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Are Fibromyalgia patients cognitively impaired?

Objective and subjective neuropsychological evidence.

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ABSTRACT

Objectives

Patients with Fibromyalgia Syndrome (FM) often complain about a cluster of cognitive disorders that strongly interferes with their work and daily life, but the relationship between impaired cognitive functions and self-reported dysfunctions remains unclear. We aimed to investigate the presence of cognitive impairments in FM patients and to analyze the relationship between the impairments and their evaluation by the patients by means of a comparison with a group of healthy controls.

Methods

30 FM patients and 30 healthy controls performed a neuropsychological and clinical evaluation of short-term, long-term and working memory, executive functions, and self-evaluation of cognitive impairment, depressive and anxiety symptoms. To thoroughly investigate the executive functions we adopted the model of Miyake and colleagues, which identifies four domains: shifting, inhibition, updating and access.

Results and Conclusions

Our results confirmed the presence of impairments of attention, long-term memory, working memory and shifting and updating executive functions in FM patients, compared to healthy controls.

These impairments are reflected in subjective complaints independently of depressive symptoms. The use of a self-report questionnaire in clinical practice would provide a first and easy screen for the presence of cognitive impairment in FM patients and, in most cases, obviate the need for a time-consuming full neuropsychological test battery.

KEY WORDS: cognitive impairments, Fibromyalgia, subjective complaints, neuropsychological tests.

Significance and Innovation

- Our study investigated the neuropsychological performance of fibromyalgia patients in short- and long-term memory, working memory and executive functions (EF), focusing on a multi-domains approach for EF.
- Our results showed that, in Fibromyalgia patients, cognitive impairments are reflected in subjective complaints independently of depressive symptoms.

INTRODUCTION

Fibromyalgia (FM) is a chronic pain syndrome characterized by widespread musculoskeletal pain associated with a heterogeneous series of other symptoms, including fatigue, stiffness, disrupted or non-restorative sleep and psychological distress, particularly mood depression [1,2].

Patients with FM often complain about the so-called "Fibro-fog", a cluster of cognitive disorders not always reflected in poor test-based performance, but which strongly interferes with work and daily life [3,4]. Bertolucci and colleagues reported that 50-80% of FM patients show a decline in working memory, attention and executive functions [5]. However, "executive functions" (EF) represent a multifaceted construct, composed of separable factors, which tap on different cognitive mechanisms and possibly involve the activity of different brain structures. Considering EF as a whole would therefore not allow identification of subtle differences in cognitive complaints.

Although the presence of cognitive impairment has recently been added to the diagnostic criteria of the American College of Rheumatology (ACR) [1], cognitive dysfunctions remain one of the least assessed and treated FM domains in general clinical practice, also because of the expertise and time required for neuropsychological tests. One possible strategy to avoid these hindrances is to use self-report tools, which may, however, be biased by the concomitant presence of depressive symptoms [6]. Indeed, previous studies have found that depressive symptoms are the strongest single contributor to complaints of cognitive deficits in chronic pain patients [7,8].

Some important questions regarding the exact nature of cognitive deficits and the relationship between impaired functions and self-reported dysfunction are therefore still unanswered. The present study aimed to address two issues: i) to analyze the neuropsychological performance of FM patients in short- and long-term memory, working memory and EF by means of a comparison with pain-free healthy controls; and ii) to investigate the relationship between

objective performance on standard neuropsychological tests and subjective self-perception of cognitive status in everyday life through a specific questionnaire, by means of explorative correlational analyses.

To thoroughly investigate EF, we referred to the model elaborated by Miyake and colleagues [9] and revised by Fisk and Sharp [10], which identifies four correlated but partially separable main factors: shifting, which involves the ability to engage and disengage attention from different tasks; inhibition, which implies holding back automatic or preponderant responses; updating, the ability to monitor and code information and replace old non-relevant with new-relevant information; and access, which mediates access to long-term memory representations and is involved in verbal fluency tasks.

METHODS

Subjects

Thirty consecutive fibromyalgia patients (FM) attending the "Città della Salute e della Scienza" Hospital, University of Turin, were enrolled. Due to the high prevalence of FM in women and in order to avoid sex-related effects, only women were enrolled in the study. All patients had a diagnosis of FM made by an expert rheumatologist according to the criteria of the ACR [1]. Exclusion criteria were: under 18 or over 70 years old; low educational level (< 5 years' education) or insufficient knowledge of the Italian language; history of medical condition associated with cognitive dysfunctions; neurological and/or severe psychiatric pathologies. 5 patients were not undergoing psychopharmacological treatments for FM, whereas 25 patients were taking antidepressants for the management of pain. As a control group, 30 healthy women (HC), balanced for age and educational level, were enrolled. In addition to the above exclusion criteria, HC were also to have no history of rheumatologic pathologies or chronic pain. The demographic characteristics of the two groups are given in **Table 1.** The mean (SD) level of

pain intensity of the sample was of 6.68 (2.59) on the Visual Analogue Scale (VAS), with an average disease severity of 63.48 (14.58), as assessed by the Fibromyalgia Impact Questionnaire (FIQ). FM patients scored an average of 9 (3.7) at the depression subscale of the Hospital Anxiety and Depression Scale, whereas controls of 5.4 (3.1).

Procedure

After giving written informed consent, all the subjects participated in a 90-minute testing session during which the clinical, neuropsychological and self-perception of cognitive dysfunction evaluations were performed.

Disease severity due to FM was measured using the Fibromyalgia Impact Scale (FIQ) [11,12], while pain intensity experienced in the previous week was measured on a 0-10 Visual Analogue Scale (VAS). The presence of depressive and anxiety symptoms was evaluated through the Hospital Anxiety and Depression Scale (HADS).

The neuropsychological assessment was made on EF, memory (Rey Auditory Verbal Learning Test) and working memory (N-Back task). In accordance with the Miyake model [9] later modified by Fisk and Sharp [10], and with reference to the article by Aboulafia-Brakha and colleagues [13], we used the Tower of London test for the inhibition, the Trail Making Test for the shifting, the Digit Span Test for the updating and the FAS test for the access EF domains.

To assess self-evaluation of cognitive impairments, we used a self-report questionnaire originally developed to assess perceived changes in cognitive functioning in cancer patients: the Functional Assessment of Cancer Therapy - Cognition Scale (FACT-Cog 2) [14]. Although specifically constructed to evaluate the so-called “chemo-fog” in cancer patients [15,16], as the scale contained no references to oncological pathology or chemotherapy, it may be used with other populations [17,18]. The FACT-Cog was specifically constructed to minimize the impact of distress on patient reports by means of behaviorally-based items [14],

which are less susceptible to depressive and anxiety symptoms. For instance, the occurrence of subjective cognitive disturbances in the FACT-Cog is quantified by reference to behavioral frequencies (once a week), instead of standard system responses (somewhat), as the latter can be more prone to psychological bias. This is of particular importance in FM, which has been described as a stress-related disorder [19] with a high occurrence of psychological comorbidities [20].

Materials

Clinical description

Fibromyalgia Impact Scale (FIQ)

The questionnaire includes 20 items assessing the severity of the disease on a scale of 0-100, with a higher score corresponding to a higher level of impairment [11,12].

Hospital Anxiety and Depression Scale (HADS)

The HADS consists of 14 items divided into two subscales: one for depression and one for anxiety. Each subscale score ranges from 0 to 21, with a score of 8 or more suggesting a clinically relevant level of depression/anxiety symptoms [21,22].

Neuropsychological evaluation

Inhibition

The Tower of London (ToL) task evaluates planning and inhibition EF [23]. The subject has to move three different colored disks from a prearranged sequence on three different pegs to match twelve predetermined goals. The task has to be done as quickly as possible, following several specific rules and in a given number of moves, a number that increases with the difficulty of the task. The execution time is registered as a dependent variable and then converted and compared with the normative data [24].

Shifting

The Trail Making Test (TMT) provides information on visual search, scanning, processing speed, mental flexibility and attention shifting [25,26]. It is composed of two parts: in the first, the subject has to connect numbers ascending from 1 to 25 (TMT-A); in the second, to alternate between numbers and letters (i.e., 1-A-2-B-3-C, etc.) (TMT-B). The test provides three scores: the times (in seconds) of parts A and B, and the difference between them (TMT-BA).

Updating

The Digit Span test (DS) assesses short-term verbal memory span and the ability to manipulate and update verbal information while in temporary storage [27,28]. Subjects are required to repeat, immediately following presentation, increasingly longer strings of single digit numbers, in either forward (DS-F) or reverse order (DS-B). For both trials, the final score is the number of digits correctly repeated.

Access

The F-A-S test assesses phonemic verbal fluency by requiring subjects to orally produce as many words as possible beginning with the letters F, A, or S within a time frame of 1 minute [29,30].

Memory

The Rey Auditory Verbal Learning Test (RAVLT) [30,31] is a word-list learning task assessing short- and long-term memory. Subjects freely recall a 15-word list 5 times (immediate recall, RAVLT-I) after oral presentation. Fifteen minutes later, subjects are asked to recall again the 15-word list (delayed recall, RAVLT-D).

Working memory

Our N-Back paradigm was gathered from the work of Legrain and colleagues [32]. Subjects are presented with 3 blocks of 61 trials each. A cross remains at the center of the monitor for the entire duration of a block. Every 2400 ms two circles are presented, one on the left and one on the right of the central cross. The circles may be both blue or both yellow and remain on the screen for 600 ms. The subject has to match the color of the current visual target to the

color of the preceding one, judging whether the color is the same or not and pressing a certain key on the keyboard as quickly as possible (1-Back Task). The dependent variables are reaction time (RT) and type of response: correct, incorrect, omitted or anticipated (less than 240 ms).

Self-perception of cognitive dysfunction evaluation

The FACT-Cog 2 [14] is a 50-item measure designed to assess cognitive complaints after chemotherapies in cancer patients. On a five-point Likert scale, subjects rate the frequency with which each statement had occurred in the previous week, with higher scores reflecting fewer cognitive problems and a better quality of life. The FACT-Cog yields seven subscale scores (Mental Acuity - MA, Concentration - Con, Verbal and Nonverbal Memory - Mem, Verbal Fluency - VF, Functional Interference - FI, Other People Noticed Deficits - OnD, and Impact on Quality of Life – QoL) and a Total (Tot) score.

Statistical analyses

The data were analyzed using the Statistical Package for Social Science - Version 20 (SPSS-20; SPSS Inc., Chicago, IL, USA). Independent sample t-tests were used to compare continuous variables between the FM and the HC groups. Pearson bivariate correlations were used to analyze the relationship between clinical, neuropsychological and metacognition variables in the FM group. To reduce Type 1 error, only the significantly different variables between the two groups were inserted into the correlational analyses. P-values lower than .05 were considered statistically significant.

RESULTS

Clinical description

FM and controls differed significantly in the level of depressive and anxiety symptoms, with FM patients presenting higher scores on the HADS (**Table 1**). In particular, 22 FM patients (73.3%) vs. 10 (33.3%) HC presented a higher score than the cut-off on the HADS-D

subscale and 19 (63.3%) FM patients vs. 9 (30%) HC presented a higher score than the cut-off in the anxiety subscale. Notably, even when HC showed above cut-off scores, this was close to it.

Neuropsychological variables

Detailed statistical values are given in **Table 2**. Groups means showed a significant difference between the two groups in the DS-B (updating/working memory), with the patients showing a worse performance compared to the HC, whereas only a trend towards a significant difference was found in the DS-F subtest (short-term memory). A significant difference was found in the RAVLT-D test (episodic memory), with the patients showing a lower number of words recalled compared to the HC. In addition, significant differences were found in the TMT-B test (attentional shifting), showing that the patients required more time than the controls to complete the task.

Regarding the 1-Back, the results showed no difference in the accuracy between the two groups, but FM patients had longer reaction times than the controls (891 vs. 722 ms respectively).

In order to bring out the individual differences that could be flattened by group analyses, we analyzed the individual scores by comparing, for each test, the number of subjects with a clinically deficient performance according to the age and education-corrected scores (equivalent score equal or minor to 1). The results showed that a significantly higher number of FM patients compared to the healthy controls had a deficient performance in both the subscale of the RAVLT test (episodic memory) and the ToL (problem solving/EF) (**Figure 1**).

Self-perception of cognitive dysfunctions

FM patients reported a significantly worse judgment compared to the control group in the total score and in all the subscales of the FACT-Cog (**Table 3**). Not only did patients declare deficits in all the cognitive abilities investigated, but also had lower scores in the "Other

People Noticed Deficits" (OnD) subscale, reporting that other people noticed their inadequate cognitive performance. In addition, FM patients reported lower scores on the QoL subscale, which evaluates the impact of cognitive performance on their quality of life.

Correlations between clinical and neuropsychological variables in FM

Given the exploratory nature of these analyses, we did not apply corrections for multiple comparisons [34].

The severity of FM, as assessed by the FIQ, showed a statistically significant positive correlation with the TMT-B (r= 0.434, p=.021) and a trend toward a significant correlation with the TRc (r= 0.375, p= .05) (**Table 4**): the higher the severity of FM, the lower the ability to shift attention (TMT-B) and the higher the reaction times in the 1-Back task. No other significant correlations were found.

Regarding the relationship between the FACT-Cog subscales and the clinical parameters (**Table 4**), the analyses showed statistically significant negative correlations between the FIQ and the Con (p=.008), the FI (p=.022), the QoL subscales (p=.002) and the Total score (p=.004): patients with more severe FM reported greater self-perception of cognitive impairments in concentration and attention, and complained of a greater negative impact of cognitive deficits on their quality of life. A significant correlation also emerged between the FIQ and the OnD subscales of the FACT-Cog (p=.012), and between the latter and pain intensity (p=.040). OnD measures how severe, in the patients' opinion, their cognitive deficits are perceived by other people. Thus, greater severity of pain and clinical symptoms are positively correlated with patients' perception that other people tend to notice the patients' cognitive impairments.

The correlational analyses between cognitive impairment perception and the psychological variables showed that the depression subscale of the HADS and the OnD subscale of the FACT-Cog were significantly and negatively correlated (r= -0.401, p=.028), suggesting that

patients with more severe depressive symptoms claim more that their cognitive deficits are noted by other people.

Finally, the correlational analyses between the neuropsychological tests and the self-perception of cognitive dysfunction showed statistically significant correlations between the VF subscale of the FACT-Cog and the DS-B (r= 0.396, p=.03), the TMT-B (r= -0.361, p=.049) and TMT-BA (r= -0.396, p=.03) scores, suggesting that a worse performance in these tests was correlated to higher complaints in the verbal fluency domain (EF) **(Table 5)**.

A significant correlation was also present between the QoL subscale of the FACT-Cog and the reaction times in the correct responses of the 1-Back task (r= -0.377, p=.04): patients with faster reaction times judged their quality of life as better **(Table 5)**.

DISCUSSION

Fibromyalgia patients often complain about a cluster of cognitive disorders that strongly interferes with their work and daily life [3]. However, cognitive dysfunctions remain under-recognized and under-treated. This because neuropsychological tests require neuropsychological expertise and are time consuming, and because the relationship between subjective cognitive complaints and objective neuropsychological tests in chronic pain patients is still controversial [6,7]. Recently, Landrø and colleagues [6] reopened this debate, finding that subjective complaints in chronic nonmalignant pain subjects were validated on objective neuropsychological assessment. Since Landrø's study, as highlighted by McGuire [34], used norm-referenced neuropsychological tests and did not have a pain-free comparison group, we investigated the presence of cognitive impairment in FM patients and analyzed the relationship between the patients and their self-evaluation of cognitive impairment by means of a comparison with a group of healthy controls.

Neuropsychological profile of FM patients

The finding that FM patients have poorer performances in working memory, attention and EF was reported by Bertolucci and colleagues [5]. However, EF represent a multifaceted construct, composed of separable factors, which tap on different cognitive mechanisms that possibly involve the activity of different brain structures. Considering EF as a whole would not allow identification of subtle differences in cognitive complaints. In the present study, we selected neuropsychological tests in order to cover the different EF aspects: inhibition, shifting, updating and access [9,10].

Our results indicated that FM patients were more impaired in long-term memory (delayed subscale of the Rey test), in the attention shifting (Trail Making Test-B) and in the updating component (Digit Span backward) of EF. In addition, although the accuracy of FM patients in visual working memory was comparable to that of the healthy controls, the former showed a significant slowdown in reaction times (1-Back task).

Complaints about working memory functions are common across a wide variety of chronic pain states and, as reviewed by Berryman, moderate impairment in working memory can be consistently observed across studies and paradigms [35]. Consistently with previous studies showing a slowdown in FM patients' response processing [36], our patients were slower in selecting whether the target was similar or different to a previous stimulus. Seo and colleagues also observed that when a greater amount of manipulation (e.g., 2-back condition) is required, FM patients also show reduced accuracy [36]. It is therefore possible that our task was sensitive enough to detect differences in reaction times, but not difficult enough to require a great amount of manipulation [37] to bring out differences in accuracy.

Regarding the EF, patients showed impairments in the shifting subcomponent, as already highlighted by previous literature [38]. Poor performances on complex tests that involve interference or attention switching have also been found in other chronic pain states [39]. Notably, although the performance at the TMT-B is usually considered a measure of shifting

abilities [13], it also requires updating abilities. Therefore, it is possible that low performances at the TMT-B result from both shifting and updating deficits. In fact, the updating subcomponent, as measured by the DS-B, also appeared to be impaired. Although the patients' mean score on the DS-B was slightly up on the normative data, FM patients showed a significantly lower performance compared to healthy controls. This result is in line with previous reports by Cherry and colleagues [40] and De Melo and colleagues [41] which showed that FM patients performed worse compared to patients with other chronic rheumatic diseases. In line with the literature, we did not observe deficits in the subcomponents of inhibition or access of EF. Veldhuijzen and colleagues [42], investigating the ability of FM patients to inhibit preponderant information, evidenced a slower performance than that of the controls, but equal accuracy. This finding parallels our results on the N-back task and may then point to an underlying problem of mental processing speed and/or psychomotor speed [42]. Evidence that FM patients are not impaired in the access domain is accumulating: FM patients did not show impairments in verbal fluency, either phonemic [43] or semantic [40]. In apparent contradiction, in a review of cognitive dysfunctions in FM [44], Glass and colleagues reported that several studies observed fluency disturbances in FM patients. Methodological problems or differences could account for contrasting results reported in the literature on cognitive deficits in FM. In fact, in some of the articles reviewed by Glass [44], the groups of FM and healthy controls were not balanced in sample size [45] or educational level [46]. Concerning the shifting function, other studies failed to show impairment in FM when comparing performances with the normative data [47,48].

The relationship between clinical and neuropsychological testing in FM patients

Landrø found an accordance between the objective performance and the subjective complaints of cognitive impairments, suggesting that, in chronic pain patients, subjective complaints might reflect genuine cognitive deficits to a larger extent than previously thought [6].

Consistently, Glass and colleagues reported a match between reported and objective deficits in memory capacity in FM patients [49].

Our results indicate a good correlation between the verbal fluency subscale of the FACT-Cog and executive functions and working memory tests, thus suggesting that FACT-Cog can be used as an effective screening tool for objective cognitive deficits. However, it should also be noted that not all the subscales showed strong correlations. Therefore, although subjective complaints can be used as an effective tool to identify objective deficits, a complete picture of patients' cognitive status is better achieved with a more in-depth neuropsychological battery. Another caveat is that the lack of strong correlations can be explained by the operational definition of the tested constructs. What is considered as "memory" in everyday life is tested at a more fine-grained level in the neuropsychological domain. As such, the objective and subjective reports do not capture the same level of definition and, consequently, may not correlate completely.

One possible confound in the interpretation of self-evaluation questionnaires is the concomitant presence of mood disturbances in the majority of chronic pain patients [50]. For instance, Williams and colleagues investigated the relationship between the self-perception of cognitive functioning and the other symptoms commonly present in FM (pain, fatigue, sleep and depressive and anxiety symptoms) [3]. They found that the domains of mood and fatigue were strongly associated with the perceived dyscognitions in FM, whereas pain was uniquely associated with perceived language deficits and, unexpectedly, was not related to attention or concentration. In agreement with this, the results of our study showed that the perceived cognitive dysfunctions were not associated with pain intensity. We found no association between the self-evaluation of cognitive functioning and depressive or anxiety symptoms. This is not surprising, as the FACT-Cog questionnaire is specifically constructed to minimize the impact of distress on patient reports [14]. It is possible that the presence of depressive

symptoms could be partially related to an increase in FM patients' complaints, but that using the FACT-Cog could help to avoid this bias.

The complaints of cognitive deficits were related to the severity of the disease as assessed by the FIQ. This result was expected, given that the FIQ evaluates the impact that FM symptoms have on patients' daily life and that the presence of cognitive deficits is often reported as causing difficulties in everyday functioning. Not only complaints of cognitive deficits, but also objective deficits, and in particular a slowdown in reaction times and shifting deficits, demonstrated a relationship with the severity of the disease. No other relationship emerged between test performance and pain intensity, depressive and anxiety symptoms. With regard to both types of symptoms, data in the literature shows undefined results: a recent review reported that poor scores on EF measures do not seem related to mood disorders, but a correlation between verbal fluency and neuropsychiatric symptoms, such as hallucinations, irritability and anxiety, was described [5].

Limitations

Our study presents some methodological limitations. First, the results of the correlational analyses should be interpreted with caution. Indeed, these results were obtained from a relatively small sample size and were not corrected for multiple comparisons given the exploratory nature of the analysis. Second, we did not select patients on the basis of their ongoing pharmacological therapy. Indeed, some medications can affect cognitive function, making it difficult to discern which cognitive deficit might be attributable to FM and which to medications. Nevertheless, most of our patients taking antidepressants for pain are treated with duloxetine, a dual antidepressant that does not significantly impair cognition [48]. In addition, this limitation does not invalidate the main result of the study, which concerns the degree of accordance between subjective and objective reports.

Conclusion

To conclude, our data indicate that the long-term and working memory, shifting of attention and updating executive functions of FM patients are impaired compared to healthy controls. These impairments are reflected in subjective complaints independently of depressive symptoms. The use of a self-report questionnaire in clinical practice would provide a first and easy screen for the presence of cognitive impairment in FM patients and, in most cases, avoid the need for a time-consuming full neuropsychological test battery.

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Table 1. Demographic and clinical characteristics of the FM and Control (HC) groups.

Variable	**FM (30)**	**HC (30)**	**T (df)**	**P value**
Age (Mean (SD))	52.8 (9.6)	53.8 (12.4)	-0.42 (58)	.680
Years of education (Mean (SD))	10.9 (3.5)	12.4 (3.1)	-1.77 (58)	.081
Marital status	***N° (%)***	***N° (%)***		
Single	*3 (10%)*	*0 (0%)*		
Cohabiting	*1 (3.3%)*	*1 (3.3%)*		
Married	*22 (73.3%)*	*23 (76.7%)*		
Divorced	*4 (13.3%)*	*4 (13.3%)*		
Widowed	*0 (0%)*	*2 (6.7%)*		
Work status	***N° (%)***	***N° (%)***		
Employed	*18 (60%)*	*24 (80%)*		
Unemployed	*3 (10%)*	*1 (3.3%)*		
Retired	*3 (10%)*	*3 (10%)*		
Housewife	*6 (20%)*	*2 (6.7%)*		
HADS	Mean (SD)	Mean (SD)		
HADS-Tot	18.2 (5.8)	11.2 (5.7)	4.7 (58)	<.0001
HADS-D	9.0 (3.7)	5.4 (3.1)	4.2 (58)	<.0001
HADS-A	9.2 (3.2)	5.5 (3.4)	4.3 (58)	<.0001

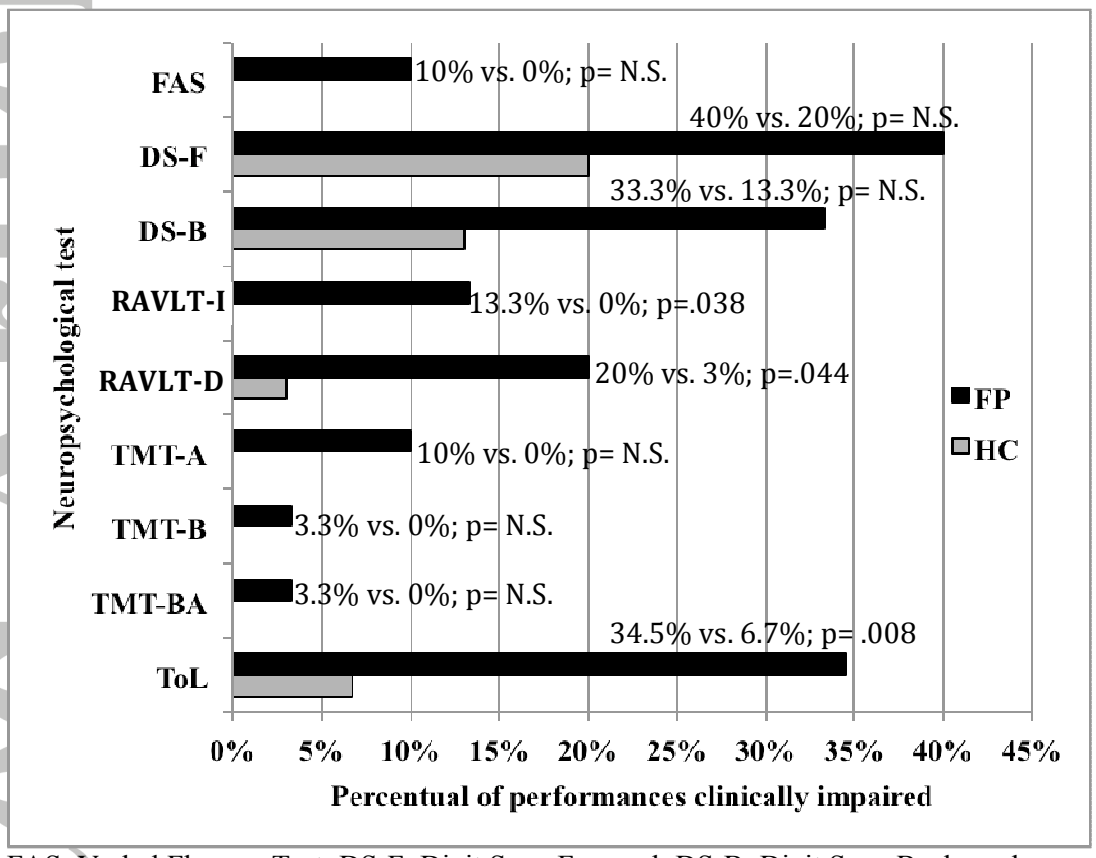
HADS: Hospital Anxiety and Depression Scale; HADS-Tot: total score of the Hospital Anxiety and Depression Scale; HADS-D: Hospital Anxiety and Depression Scale – Depression subscale; HADS-A: Hospital Anxiety and Depression Scale – Anxiety subscale.

Table 2. Neuropsychological performance of FM patients (FM) and Healthy Controls (HC). Mean (SD) scores and t-test analyses are listed.

	FP	HC	T (df)	P value
Verbal fluency/Access				
FAS	37.7 (13.9)	42.1 (7.6)	-1.54 (44.9)	.131
Short-term memory				
DS-F	5.1 (1.0)	5.7 (1.2)	-1.98 (58)	.053
Updating/working memory				
DS-B	3.8 (1.1)	4.4 (0.9)	-2.21 (58)	.031
Episodic memory				
RAVLT-I	47.7 (11.6)	52.0 (7.5)	-1.72 (49.7)	.092
RAVLT-D	9.9 (3.6)	11.7 (2.4)	-2.19 (50.4)	.033
Attentional shifting				
TMT-A	42.4 (19.4)	35.8 (12.0)	1.60 (48.4)	.117
TMT-B	97.3 (39.9)	75.7 (28.6)	2.40 (52.5)	.020
TMT-BA	53.7 (29.9)	39.7 (21.5)	2.08 (52.6)	.042
Problem solving/Inhibition				
ToL	26.9 (3.7)	27.5 (2.9)	-0.57 (58)	.567
Working memory				
1-Back				
TRc	891.2 (185.0)	722.4 (131.9)	4.07 (58)	<.0001
Ne	17.9 (20.6)	14.1 (7.9)	0.95 (37.51)	.349
NV	3.8 (5.4)	4.6 (4.7)	-0.61 (58)	.543

FAS: Verbal Fluency Test; DS-F: Digit Span Forward; DS-B: Digit Span Backward; RAVLT-I: Rey Auditory Verbal Learning Test – immediate recall; RAVLT-D: Rey Auditory Verbal Learning Test – delayed recall; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; TMT-BA: Trail Making Test B minus A score; ToL: Tower of London Test; TRc: reaction time of correct responses; Ne: number of errors; NV: anticipations and omissions.

Figure 1. Percentage of FM patients (FM) and Healthy Controls (HC) with a clinically impaired performance (P.E= 0-1).



FAS: Verbal Fluency Test; DS-F: Digit Span Forward; DS-B: Digit Span Backward; RAVLT-I: Rey Auditory Verbal Learning Test – immediate recall; RAVLT-D: Rey Auditory Verbal Learning Test – delayed recall; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; TMT-BA: Trail Making Test B minus A score; ToL: Tower of London Test.

Table 3. Self-perception of cognitive dysfunctions (Fact-Cog). Mean (SD) and t-test analyses are listed.

	FM	HC	T (df)	P value
MA	2.6 (0.8)	3.3 (0.7)	-3.25 (58)	.002
Con	2.3 (0.8)	3.1 (0.7)	-4.18 (58)	<.0001
Mem	2.4 (0.7)	3.1 (0.6)	-3.79 (58)	<.0001
VF	2.2 (0.8)	2.9 (0.6)	-3.97 (52.1)	<.0001
FI	2.4 (0.7)	3.2 (0.5)	-5.89 (51.6)	<.0001
OnD	2.7 (1.0)	3.4 (0.4)	-3.60 (39.3)	.001
QoL	2.1 (1.1)	3.5 (0.6)	-5.93 (45.6)	<.0001
Tot	2.2 (0.6)	2.9 (0.4)	-5.27 (52.9)	<.0001

MA: Mental Acuity; Con: concentration; Mem: Verbal and Nonverbal Memory; VF: Verbal Fluency; FI: Functional Interference; OnD: Other People Noticed Deficits; QoL: Impact on Quality of Life; Tot: Total score.

Table 4. Correlational analyses in FM patients. Pearson's correlation coefficients are listed.

		FIQ	VAS	HADS-D	HADS-A
DS-B		-0.173	-0.150	-0.236	-0.065
RAVLT-D		-0.169	-0.223	-0.189	-0.028
TMT-B		0.434*	0.336	0.046	0.082
TMT-BA		0.369	0.207	-0.038	0.055
TRc		0.375*	0.244	0.139	0.181
FACT-Cog	**MA**	-0.262	-0.162	-0.182	0.017
	Con	-0.493**	-0.314	-0.272	-0.233
	Mem	0.079	-0.144	-0.256	0.094
	VF	-0.355	-0.245	-0.35	-0.181
	FI	-0.430*	-0.214	-0.296	-0.119
	OnD	-0.467*	-0.390*	-0.401*	-0.24
	QoL	-0.568**	-0.254	-0.245	-0.171
	Tot	-0.523**	-0.325	-0.315	-0.162

* p< .05; ** p< .01

FIQ: Fibromyalgia Impact Scale; VAS: Visual Analogue Scale; HADS-D: Hospital Anxiety and Depression Scale – Depression subscale; HADS-A: Hospital Anxiety and Depression Scale – Anxiety subscale; DS-F: Digit Span Forward; DS-B: Digit Span Backward; RAVLT-D: Rey Auditory Verbal Learning Test – delayed recall; TMT-B: Trail Making Test B; TMT-BA: Trail Making Test B minus A score; TRc: reaction time of correct responses; MA: Mental Acuity; Con: concentration; Mem: Verbal and Nonverbal Memory; VF: Verbal Fluency; FI: Functional Interference; OnD: Other People Noticed Deficits; QoL: Impact on Quality of Life; Tot: Total score.

Table 5. Correlational analyses between the FACT-Cog and the neuropsychological tests in FM patients. Pearson's correlation coefficients are listed.

	DS-B	RAVLT-D	TMT-B	TMT-BA	TRc
MA	0.073	0.058	-0.153	-0.11	-0.1
Con	0.163	0.071	-0215	-0.258	-0.124
Mem	0.21	0.08	-0.122	-0.144	-0.006
VF	0.396*	-0.033	-0.361*	-0.396*	-0.116
FI	0.143	0.119	-0.201	-0.196	-0.214
OnD	0.313	0.023	-0.293	-0.266	0.081
QoL	0.119	0.177	-0.307	-0.357	-0.377*
Tot	0.137	0.13	-0.239	-0.28	-0.304

*p <.05

DS-B: Digit Span Backward; RAVLT-D: Rey Auditory Verbal Learning Test – delayed recall; TMT-B: Trail Making Test B; TMT-BA: Trail Making Test B minus A score; TRc: reaction time of correct responses; FACT-Cog subscales: MA: Mental Acuity; Con: concentration; Mem: Verbal and Nonverbal Memory; VF: Verbal Fluency; FI: Functional Interference; OnD: Other People Noticed Deficits; QoL: Impact on Quality of Life; Tot: Total score.