes 39 items in a 6-point Likert scales and assesses the frequency of the use of adaptative and maladaptive pain coping strategies. This instrument was used to evaluate pain catastrophizing. The pain catastrophizing subscale score ranges between 0 and 36. Higher score is indicative of greater tendency to catastrophizing to cope with pain. The Spanish adaptation by Rodriguez et al. [50] was applied. The Cronbach's α for pain catastrophizing is 0.89 [50].

2.3. Procedure. The G∗Power 3.1.7 program [51] was used within the purpose to stablish the optimal sample size for the correlation and regression analyses. Assuming an alpha level of 0.05, an effect size of 0.50, and a Beta error of 5%, a sample size of 34 participants arose as optimal. The sample size selected was also optimal for the mediation analysis. In single models with one mediator, as in the present, the standard error is accurate for sample sizes of at least 50 [52–54]. The study was conducted in two sessions that took place in the same day. In the first session, a clinical psychologist recorded the sociodemographic data, patients' clinical history, and medication use, assessed the exclusion and inclusion criteria, and performed the SCID interview. During the second session, the questionnaires were fulfilled in a counterbalanced order to avoid the effect of fatigue. Participant details were blinded by a code. The Ethics Committee for Human Research of the University of Jaén approved the study protocol, and all participants provided written informed consent.

2.4. Statistical Analysis. First, descriptive analyses were conducted. Pearson correlations between Fibromyalgia Impact Questionnaire (FIQ) score and the clinical and emotional variables measured were computed and tested for significance in an exploratory analysis. Second, multiple regression analyses were performed. Two blocks of variables were entered as predictors in the analyses: (1) age, educational level, and body mass index (simultaneously; enter method) and (2) questionnaire scales, which showed significant correlations with FIQ score in the preceding exploratory analysis (stepwise method). Mediation analysis was performed using the PROCESS macro for SPSS. The mediator variables were determined based on the regression results, and FIQ score was taken as the dependent variable. Moreover, to ensure the sturdiness of the analyses, confidence intervals from bootstrapping estimation techniques were used. For a significant mediation effect, the limits of the confidence interval do not include the 0 value [55, 56]. Mediation analysis fulfilled the assumptions of significant correlations (1) between predictor and dependent variables, (2) between predictor and mediation variables, and (3) between mediation and dependent variables [55, 56]. A total of 5000 bootstrap resamples were used to generate bias-corrected 95% CIs for the indirect effect.

3. Results and Discussion

3.1. Participants' Demographic and Clinical Data. Table 1 displays the participants' demographic and clinical data.

3.2. Associations between Fibromyalgia Impact Questionnaire Scores and the Emotional and Clinical Variables Measured. FIQ scores were positively associated with trait anxiety ($r = 0.432$, $p \leq 0.001$), depression ($r = 0.510$, $p \leq 0.001$), fatigue ($r = 0.315$, $p \leq 0.001$), insomnia ($r = 0.368$, $p \leq 0.001$), total pain ($r = 0.280$, $p = 0.002$), pain intensity ($r = 0.372$, $p \leq 0.001$), and pain catastrophizing ($r = 0.453$, $p \leq 0.001$). No associations were observed for state anxiety ($r = 0.050$, $p = 0.598$), body mass index ($r = 0.054$, $p = 0.566$), age ($r = 0.152$, $p = 0.105$), and educational level ($r = -0.019$, $p = 0.840$).

3.3. Results of Multiple Regression Analysis. Significant results of the multiple regression analyses, with respect to the prediction of FIQ score, are presented in Table 2. After controlling for the effects of age, educational level, and body mass index in the first block, depression was the strongest (positive) predictor of FIQ score, explaining the 29% of the variance. Regarding the second regression model, depression followed by fatigue was positively related to FIQ score. Regarding the third regression model, depression, fatigue, and pain catastrophizing (in this sequence) were positively related to FIQ score.

3.4. Results of Mediation Analysis. Depression and pain catastrophizing were significant mediators of the relation between clinical pain (total and intensity) and fibromyalgia capacity (FIQ score). Clinical pain, not only the total but also the intensity (assessed via VAS), increases the levels of depression and pain catastrophizing, provoking a higher

Table 1: Mean (M) and standard deviation (SD) of participants' demographic and clinical data.

	$n = 115$	
	M	SD
Age	51.98	8.23
Body mass index	28.15	2.79
Educational level	9.82	4.00
State anxiety (STAI)	26.55	9.38
Trait anxiety (STAI)	44.09	12.37
Depression (BDI)	33.70	17.10
Fatigue (FSS)	51.12	11.04
Insomnia (COS)	34.91	10.51
Pain intensity (VAS)	5.65	2.51
Total pain (MPQ)	68.70	35.81
Pain catastrophizing (CSQ)	21.63	9.78
Fibromyalgia impact (FIQ)	70.20	16.29

Note. STAI: State-Trait Anxiety Inventory; BDI: Beck Depression Inventory; CSQ: Coping Strategies Questionnaire; FIQ: Fibromyalgia Impact Questionnaire; MPQ: McGill Pain Questionnaire; COS: Oviedo Quality of Sleep Questionnaire; FSS: Fatigue Severity Scale; VAS: Visual Analogue Scale.

negative impact of FMS disease. No mediation effects were found for fatigue (FSS). Further details are provided in Table 3 and Figure 1.

4. Discussion

The present study is aimed at comprehensively assessing the association between FMS functional capacity (measured by FIQ) and FMS clinical (fatigue, insomnia and clinical pain) and emotional (anxiety and depression) symptoms and psychological cognitive processes (pain catastrophizing), as well as the possible mediating role of these factors on the association between pain and functional capacity of FMS patients.

FMS patients exhibited similar levels of anxiety, depression, clinical pain, fatigue, insomnia, and pain catastrophizing than previous studies (e.g., [15, 28, 29, 57–61]).

Consistent with our predictions and previous findings, correlation analyses indicated significant positive associations between FMS functional capacity, the FMS symptoms (except state anxiety), and pain catastrophizing (e.g., [23–27, 33, 34]). Depression and anxiety scores have been previously related to higher FIQ score, that is, lower FMS functional capacity (e.g., [62]). The present findings underscore the latter. Though it should not overlook, no significant associations between state anxiety and FMS functional capacity were observed in the present study; which may reflect a specific influence of long-lasting anxiety levels—personality trait—versus temporary anxiety levels in FMS functional capacity.

The mean body mass index in the FMS patients' sample of this study was 28.15 kg/m^2, which indicates obesity degree in level I [63]; despite the high mean body mass index, this was not related with functional impairments. No significant associations were observed between FMS functional capacity and body mass index. These findings are not in line with previous notions about the contribution of obesity (or elevated body mass index) in FMS severity [64–66], but on the contrary with more recent evidence that does not find a significant association between body mass index and both self-report and performance-based physical functioning [67]. The same occurred with educational level, questioning previous findings revealing a positive impact of education level on the course of the FMS, and considering it as a protective factor for FMS [68].

Regression analyses confirmed a greater prediction for FMS functional capacity by depression, fatigue, and pain catastrophizing, in this sequence. The lack of FMS functional capacity prediction by pain intensity—oppositely to previous studies—may reside in the measuring method used, the MPQ (in the present study) vs. others such as the Brief Pain Inventory (e.g., [69]). Nonetheless, although pain intensity did not account for the prediction of FMS functional capacity as reported in previous research [23–25, 69], the objective of the present study was to explore the mediating impact of clinical, emotional, and psychological factors and also consider to impact on FMS functional capacity, on the well-stablished relation between pain and FMS functional capacity [23–25]. Mediation analysis to this regard has shown that greater levels of pain catastrophizing and depression were significant mediators of the relationship between pain (both pain intensity and total pain) and FMS functional capacity. Similarly, Paschali et al. [69] observed a significant indirect effect of pain catastrophizing on the relationship between pain intensity and FMS functional capacity—also assessed by FIQ revised version.

The tendency to catastrophizing has been proposed to interact with attention-resource allocation and represent a mechanism of chronic pain exacerbation and/or maintenance [20] and may be mediated by preference for fatigue-avoidance goals [34]. Present findings expand this notion. Catastrophizing seems not only exacerbate pain, as proposed by previous research [20], but also intensify the association between pain and FMS functional capacity. It is important note that although there exist studies that confront this assumption; for instance, Lami et al. [70], though found significant associations between FMS disability and pain catastrophizing, not observed a significant mediation effect of pain catastrophizing in the relationship between pain and FMS impact; pain catastrophizing anywise seems to be an important variable contributing to reduced functioning in FMS [69]. To sum up, the findings, from the mediation analysis, support the strong association between negative states (pain catastrophizing and depression) in FMS, the greater intensity and severity of pain symptoms and negative impact on function/quality of life [17, 28–32]; therefore, also the vicious circle that occurs between all these variables.

Considering these results, it is plausible to propose that reducing pain catastrophizing and depression might improve the disability associated to pain in FMS. Treatment goals directed to lessen pain catastrophizing and depression levels should be promoted to reduce the impact of pain in FMS patients' daily function. Indeed, in a recent study, pain catastrophizing has been put forwarded as a potential prognostic factor for rehabilitation associated changes in pain

Table 2: Regression analysis for the prediction of FIQ score by the emotional and clinical variables evaluated.

Dependent variable	Model	Predictor	β	r^2	t	p
FIQ	1	Depression (BDI)	0.512	0.285	6.33	≤0.001
	2	Depression (BDI)	0.480	0.345	6.12	≤0.001
		Fatigue (FSS)	0.250		3.16	0.002
	3	Depression (BDI)	0.358	0.379	3.88	≤0.001
		Fatigue (FSS)	0.247		3.20	0.0002
		Pain catastrophizing (CSQ)	0.221		2.40	0.018

Note. BDI: Beck Depression Inventory; CSQ: Coping Strategies Questionnaire; FIQ: Fibromyalgia Impact Questionnaire; FSS: Fatigue Severity Scale.

Table 3: Results of mediation analysis of the predictors of FIQ score.

Independent variables	Mediator variables	Effect	SE	p	Boot LLCI	Boot ULCI
Fibromyalgia impact (FIQ)						
Total clinical pain (MPQ)	Depression (BDI)	0.212	0.052	≤0.001	0.119	0.320
	Pain catastrophizing (CSQ)	0.144	0.045	0.0001	0.066	0.240
Pain intensity (VAS)	Depression (BDI)	0.254	0.062	≤0.001	0.135	0.380
	Pain catastrophizing (CSQ)	0.149	0.042	≤0.001	0.073	0.240

Note: indirect effects are reported. SE: standard error; Boot: bootstrapping results with confidence intervals for the lower (LLCI) and upper limits (ULCI). All coefficients are standardized. BDI: Beck Depression Inventory; CSQ: Coping Strategies Questionnaire; FIQ: Fibromyalgia Impact Questionnaire; MPQ: McGill Pain Questionnaire; VAS: Visual Analogue Scale.

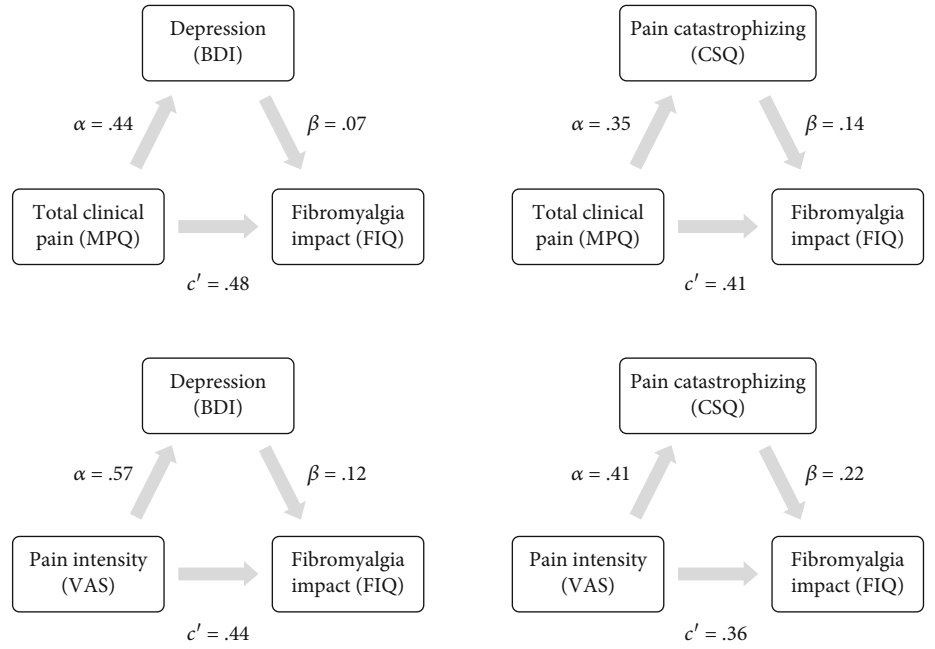

Figure 1: Statistical diagrams of partial mediation effects of depression and pain catastrophizing between clinical pain (total and intensity) and FIQ score. Note: all coefficients are standardized and significant at $p < 0.01$ ∗. BDI: Beck Depression Inventory; CSQ: Coping Strategies Questionnaire; FIQ: Fibromyalgia Impact Questionnaire; MPQ: McGill Pain Questionnaire; VAS: Visual Analogue Scale.

and self-rated physical function (this last in a less extent) in FMS and low back pain [71]. At this regard, acceptance and commitment therapy (ACT), which is considered an effective therapeutic approach for FMS [72, 73], has shown medium-large effect size in the reduction of the FMS impact, measured by the FIQ [74–77]. However, it is important to be cautious with the expected ACT benefits. Lami et al. [70], in an attempt to elucidate the association between pain acceptance and pain, did not find any correlation but a significant influence of pain acceptance on FMS disability. Similar results were observed by Esteve et al. [78].

Regarding depression, it has been proposed to be significantly predicted by pain catastrophizing in patients with persistent pain [79]. Likewise, depression association with pain is suggested to be mediated by pain catastrophizing [70]. So that, the indirect effect of depression in the relation

between pain and FMS functional capacity observed in the present study might be likely explained in some part by the associated pain catastrophizing. Notwithstanding, the relevance of emotional factors and coping strategies—supported by present findings—is in line with the increasing transdiagnostic perspective on emotional dysregulation [80]. Assuming depression and pain catastrophizing as part of the transdiagnostic perspective might be important for personalized behaviour management, which is essential for mood regulation as an alternative to pharmacologic treatment in FMS [81]. Most of the studies prompt to include the replacement of maladaptive coping strategies (especially pain catastrophizing) by others more adaptative and mature in the treatment of chronic pain (e.g., [71]); however, our findings go further and encourage a more integrated approach on the management of FMS, not only centred in coping strategies but also in the emotional disturbances—either because of their association with maladaptive coping.

The main limitations of our study pertain to its cross-sectional design which does not account for causal associations, and the no correction for type I errors. Moreover, given the apparent gender bias in the diagnosis of FMS [3, 4], it would be advisable for future research to include males in their samples for making enable gender differences' exploration. In addition, the analyses were based on self-reported measures, which could be highly sensitive to biases such as those related to participant emotional states, in terms of symptom impact and severity [82]. Also, although the relevance of pain catastrophizing and depression in the functional impact of the FMS is clear, possible mediating mechanisms, like the practice of physical exercise or levels of fitness, have been not assessed. Nonetheless, studies to this respect are not clear, even with some of them not showing improvement in FMS functional capacity (measured by FIQ) as a function of fitness and physical exercise accomplishment (e.g., [83]). FMS functional capacity seems to be dependable on the intensity and the kind of the physical exercise. Moderate intensity aerobic aquatic exercise is the one that is suggested to exert greater clinically meaningful improvements in FIQ score [84, 85]. Similarly, studies measuring melatonin secretion as mediating mechanism of depression influence in the relationship between pain and FMS functional capacity are recommended. This recommendation is based on the high demonstrated correlation between the disruption in melatonin secretion and FMS clinical symptoms [86]. Finally, although the sample of patients in this study was sufficient to perform the mediation analysis, future studies with a much larger sample should not be ruled out to increase the effect size for mediation [52].

One strength of this research is to include both clinical and emotional variables; thus, providing a clearer picture of predictors of functional capacity in FMS. In addition, the mediation analysis conducted provides better insight into the complex interrelation between predictors. Finally, the results of the current research have a clear clinical relevance in the development and improvement of FMS treatments.

5. Conclusions

In conclusion, findings confirm that the FMS functional impairment is positively related to the majority of FMS symptoms. Among these symptoms, depression, fatigue, and pain catastrophizing (in this sequence) are those with more predictable power. Furthermore, the relevant factors affecting the relationship between pain and FMS functional capacity are pain catastrophizing and depression. Findings support the key role of pain catastrophizing and depression in the disability associated to pain in FMS. Treatment goals directed to lessen depression and pain catastrophizing are strongly recommended to reduce the impact of pain in FMS patients' daily function. The inclusion of these factors in therapy protocols could improve the functional capacity in FMS patients directly and indirectly by the associated reduction in pain perception (intensity and total).

Data Availability

The data presented in this study are available on request from the corresponding authors.

Ethical Approval

The procedure followed the general criterion of the local Ethics committee, based on the Helsinki Declaration principles, and was approved by the Bioethics Committee of the University of Jaén.

Conflicts of Interest

All the authors declare that they have no conflicts of interest derived from the outcomes of this study.

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Research Article

Variability of Reaction Time as a Marker of Executive Function Impairments in Fibromyalgia

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In addition to chronic widespread pain and depression and anxiety symptoms, patients with fibromyalgia frequently experience cognitive problems. This study investigated executive functions in fibromyalgia via a Go/No-Go task. To obtain comprehensive information about performance, traditional and ex-Gaussian parameters of reaction time (RT) variability were used, in addition to speed and accuracy indices. Ex-Gaussian parameters show an excellent fit to empirical RT distributions. Fifty-two female fibromyalgia patients and twenty-eight healthy controls participated. The task included 60 visual stimuli, which participants had to respond to (Go stimuli) or withhold the response to (No-Go stimuli). After 30 trials, the task rule changed, such that previous No-Go stimuli had to be responded to. Performance was indexed by the hit rate, false alarm rate, and mean (*M*) and intraindividual standard deviation (SD) of RT and the ex-Gaussian parameters mu, sigma, and tau. Mu and sigma indicate the *M* and SD of the Gaussian distribution; tau reflects the *M* and SD of the exponential function. Patients exhibited a lower hit rate, higher *M* RT, and higher tau than controls. Moreover, patients showed greater decrease of the hit rate after the change of task rule. In the entire sample, SD, sigma, and tau were inversely associated with the hit rate and positively associated with the false alarm rate. While the greater decline in hit rate after the change in task rule indicates deficient cognitive flexibility, the lack of any difference in false alarm rate suggests intact response inhibition. Higher *M* RT reflects reduced cognitive or motor speed. Increased tau in fibromyalgia indicates greater fluctuations in executive control and more frequent temporary lapses of attention. For the first time, this study demonstrated that indices of RT variability, in particular those derived from the ex-Gaussian function, may complement speed and accuracy parameters in the assessment of executive function impairments in fibromyalgia. Optimized assessment may facilitate the personalization of therapies aimed at improving the cognitive function of those with the disorder.

1. Introduction

Fibromyalgia syndrome (FMS) is a chronic condition of widespread pain accompanied by symptoms like fatigue, sleep disturbance, depression, and anxiety [1, 2]. The prevalence of FMS is estimated at 2 to 4% in the general population, where women are more frequently affected than men [2]. FMS symptoms cause severe reductions in well-being and quality of life [3, 4]. Although the precise etiology of FMS remains unknown, sensitization of central nociceptive pathways and deficient pain-inhibiting mechanisms are believed to play a key role [5]. In addition to physical and emotional symptoms, FMS is frequently associated with cognitive disruption, reflected in problems with attention and

memory or reduced processing speed, for example [6–8]. According to patients' reports, these difficulties can significantly affect social and professional functioning and are among the most serious symptoms of the disorder [9, 10].

The present study is concerned with executive functions in FMS. The term executive functions refer to complex cognitive abilities that enable the regulation, coordination, and sequencing of basic mental operations [11, 12]. Executive functions are essential for the control of most behaviors, and deficits therein may greatly impede activities of daily life. Several studies have documented executive function impairments in FMS. For example, patients performed worse than healthy controls on tasks assessing cognitive flexibility [13], working memory updating [6], decision-making [13, 14], mental planning [15], and arithmetic processing [16, 17]. However, negative findings have also been reported, including for response inhibition tests [18, 19] and by a study quantifying multiple executive functions [20]. Discrepancies between studies may be explained by differences in the tasks used, as well as in sample size and composition (see [15] for an overview of the findings of previous studies and a discussion of their differences).

In the present study, executive functions were assessed in FMS patients and healthy controls using a Go/No-Go task; in addition to task accuracy, intraindividual variability of reaction time (RT) was taken as an indicator of executive functions [21]. Short-term trial-by-trial RT fluctuations during cognitive tasks have been related to the coordination of cognitive operations and integrity of brain regions involved in executive functions [22, 23]. High RT variability is associated with poor performance on executive function tasks, indexed by traditional parameters like the correct response rate or RT [24–26]. Moreover, it is widely acknowledged that RT variability reflects fluctuations in executive functions; therefore, it can serve as an index of lapses in attentional control [27, 28].

The RT distribution can be described in various ways, such as by traditional and ex-Gaussian models, which provide different parameters [29–31]. Mean (M) and standard deviation (SD) are the most frequently used traditional indices of the RT distribution. The ex-Gaussian function is a convolution of a Gaussian (normal) and exponential function characterized by the following three parameters. Mu provides an estimate of the M of the Gaussian distribution; sigma is an index of the SD of the Gaussian function; tau reflects the combined M and SD of the exponential function, serving as an indicator of extreme values, i.e., the "right tail" of a positively skewed distribution. The ex-Gaussian distribution provides an excellent fit to empirical RT distributions [32]. In cognitive tasks, tau of RT represents unusually slow responses, which follow an exponential distribution and are closely related to short-term lapses of attention [33–35]. In contrast, mu and sigma reflect the M and variability of RT, irrespective of extremely slow responses [36, 37].

Intraindividual variability in RT may constitute useful information for investigations of executive function deficits in FMS; subtle impairments, which are not reflected in traditional measures such as the rate of correct responses or M RT, may be reflected in the SD, sigma, or tau of RT. Therefore, in this study, RT variability was compared between FMS patients and healthy controls. Moreover, the relationship between variability indices and task accuracy was investigated. As interindividual differences in RT variability may depend on the RT magnitude, the M RT was controlled for in the analyses (c.f. [38]).

In the Go/No-Go task, the participant is required to respond to a defined stimulus or set of stimuli (Go stimuli) and to withhold the response to another stimulus or set of stimuli (No-Go stimuli) [39]. In addition to selective attention, the task enables quantification of response inhibition [40]. As Go trials are typically more frequent than No-Go trials, the participant develops a tendency to respond, which must be suppressed during No-Go trials. Therefore, poor inhibition performance is reflected in an increased response rate to No-Go stimuli (false alarms). Moreover, the Go/No-Go task may be designed such that the task rule changes during execution, for example, by reversal of the assignment of stimuli to the Go and No-Go conditions [41]. This enables assessment of the ability to quickly adjust behavior to the new rule, i.e., cognitive flexibility.

The following main hypotheses were tested in this study: (1) lower executive function performance was expected in FMS patients than controls, reflected in a lower rate of hits (i.e., responses to Go trials), higher rate of false alarms (inhibition deficit), and greater decline in performance after the change of task rule (reduced cognitive flexibility). (2) Moreover, a longer RT was expected in FMS patients than controls, reflecting reduced speed of cognitive processing. (3) Poor executive function would also be reflected in greater intraindividual RT variability in patients than controls, i.e., higher SD for the traditional model and higher sigma and tau for the ex-Gaussian model. (4) RT variability was hypothesized to predict traditional performance parameters. Accordingly, SD, sigma, and tau were expected to be inversely associated with hit rate and positively associated with the false alarm rate. These associations should persist after controlling for RT magnitude (M or mu). In addition, to test for possible effects of comorbid depression and anxiety disorders on executive functions, task performance was compared between FMS patients suffering and not suffering from these disorders.

2. Materials and Methods

2.1. Participants. This study was part of a larger project investigating cognition and emotional processing in FMS [15, 42]. While the same sample was investigated in [15, 42], none of the data have previously been published, except for the Beck Depression Inventory (BDI) and McGill Pain Questionnaire (MPQ) scores. In total, 52 female FMS patients and 28 healthy women participated in the study. Patients were recruited via the Fibromyalgia Association of Jaén and Úbeda (Spain). All diagnoses were made by a rheumatologist according to the 2010 American College of Rheumatology (ACR) criteria for FMS [2]. Controls were recruited from voluntary and neighborhood associations. The exclusion criteria for both study groups were metabolic abnormalities, neurological disorders (e.g., traumatic head

Table 1: Demographic and clinical data of the sample; statistics of the group comparison.

	FMS patients ($N = 52$)	Control group ($N = 28$)	$t[78]/\chi^2$	p
Age in years ($M \pm$ SD)	51.25 ± 8.67	52.25 ± 6.65	.-53	.60
Years of education ($M \pm$ SD)	9.27 ± 3.52	10.57 ± 3.54	-1.57	.12
Body mass index ($M \pm$ SD)	28.29 ± 4.49	26.41 ± 4.61	1.77	.080
Depression (N, %)	22 (42.3)	2 (7.1)	10.72	.001
Anxiety disorder (N, %)	25 (48.1)	5 (17.9)	7.09	.008
Antidepressant medication (N, %)	27 (51.9)	2 (7.1)	15.79	<.001
Opioid medication (N, %)	23 (44.2)	0 (0.0)	17.38	<.001
Non-opioid analgesic medication (N, %)	45 (86.5)	6 (21.4)	33.39	<.001
Anxiolytic medication (N, %)	35 (67.3)	7 (25)	13.06	<.001
Beck Depression Inventory ($M \pm$ SD)	21.90 ± 12.56	4.57 ± 5.89	8.39	<.001
McGill Pain Questionnaire: sum score ($M \pm$ SD)	52.12 ± 30.31	19.50 ± 5.50	7.35	<.001
McGill Pain Questionnaire: pain intensity ($M \pm$ SD)	3.31 ± .88	1.44 ± .51	8.52	<.001

Notes. M: mean; SD: standard deviation; N: number of cases; $t[78]$: statistic of the t test for the group comparison (78 degrees of freedom); χ^2: statistic of the chi-squared test for the group comparison; p: p value of the group comparison. Patients were using the following analgesic drugs: nonsteroidal anti-inflammatory drugs, 29 patients; paracetamol, 34 patients; metamizole, 7 patients; anticonvulsants, 10 patients; tramadol, 20 patients; and codeine, 4 patients. Thirty-six (69.2%) patients and twenty (62.5%) controls reported to be in the menopausal or premenopausal phase. Among the participants of reproductive age, the distribution of the menstrual phase was as follows: menstruation, 4 patients and 2 controls; follicular phase, 3 patients and 4 controls; ovulation phase, 3 patients and 1 control; and lutein phase, 6 patients and 5 controls.

injury), and other severe somatic (e.g., cancer) or psychiatric (e.g., drug dependency and psychosis) diseases. The control group was additionally required to be free from acute or chronic pain of any kind. Table 1 includes the demographic and clinical data of the sample.

2.2. Clinical Assessments. The Structured Clinical Interview for Axis I Disorders of the Diagnostic and Statistical Manual for Mental Disorders (DSM-4) (SCID, [43]) was applied to diagnose mental disorders. The severity of depressive symptoms was assessed using the Spanish version of the BDI [44] (score range: 0-63). The sum score (range: 0-146) and current pain intensity score (range: 0-5) of the MPQ (Spanish adaption [45]) were used for quantification of clinical pain. The questions of the BDI refer to the past week, including the present day; those of the MPQ refer to the present moment.

2.3. Cognitive Assessment. The Go/No-Go task was presented using the E-Prime software (Psychology Software Tools, Inc., Sharpsburg, PA). The task consisted of six blocks of 10 trials each. During blocks 1-3, the participants were required to press a key as quickly as possible when a Go stimulus (a letter, randomly chosen for each participant; stimulus height = 1.4 cm) appeared on the screen and to withhold the key press when a No-Go stimulus (a different letter, randomly chosen for each participant) appeared. During blocks 4-6, the instruction was reversed such that the participants had to respond to stimuli that were No-Go stimuli during blocks 1-3 and to withhold responses to previous Go stimuli. After each trial, participants received acoustic feedback on whether the response was correct or not (two tones differing in pitch and sound). Each stimulus was presented for 750 ms; the intertrial intervals were 3,000 ms. The ratio between Go trials and No-Go trials was 7/3 in all blocks. Responses were classified as hits (key press in Go trials during stimulus presentation or the following intertrial interval), false alarms (key press in No-Go trials during stimulus presentation or the following intertrial interval), missing responses (no key press in Go trials), and correct rejections (no key press in No-Go trials). Participants were instructed regarding how to perform the task, orally and in writing. Prior to the task, they were informed that the rule would change after block 3; the change was indicated by a buzzing sound during the actual task. The main parameters of task performance were the hit rate, false alarm rate, and M RT in each of the six blocks. In addition, intra-individual SD, mu, sigma, and tau were computed across all trials. Ex-Gaussian parameters (mu, sigma, and tau) were computed in R using the package retimes (version 3.6.2; Massida, 2013; R Core Team, 2019). Only the RTs of correct responses (hits) were included in the analysis. Anticipatory responses (RT < 200 ms) were discarded.

2.4. Procedure. The study was conducted over two sessions performed on two consecutive days. During the first session, a clinical psychologist recorded sociodemographic data and medication use, checked for violations of the exclusion criteria, carried out the SCID interview, and administered the self-report questionnaires. During the second session, the Go/No-Go task was performed as described previously. Participants were asked not to consume analgesic drugs, alcohol, or caffeine and not to engage in rigorous physical exercise, for 24 hours before the study. Written informed consent was obtained from all participants. The research adhered to all relevant regulations and institutional policies and was performed in accordance with the Helsinki Declaration and approved by the Ethics Committee of the University of Jaén (Spain).

2.5. Statistical Analysis. Statistical analyses were performed using SPSS (ver. 21.0; IBM Corp., Armonk, NY). Demographic and clinical data were compared between FMS patients and controls using *t* tests and chi-squared tests (see Table 1). For the comparison between FMS patients and controls in the performance parameters of the Go/No-Go task, ANOVAs were applied. The dependent variables were the hit rate and false alarm rate, as well as the *M*, intraindividual SD, mu, sigma, and tau of RT, averaged across all blocks of the task. In the ANOVAs for SD, sigma, and tau, *M* (for SD) and mu (for sigma and tau) values were included as covariates. Moreover, to analyze the effect of the change in task rule between blocks 3 and 4, repeated measures ANOVAs were computed for the hit rate, false alarm rate, and *M* RT, with the between-subject factor of group (FMS patients vs. controls) and within-subject factor of block (block 3 vs. block 4). Finally, univariate ANOVAs were computed to compare FMS patients suffering and not suffering from depression and anxiety disorders. Dependent variables correspond to those of the comparison between FMS patients and controls.

Linear associations between parameters were quantified, as a first step, by regression analysis including traditional performance indices (hit rate, false alarm rate, *M*, of RT) as the dependent variables and M, SD, mu, sigma, and tau as predictors, in separate regression models. Moreover, stepwise regression analyses were performed to estimate the relative contributions of traditional and ex-Gaussian parameters of RT to the variance in the hit and false alarm rates. Separate models were computed, including traditional parameters (*M* and SD of RT) and ex-Gaussian parameters (mu, sigma, and tau of RT) as predictors.

To account for possible differences in relationships between FMS patients and controls, group was used as a dummy variable in all regression models. Alpha was set at .05 in all analyses. Given the possibility of type I error inflation due to multiple statistical testing, the use of a significance threshold of 5% can be considered. However, this would substantially reduce the power of the tests, i.e., increase the chance of type II errors and reduce the probability of detecting any effects present.

3. Results and Discussion

3.1. Group Differences in Task Parameters. FMS patients exhibited a lower overall hit rate on the task than controls, as well as a longer *M* RT and higher tau (Table 2). Group differences in the false alarm rate, mu, and sigma did not reach significance. The group difference in the intraindividual SD of RT was significant without controlling for the M RT ($p = .017$), but not after including the *M* RT as a covariate. Figure 1 displays the hit rate across the six task blocks. While FMS patients showed a marked decrease in hit rate from blocks 3 to 4, only a slight decline was seen in controls. The ANOVA revealed a main effect of block (block 3 vs. block 4) ($F[1, 78] = 20.57$, $p < .001$, and $n_p^2 = .21$) and a group x block interaction ($F[1, 78] = 5.09$, $p = .027$, and $n_p^2 = .06$). Post hoc analysis indicated that the reduction in hit rate was significant in both groups, but with a larger effect size in FMS patients ($F[1, 51] = 25.14$, $p < .001$, and $n_p^2 = .33$) than controls ($F[1, 27] = 4.83$, $p = .037$, and $n_p^2 = .15$). The main effect of block and interaction effect were not significant for the false alarm rate or RT. The ANOVAs did not reveal differences between patients suffering and not suffering from depression or anxiety disorders (all $Fs < .92$, all $ps > .34$).

3.2. Linear Associations between Task Parameters. Table 3 includes the associations of hit rate, false alarm rate, and the *M* RT with the remaining task parameters in the entire sample, after controlling for the effect of group. Hit rate was inversely associated with all RT parameters except tau; the false alarm rate was positively associated with all RT parameters. Moreover, the *M* RT was positively related with all of the remaining RT parameters.

Results of the stepwise regression analyses with hit rate and false alarm rate as dependent variables and traditional RT parameters and ex-Gaussian parameters as predictors, controlling for group, are presented in Table 4. In the model for hit rate and traditional RT parameters, *M* was included in the first step and intraindividual SD in the second step. *M* was the only significant predictor of false alarm rate. Concerning ex-Gaussian parameters, mu was included in the first step of the model for hit rate; in the second step, tau further improved the predictive power. In the model for false alarm rate, tau was included as a predictor in the first step; in the second step, mu further improved the predictive power.

4. Discussion

This study investigated executive functions in FMS based on a Go/No-Go task. Performance was indexed by traditional parameters of task accuracy and RT and by indices of RT variability. FMS patients exhibited a lower overall hit rate and longer RT on the task than healthy controls. Moreover, they showed a greater reduction of hit rate after the change of task rule. The false alarm rate did not differ between the groups. Intraindividual RT variability, indexed by the ex-Gaussian parameter tau, was higher in patients than controls. In contrast, no group difference arose for the SD or sigma of RT. Regression analysis of the entire sample suggested that SD, sigma, and tau were inversely related to the hit rate and positively related to the false alarm rate.

4.1. Executive Function Impartments in Fibromyalgia Assessed via Traditional Performance Parameters. The lower hit rate in FMS patients confirms previous observations of executive function impairments in the disorder (for an overview, see [15]). While the overall hit rate constitutes a relatively nonspecific parameter of executive functions, the decline of hit rate seen after the change in task rule reflects deficits in cognitive flexibility in FMS. Between blocks 3 and 4, the hit rate decreased by approximately 15% in patients and 5% in controls, indicating that patients had greater difficulty in adjusting their behavior to the new rule. This is consistent with previous observations of reduced performance in FMS patients on the Wisconsin Card Sorting

Table 2: Descriptive statistics ($M \pm SD$) for the task parameters; statistics of the comparison between FMS patients and controls (main effect of group in the ANOVAs). The M RT was controlled for in the group comparison of intraindividual SD, and mu was controlled for in the group comparisons of sigma and tau.

	FMS patients($N = 52$)	Controls($N = 28$)	F	p	η_p^2
Hit rate	.92 ± .09	.96 ± .04	6.60	.012	.08
False alarm rate	.29 ± .19	.22 ± .22	2.11	.151	.03
M of RT	494.50 ± 145.96	427.34 ± 78.87	5.10	.027	.06
Intraindividual SD of RT	218.99 ± 115.58	157.02 ± 91.91	1.00	.32	.01
mu of RT	293.98 ± 132.57	269.47 ± 80.02	0.80	.38	.01
sigma of RT	113.93 ± 92.45	83.15 ± 63.06	1.85	.18	.02
tau of RT	200.52 ± 102.64	157.87 ± 108.58	4.68	.034	.06

Notes. M: mean; SD: standard deviation; RT: reaction time; N: number of cases; F: statistic of the group effect in the ANOVA; p: p value of the group effect; η_p^2: effect size of the group effect (partial eta squared).

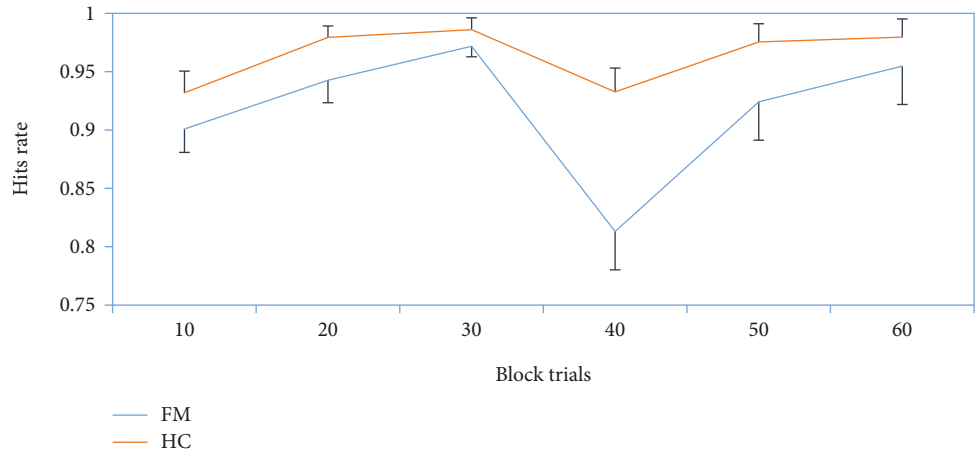

Figure 1: Hit rate across the six blocks of the Go/No-Go task.

Table 3: Standardized β coefficients from the regression analysis conducted in the entire sample to identify predictors of the hit rate, false alarm rate, and M RT after controlling for the effects of group.

	Hit rate	False alarm rate	M of RT
M of RT	-.51**	.48**	-
Intraindividual SD of RT	-.31*	.46**	.83**
mu of RT	-.43**	.24*	.62**
tau of RT	-.13	.30**	.50**
sigma of RT	-27*	.25*	.72**

Note. M: mean; SD: standard deviation; RT: reaction time. *$p < .05$; **$p < .01$.

Test, which measures cognitive flexibility in terms of the ability to rapidly detect and adjust to, changing rules in a categorization task [13]. Moreover, FMS patients showed a smaller shifting index in the Five Digits Test, reflecting problems in quickly shifting between different task modes ([15]; however, see [46] for negative findings pertaining to impaired flexibility in FMS). The lack of any group difference in false alarm rate in this study suggests intact response inhibition in FMS. Previous studies on this component of executive function in FMS revealed inconsistent results. While lower performance on the Stroop test in patients pointed towards reduced inhibition capacity ([15, 46]; however, see [19] for a divergent finding), patients did not differ from controls in false alarms on a Go/No-Go task [18], nor in performance on the Multisource Interference Test [19]. Therefore, further research is warranted to achieve clarity regarding the inhibition impairments in FMS. The M RT was markedly longer in our FMS patients than controls, which replicates various studies demonstrating reduced cognitive speed in FMS (e.g., [16, 17, 19, 47, 48]).

4.2. Executive Function Impartments in Fibromyalgia Assessed via Analysis of Intraindividual RT Variability. As an alternative methodological approach, executive functions were also quantified using intraindividual trial-to-trial RT variability. To avoid confounding between RT magnitude and RT variability, RT magnitude (M or mu) was controlled for in the group comparison of variability parameters (c.f. [38]). While RT variability (indexed by the ex-Gaussian parameter tau) was higher in FMS patients than controls,

Table 4: Statistics of the stepwise regression analyses conducted in the entire sample for predicting the hit and false alarm rates using traditional parameters (*M* and SD of RT) and ex-Gaussian parameters (mu, sigma, and tau of RT) after controlling for the effects of group.

Models for traditional parameters (*M* and SD of RT)						
Dependent variable		Predictor	β	R^2	F	p
Hit rate	Step 1	*M*	-.52	.33	28.53	<.001
	Step 2	*M*	-.82	.37	5.14	.026
		SD	.38			
False alarm rate	Step1	M	.48	.24	22.14	<.001
Models for ex-Gaussian parameters (mu, sigma, and tau of RT)						
Dependent variable		Predictor	β	R^2	F	p
Hit rate	Step 1	mu	-.43	.26	19.30	<.001
	Step 2	mu	-.54	.35	10.03	.002
		tau	-.32			
False alarm rate	Step1	tau	.30	.11	7.45	.008
	Step 2	tau	.44	.25	13.77	<.001
		mu	.40			

Notes. *M*: mean; SD: intraindividual standard deviation; RT: reaction time; β: standardized β coefficient for the predictor; R^2: determination coefficient for the step; *F*: *F* statistic for the step; *p*: *p* value for the step.

the group difference did not reach significance for SD or sigma. It may be that tau is more sensitive to group differences than SD and sigma; moreover, the different variability parameters may relate to different aspects of cognitive performance [30]. Importantly, tau represents the *M* and variability of the exponential component of the ex-Gaussian function and thus the skew of the distribution. Therefore, tau reflects extremes in the RT distribution related to infrequent, slow responses [34, 35]. High values of tau are commonly interpreted as a manifestation of increased lapses of attentional control [49, 50]. Lapses of attention result from temporary failure in executive functions and constitute a transdiagnostic symptom of mental and physical conditions including psychotic disorders [51], attention-deficit/hyperactivity disorder [34], drug abuse [52], traumatic head injury [53], sleep disorders [54, 55], and age-related cognitive decline [25].

4.3. RT Variability, Brain Activity, and Psychological Factors. Intraindividual RT variability during cognitive tasks has been related to prefrontal cortex function [38]. Consistent with this hypothesis, prefrontal lesions in dementia were accompanied by increased RT variability [56]. Moreover, patients with prefrontal lesions due to traumatic head injury exhibited higher RT variability than healthy individuals and patients with nonfrontal cortical lesions [57]. The role of the prefrontal cortex in RT variability is also supported by fMRI studies [21, 38]. For example, higher RT variability during Go/No-Go tasks was associated with lower activity in prefrontal areas and the anterior cingulate [22, 58]. Event-related fMRI during a selective attention task revealed that lapses of attention are preceded by reduced activity in the right prefrontal cortex and anterior cingulate [28]. It is widely acknowledged that prefrontal activity plays a key role in executive functions [12, 59], such that RT variability may be viewed as a correlate of the neural processes underlying these abilities.

Various physiological factors have been considered to mediate increased RT variability in clinical conditions, including changes in grey matter density, white matter integrity, and catecholaminergic and cholinergic neurotransmission (for a review, see [21]). Functional interference between the neural pathways mediating pain and cognition may play a role in the increased RT variability and executive function impairments seen in FMS [15]. A central nervous system pain matrix has been identified, which includes the somatosensory cortex, anterior cingulate, insula, thalamus, and prefrontal cortex [60]. There is strong evidence implicating exaggerated activity in this network in the hyperalgesia that characterizes FMS [5]. Various neuroimaging studies demonstrated that this hyperactivity is also present in prefrontal areas [5, 61, 62]. As delineated above, activity in the prefrontal cortex is the main physiological correlate of executive functions and RT variability. Increased demands on prefrontal areas due to exaggerated nociceptive processing may reduce the neural resources available for cognition, thus leading to the observed deficits. Regarding cerebral metabolism, catecholaminergic neurotransmission may play a role. Dopamine is involved in pain inhibition, and reduced dopaminergic activity has been documented in FMS [63, 64]. In turn, dopamine is an essential transmitter for executive function processing in the prefrontal cortex [65], and deficient dopaminergic metabolism has been related to increased RT variability [21, 23].

4.4. Combination of Traditional Performance Indices and Ex-Gaussian Parameters of RT Variability. The suitability of intraindividual RT variability for indexing executive functions was confirmed by the relationships of variability parameters with the rate and false alarm rates seen in our entire sample. This corroborates previous reports of close

associations between RT variability and performance accuracy on executive functions tasks [24–26]. According to individual regression analyses, hit rate was associated with the *M*, SD, mu, and sigma of RT, while the false alarm rate was associated with the *M*, SD, mu, tau, and sigma. When RT magnitude (*M* or mu) was controlled for in stepwise regression analysis of variability parameters, the hit rate was still significantly related to SD and tau, and the false alarm rate was still related to tau. Regarding the regression analysis of ex-Gaussian parameters, it is important to note that inclusion of mu and tau in the second step of the models led to a greater proportion of the variance in performance being explained compared to the inclusion of one of the parameters in the first step (mu for hit rate and tau for false alarm rate). This suggests that the combination of both variables may facilitate the prediction of performance. In contrast, sigma did not explain any additional variance in the hit or false alarm rate, relative to that explained by mu and tau, which suggests that this parameter may play a subordinate role in the prediction of performance.

4.5. Limitations. A limitation of this study was the lack of control for possible effects of medication on task performance in FMS. Such effects could be investigated by comparing subgroups distinguished according to the use of particular medications or combinations thereof; due to the small sizes of the subgroups, this was not feasible in the present study. However, most available studies comparing FMS patients using antidepressants, anxiolytics, and opiates and nonopioid analgesics with those not using these medications did not reveal differences in performance on cognitive tasks [13, 15–17, 48]. Pain medications were discontinued prior to the testing session, which may have influenced cognitive performance (via a transient increase in pain severity). The comparison between FMS patients suffering and not suffering from depression or anxiety disorders did not reveal significant differences in task performance. Although executive function impairments have been observed in patients with major depression [66], our finding is in line with previous studies suggesting that comorbid depression and anxiety disorders play a subordinate role in the cognitive impairments seen in FMS [6, 13, 17, 48, 67].

5. Conclusions

In conclusion, this study confirmed the presence of executive function impairments in FMS, which may be reflected in cognitive flexibility rather than response inhibition [15, 19]. Moreover, the results replicate previous observations of reduced processing speed in FMS patients (e.g., [16, 19]). The ex-Gaussian parameter tau suggested increased RT variability in FMS, reflecting fluctuations in the control of basic mental operations and temporary lapses of attention [38]. Indices of RT variability, in particular those derived from the ex-Gaussian function, may be a useful compliment to traditional parameters of speed and accuracy for investigations of executive function impairments in clinical disorders, such as fibromyalgia. The findings suggest that the combination of traditional performance indices and ex-Gaussian parameters of RT may facilitate the assessment of executive function performance. Improved assessment may in turn be useful with respect to the personalization of therapies aiming at reducing cognitive impairments, which are among the most serious symptoms of the disorder. Recent studies underline the importance of going beyond conventional medical measures (i.e., pharmacological approaches targeting symptoms) to optimize the treatment of fibromyalgia [68].

Data Availability

The dataset has been posted in a permanent public repository with open access and can be downloaded from this URL: https://osf.io/d9u3f/?view_only=9a05b0fa35f64f6cb32825a44f1c805d.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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