Rev Med Chile 2022; 150: 1450-1457

Self-perceived cognitive function and neuropsychological performance in women with fibromyalgia

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Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of interest: none.

Recibido el 10 de septiembre de 2021, aceptado el 3 de agosto de 2022.

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ABSTRACT

Background: *Cognitive dysfunction is a common complain in patients with fibromyalgia (FM).* ***Aim****: To assess the perceived cognitive function and cognitive performance in women with FM.* ***Material and Methods:*** *Cross-sectional study including 100 women with FM (FMG) and 100 healthy controls (CG). Self-perceived cognitive functioning was evaluated using the Functional Assessment of Cancer Therapy Cognition scale (FACT-Cogv3). The neuropsychological performance was assessed with the Trail Making Test (TMT-A, TMT-B), Digit Span test (DS), Barcelona test (DS-F/B) and the Frontal Assessment Battery (FAB-E), Spanish version test.* ***Results****: The mean scores of all cognitive self-perception factors and all neuropsychological tests were lower in the FMG ($p < 0.001$). Over 90% of the FMG took longer than the population mean (P_{50}) to complete the TMT-A and TMT-B tests, while in the CG, 1/3 took longer than the P_{50} in both tests. The minimum expected scores for the DS-F and DS-B tests were not achieved by 40 and 9% of FMG participants, respectively. According to FAB-E, 54% and 24% of FMG were categorized as fronto-subcortical deficit and fronto-subcortical dementia, respectively.* ***Conclusions****: Women with FM have a higher perception of cognitive dysfunction and lower cognitive performance in objective tests than healthy women. More research is needed to explore the clinical, psychosocial, and sociodemographic characteristics that predispose to cognitive deficits in this group of patients.*

(Rev Med Chile 2022; 150: 1450-1457)

Key words: *Cognitive Dysfunction; Executive Function; Fibromyalgia.*

Función cognitiva autopercibida y desempeño neuropsicológico en mujeres con fibromialgia

Antecedentes*: La disfunción cognitiva es una queja común en pacientes con fibromialgia (FM).* ***Objetivo:*** *Investigar la función cognitiva percibida y el desempeño cognitivo en mujeres chilenas con FM.* ***Material y Métodos****: Estudio transversal incluyendo a 100 mujeres con FM (GFM) y 100 mujeres como controles sanos (GC). El funcionamiento cognitivo autopercibido se evaluó mediante la prueba Functional Assessment of Cancer Therapy Cognition scale (FACT-Cogv3). El rendimiento neuropsicológico se evaluó mediante las pruebas Trail Making Test (TMT-A, TMT-B) y Digit Span test (DS), Barcelona test*

(DS-F/B) y la prueba Frontal Assessment Battery, versión española (FAB-E). ***Resultados****: Las puntuaciones medias de todos los factores de autopercepción cognitiva y todas las pruebas neuropsicológicas fueron significativamente menores en el GFM. Para TMT-A y TMT-B, más del 90% del GFM tardó más que la media poblacional (P_{50}) para completar las pruebas, mientras que en el GC aproximadamente 1/3 requirió más tiempo que el P_{50} en ambas pruebas. Un 40 y 9% del GFM no obtuvo la puntuación mínima esperada para las pruebas DS-F y DS-B, respectivamente. Según FAB-E, el 54% y 24% del GFM se clasificó como déficit fronto-subcortical y demencia fronto-subcortical, respectivamente.* ***Conclusiones****: Las mujeres con FM tienen una mayor percepción de disfunción cognitiva y menor rendimiento cognitivo en pruebas objetivas que mujeres sanas. Se necesita más investigación para explorar las características clínicas, psicosociales y sociodemográficas que predisponen a los déficits cognitivos en este grupo de pacientes.*

Palabras clave: *Disfunción cognitiva; Fibromialgia; Función ejecutiva.*

Fibromyalgia (FM) is a syndrome characterized by generalized chronic musculoskeletal pain accompanied by heterogenous cognitive-physical symptoms[1]. It is speculated that genetic, environmental, neurohormonal, and inflammatory factors play an essential role in its pathogenesis[1]. In the US and Europe, the total prevalence of FM is estimated at 6,4% and 4,7% respectively, but lower estimates have been reported from survey data for other regions, such as Latin American countries[2,3]. The average worldwide female/male ratio is 3:1[2]. In Chile, there are few reports of FM prevalence, however, it has been estimated at around 1% to 2%[4].

FM has been considered a dysfunction of the central nervous system (CNS) and cataloged as a central sensitization syndrome along with peripheral sensitization or neuropathology[5]. The CNS dysfunction arises from the activation of plasticity, neuroinflammation and neurostructural remodeling[6], resulting from stressful events or chronic pain states altering cortical and subcortical areas associated with memory, pain processing and cognitive function[5,7].

Cognitive manifestations are common among people with FM. The term "fibrofog" refers to a group of subjective complaints related to daily cognitive functioning[8]. FM patients report problems related to concentration, memory and multitasking[9]. Self-reported cognitive difficulties have also been associated with greater pain, stiffness, poor sleep and anxious-depressive symptoms[9].

In addition to the subjective component, the term "dyscognition" implies the objectification of more complex cognitive process deficits[10]. Thus, a series of neuropsychological tests have been proposed to assess different domains of cognitive function[11]. Although self-reported difficulties are common, the evidence for objective cognitive dysfunction remains contradictory, suggesting an overvaluation of cognitive symptoms and therefore, indicating the need for further studies[11]. Moreover, cognitive disorders can severely affect the daily functionality of FM patients, however, health professionals usually do not sufficiently consider this aspect, prioritizing pain management[12].

In Chile, there are certain antecedents about the clinical profile and therapeutic approach in FM patients[13,14]. However, to the best of the authors' knowledge, this is the first Latin American study focused on describing cognitive aspects in this condition. Therefore, considering its relevance for its comprehensive treatment, the purpose of this research was to analyze the perceived cognitive function and cognitive performance of Chilean women with FM.

Material and Methods

Participants

This cross-sectional study was guided by the STROBE statement. Via non-probabilistic sampling, a group of 100 women with FM (FMG) and a group of 100 healthy women as control (CG) were formed. The CG was recruited from

a medical center located in the commune of Concepción, which they attended for a periodic health check-up. The FMG was recruited from two organizations for people with FM (located in the communes of Concepción and Hualpén). This group carried out their medical check-ups at the same center as the CG. To reduce possible bias, both study groups had the same socioeconomic and sociocultural level. The inclusion criteria for CG and FMG were: aged 30 to 50 years, Chilean nationality, to present at least a completed secondary education, beneficiaries of public health insurance (FONASA), to belong the most vulnerable 70% of the Chilean population according to the social registry of households, and have been born and reside in the province of Concepción. Also, the FMG should have been diagnosed as FM according to the American College of Rheumatology criteria[15]. Exclusion criteria were: Severe neurological/psychiatric pathology, sequelae of musculoskeletal trauma and any pharmacological treatment beyond the typical FM prescriptions. All participants signed an informed consent form, and the procedure was in accordance with the Declaration of Helsinki (2013 version). The protocol was approved by the Scientific Ethics Committee of the Concepción Health Service, Chile (Code.08-19-59).

Procedures and sample characterization

After explaining the study's requirements, data collection was carried out through an interview to register sociodemographic information and the application of the tests. All procedures were performed individually by a professional in an isolated room without interruptions. Depressive symptoms were assessed using the Beck Depression Inventory (BDI-II), Spanish version[16]. The impact of FM on functionality, symptoms and emotional state was evaluated using the Fibromyalgia Impact Questionnaire (S-FIQ), Spanish version[17].

Cognitive assessment

Cognitive impairment self-reporting

Functional Assessment of Cancer Therapy Cognition scale (FACT-Cogv3)[18]. Self-report questionnaire consisting of 37 items comprising four broad factors: perceived cognitive impairment, perceived cognitive ability, noticeability by others, and impact on life quality. Participants rate each statement's frequency according to their experience in the last week on a 5-point scale. A higher score is a greater perceived cognitive function (where: 0 = never/not at all; and 4 = several times a day/a lot).

Neuropsychological evaluation

Trail Making Test (TMT-A, TMT-B)[19]. Evaluates the ability to visual search, scanning, processing speed, mental flexibility, and attention shifting. In TMT-A, numbers from 1 to 25 are joined sequentially, evaluating visual attention/search skills and psychomotor speed. TMT-B numbers and letters are joined alternately and sequentially (1-A-2-B-3-C, etc.), evaluating executive control, cognitive flexibility, and set-shifting. A longer response time indicates lower performance. Times reached were categorized by percentiles according to age and education level.

Digit Span test (DS), Barcelona test[20]. Assesses short-term verbal memory span, and the ability to manipulate and update verbal information while in temporary storage (updating). In forward digit span (DS-F), a sequence of numbers is repeated in the same order as presented (verbal attention). In backward digit span (DS-B), numbers are repeated in inverse order of their presentation, implying mental tracking (verbal and visual processes and working memory). The score corresponds to the number of digits in the longest series repeated without errors (maximum score of 9 and 8 points, respectively). Higher scores indicate better performance, and the lowest expected score is 5 for DS-F and 3 for DS-B. The scores were also categorized by percentiles according to age and educational level.

Frontal Assessment Battery (FAB-E), Spanish version[21]. Designed for the assessment of executive function. It uses a score of 0 to 3 depending on the number of correct answers in each subitem (conceptualization, mental flexibility, motor programming and planning, sensitivity to interference, inhibitory control, and environmental autonomy). The total score is 18, with a cut-off score for fronto-subcortical deficit at 16-15 and for fronto-subcortical dementia at 13-12.

Statistical analysis

Since the FMG considered all the people available for evaluation, no sample size calculation was

performed. The quantitative and qualitative variables were described as mean, standard deviation and percentage, respectively. The data distribution was analyzed using the Kolmogorov-Smirnov test. The quantitative variables were compared using the t-test for independent samples and the qualitative variables using the two-proportion Z test. Comparisons were made with JASP version 0.14.0 (https://jasp-stats.org). Statistical significance was established at $p < 0,05$. The effect size (Cohen's d) was determined using G*Power version 3.1.9.7 (http://www.gpower.hhu.de) and the categories were: small 0,2-0,4; medium 0,5-0,7 and large ≥ 0,8.

Results

Data analysis was performed on all recruited women (n = 200). There was no missing data, and no adverse events were recorded during procedures. Sample characteristics are presented in Table 1. The mean age was 42,6 ± 7,3 years (FMG 44,4 ± 6,5 and CG 40,7 ± 7,6). The mean time since FM diagnosis was 6,7 ± 4,3 years. In the FMG, 81% were under drug treatment for FM, while 19% were not medicated, as was the entire CG. The drugs most used were antidepressants (52%), opioid analgesics (31%), and pregabalin (31%).

The mean scores of all cognitive self-perception factors were lower in the FMG ($p < 0,001$) (Table 2). The mean scores of all cognitive neuropsychological tests were lower in the FMG ($p < 0,001$) (Table 3).

For TMT-A, 95% of the FMG and 28% of the CG took longer than the population mean (P_{50}), while for TMT-B, 91% of the FMG and 29% of the CG required more time than the P_{50} to complete the test. Only in FMG, 40% and 9% did not obtain the minimum expected score for the DS-F and DS-B tests, respectively. For DS-F, 86% of the FMG and 35% of the CG scored below the P_{50}, while for DS-B, 75% of the FMG and 45% of the CG scored below the P_{50}. Finally. for FAB-E, only the mean of FMG represented a deficit in executive function, with 78% scoring below the cut-off points. Of these women, 54% were categorized as fronto-subcortical deficit and 24% as fronto-subcortical dementia.

Table 1. Characteristics of the participants

Characteristics	FMG (n = 100)	CG (n = 100)	p-value
Education level			
Secondary complete (%)	100.0	100.0	-
Tertiary complete (%)	33.0	60.0	< 0.001
Working status			
Jobless/unemployed (%)	62.0	25.0	< 0.001
Dependent worker (%)	21.0	64.0	< 0.001
Independent worker (%)	17.0	11.0	0.222
Depressive symptoms (BDI-II)			
Minimal depression	17	75	< 0.001
Mild depression	17	15	0.696
Moderate depression	36	0	< 0.001
Severe depression	30	10	< 0.001
Impact of FM (S-FIQ)			
Mild impairment (%)	2	-	-
Moderate impairment (%)	35	-	-
Severe impairment (%)	63	-	-

FMG fibromyalgia group; CG control group; % percentage.

Table 2. Self-perceived cognitive function

Factors (score)	Total (n = 200) M ± SD	FMG (n = 100) M ± SD	CG (n = 100) M ± SD	p-value
Perceived cognitive impairment	49.2 ± 22.3	34.3 ± 18.1†	64.0 ± 15.1	< 0.001
Perceived cognitive ability	12.4 ± 4.3	9.9 ± 4.7†	14.9 ± 1.4	< 0.001
Noticeability by others	21.6 ± 9.0	16.0 ± 7.5†	27.2 ± 6.6	< 0.001
Impact on quality of life	9.4 ± 5.5	5.0 ± 4.0†	13.8 ± 2.3	< 0.001

FMG fibromyalgia group; CG control group; M mean; SD standard deviation; † large difference.

Table 3. Neuropsychological performance

Tests	Total (n = 200) M ± SD	FMG (n = 100) M ± SD	CG (n = 100) M ± SD	p-value
TMT-A (s)	48.5 ± 18.7	61.5 ± 18.1†	35.5 ± 6.2	< 0.001
TMT-B (s)	100.3 ± 61.2	138.6 ± 65.9†	62.1 ± 15.3	< 0.001
DS-F (n°)	6.2 ± 1.6	5.2 ± 1.2†	7.3 ± 1.2	< 0.001
DS-B (n°)	4.3 ± 1.2	3.6 ± 0.9†	4.9 ± 1.1	< 0.001
FAB-E (score)	16.0 ± 2.4	14.3 ± 2.4†	17.7 ± 0.4	< 0.001

FMG fibromyalgia group; CG control group; M mean; SD standard deviation; s seconds; n° number of digits; † large difference.

Discussion

This study focused on exploring the cognitive component of a sample of Chilean women with FM. The term dyscognition incorporates both the subjective/self-perceived cognitive impairment experience and the objective reduction in cognitive performance[10].

Therefore, in addition to neuropsychological testing, it is important to assess perceived cognitive function. The FACT-Cogv3 has been used in different clinical settings and validated in different cultures and languages[18]. Furthermore, although it is widely used in people with cancer, cross-validation of its factorial structure in non-cancer populations has been advocated, because its items do not mention cancer[22].

The results show that the FMG presented a noticeably higher self-perception of cognitive problems than the CG, suggesting that the fibrofog is relevant. People with FM have reported being distracted, forgetful, having speech/language problems and disorganized thinking[9]. The proportion of cognitive symptoms in FM ranges between 50% and 90%, higher than in healthy subjects or people with rheumatic disorders[11]. Pain, fatigue, depressive states and sleep deficits have been described as contributing factors to the severity of cognitive symptoms[23]. The results are consistent with previous studies[8,10,11,23]. Moreover, although cognitive impairments are often underestimated by the clinical community[12], the perception of memory problems are relevant in FM patients[24].

In general, young people present poorer self-perception of mental health and greater severity of chronic pain-related symptoms, which may be explained by lower levels of resilience compared to elderly[25]. In the specific case of FM patients, resilience has positively influenced their symptoms, increasing positive affect and reducing negative affect[26]. Resilience was not assessed in this study; however, these antecedents may help to explain the low cognitive self-perception expressed by the FMG.

The results clearly show a lower cognitive performance of executive functions in the FMG, in agreement with previous studies and reinforcing the presence of dyscognition[27,28]. In this regard, several studies based on neuroimaging techniques have provided evidence about the disruption of

the brain network in FM[29]. Furthermore, there are no biological markers that can objectify cognitive disorders in this condition, so standardized neuropsychological tests continue to be the best option[28]. A recent meta-analysis has reported worse cognitive performance in people with FM compared to healthy controls in various cognitive domains[30], although controversial results in this area cannot be ignored[11] and FM patients may even present normal cognitive function[31].

Consistently with other studies carried out in Chile[13,14], it was found that the perception of depressive symptoms, as well as the negative impact that FM has on quality of life are very important to consider, due to its possible implications for daily functionality and work status, among others. The cognitive dysfunction can be explained either by the effects of a baseline depressive state or by the specific effects of FM[13,14]. Nevertheless, these variables cannot be identified individually, since they share many common pathophysiological aspects and would probably be manifestations of a single affective spectrum disorder[14]. At the same time, it has been reported that body awareness is altered in FM, along with increased anxiety and depression, suggesting the need to explore this area more comprehensively[13].

People with FM present a complex interrelation between pain, central sensitization, emotion, and cognitive function[31]. It has been hypothesized that the central sensitization and its neurophysiological changes, along with the perceptual amplification and hypervigilance present in FM, could interact to generate the cognitive function deficits[32]. Simultaneously, high levels of pain, depression, anxiety, negative affect, alexithymia and catastrophizing are related to lower cognitive performance[33].

The activation of neurogenesis and neuroplasticity shows that the adult brain experiences neuroglial remodeling due to gene expression changes, not only after stress but also in chronic pain conditions like FM[6]. This plasticity observed in structures like the hippocampus, amygdala, and prefrontal cortex (PFC) produces alterations in memory, concentration, attention, mood, and pain processing. To explain dyscognition in FM, multiple researchers have objectified grey matter loss induced by neuroinflammation in the left supplementary motor cortex[34], as well as in the parahippocampal gyrus, cingulate cortex and amygdala[5], frontoparietal lobe alteration, PFC hypoactivation in working memory tasks, and a hypodopaminergic state in the PFC that decreases working memory performance[7]. Functional, structural and molecular plasticity, the neuroinflammatory state, the alteration in the communication pathways between cognitive processing structures and superposition between networks involved in pain and executive control, explains why chronic pain patients develop cognitive deficits and/or must use more resources in the execution of controlled cognitive processes[34]. All these interactions could be the basis for the cognitive performance and self-perception deficits identified in this study.

A possible limitation of this study corresponds to the difference in the tertiary education level between both groups. In fact, an individual with five additional years of education (for example, a university degree) could have an advantage of about 0,2 to 0,4 SD in cognitive performance[35]. However, educational achievement could be much better related to skills like language or academic knowledge[35,36]. Even in the TMT-A test, which requires quick responses based on simple rules, the effect of educational level has been considered weak[37]. Another possible limitation is related to the pharmacological treatment of FMG since this group did not conform to this criterion. In this study, 31% of FMG had medical indication for pregabalin (20% with a regular dose of 75-150 mg/day, and 11% with a dose of 75 mg/day SOS). Studies have reported that pregabalin can cause cognitive alterations[38,39], however, the alterations occurred with doses over 300 mg/day[38] and 600 mg/day[39], corresponding up to 8 times the dose prescribed to women in the FMG. Regarding antidepressants and opioids, their clinical relevance on the cognitive dimension is rather limited. It has been shown that the impairment of psychomotor and memory functions associated with the chronic use of antidepressants appears to be of low intensity and questionable clinical relevance[40]. On the other hand, opioid therapy for chronic non-cancer pain does not affect cognitive performance and even improves it in certain domains. Attention and memory deficits are probably more pain-related than opioid use[41].

The results of this study are considered valid only for the evaluated sample without the possibility of generalizing them, however they can contribute to an area not previously studied in

our country. Finally, the need to advance in new studies that analyze the influence of clinical, psychological, and sociodemographic characteristics on the cognitive performance of FM patients is recognized.

In conclusion, this research indicates that Chilean women with FM present a greater self-perception of cognitive dysfunctions and lower objective cognitive performance than their healthy counterparts. This reinforces the relevance of considering dyscognition as part of the comprehensive clinical management in this health condition.

Acknowledgements: The research group thanks all study participants for their time and commitment.

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