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Cognitive deficits in patients with chronic fatigue syndrome compared to those with major depressive disorder and healthy controls☆

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ABSTRACT

Object: Chronic fatigue syndrome (CFS) patients report usually cognitive complaints. They also have frequently comorbid depression that can be considered a possible explanation for their cognitive dysfunction. We evaluated the cognitive performance of patients with CFS in comparison with a control group of healthy volunteers and a group of patients with MDD.
Patients and methods: Twenty-five patients with CFS, 25 patients with major depressive disorder (MDD), and 25 healthy control subjects were given standardized tests of attention, working memory, and verbal and visual episodic memory, and were also tested for effects related to lack of effort/simulation, suggestibility, and fatigue.
Results: Patients with CFS had slower phasic alertness, and also had impaired working, visual and verbal episodic memory compared to controls. They were, however, no more sensitive than the other groups to suggestibility or to fatigue induced during the cognitive session. Cognitive impairments in MDD patients were strongly associated with depression and subjective fatigue; in patients with CFS, there was a weaker correlation between cognition and depression (and no correlation with fatigue).
Conclusions: This study confirms the presence of an objective impairment in attention and memory in patients with CFS but with good mobilization of effort and without exaggerated suggestibility.

1. Introduction

Chronic fatigue syndrome (CFS) is a debilitating condition that is characterized by chronic fatigue, impairment of short-term memory and musculoskeletal pain [1]. CFS is marked by persistent or relapsing debilitating fatigue that: (1) does not resolve with bed rest; (2) is severe enough to reduce daily activity; and (3) has no somatic explanation [2]. A number of symptoms may be present, including myalgia, headache, sore throat, and pains in the joints. Cognitive complaints are also frequently reported, particularly in relation to memory and concentration [3–7]. However, although patients with CFS often complain of cognitive difficulties, neuropsychological studies that have attempted to objectively measure cognitive deficits in such patients have yielded conflicting results. Subjective ratings of cognitive competence are poor predictors of laboratory results [7], because they can be based on factors other than competence, such as emotional distress, fatigue, or malaise. In objective cognitive tests, authors have found that patients with CFS usually perform in the normal range for general intellectual abilities (WAIS: [3,8]; and NART: [8]) and higher cognitive functions (planning, verbal fluency, abstract reasoning, problem solving; see: [3–5,9–12]). Data are less consistent for attention and memory: some authors have reported impairment in verbal memory [5,10,13], visual memory [5], concentration [6,11,13], attention span [6], reaction times [14–16], and speed of information processing [4,10], while others found no abnormalities in verbal memory [3,12,13,15], visual memory [3,5,11,17], concentration [7,10], attention span [5,6,10,11], or reaction times [5]. These conflicting results raise questions about the methodology of these studies and the objectivity of the tests used to assess the cognitive impairments. There is, indeed, a marked discrepancy between subjective complaints and objective performance that casts doubt on the validity of the cognitive symptoms. In one study [10], despite no memory deficits on neuropsychological tests, patients with CFS had more subjective complaints of cognitive impairment on

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Table 1
Groups description.

	n	Age			Sex	Years of education			Length of illness (in years)		
		Mean	SD	Range	M/W	Mean	SD	Range	Mean	SD	Range
Chronic fatigue group (CFS)	25	42.5	9.8	21–55	4/21	15.3	1.1	12–17	4.2	3.5	1–16
Depression group (DG)	25	45.8	11.0	21–68	9/16	12.7	3.1	6–17	–	–	–
Control group (CG)	25	42.1	16.4	21–64	9/16	14.8	1.8	12–17	–	–	–

a metamemory questionnaire than patients with major depressive disorder (MDD) or multiple sclerosis, or healthy controls.

Moreover, because cognitive deficits are core symptoms of MDD [18,19] and because CFS patients have high rates of major current and lifetime depressive episodes [20], depression must be considered a possible explanation for the cognitive dysfunction in CFS. Indeed, it has been suggested that cognitive complaints in CFS may be attributable to a depressive process in somatically focused individuals [17]. Such an explanation would suffice if a correlation between symptoms of depression and anxiety and certain neuropsychological measures had been observed (as for example in studies [6,7,11,17,21]). However, this is not the case in all studies [3–5,13,15,22–25]. In addition, the possible direct effect of fatigue on cognitive performance in CFS has also been examined. Although most authors [5,6,25–27] found no relationship between the level of fatigue and performance on memory and attention tests, one was noted by Joyce et al. [13]. Thus, the direct effect of fatigue on cognitive performance in CFS remains unclear. In another condition, the post-polio syndrome, Ostlund et al. [28] also did not find a relationship between general fatigue and cognitive deficits. Finally, there are multiple methodological difficulties in the neuropsychological literature on CFS, for example, heterogeneity in the diagnosis of CFS across studies, presence of comorbid depression, and lack of control groups.

It is, therefore, difficult to clarify whether there are objective cognitive deficits in patients with CFS, particularly in terms of memory and executive functions, or whether the cognitive impairments are directly associated with the depressive symptoms in this condition. Hence, we evaluated as a primary objective, the cognitive performance of patients with CFS using standardized verbal and visual memory tests, as well as sustained attention, phasic alertness, and the fatigue effect, compared with a control group of healthy volunteers. We investigated the same variables in a group of patients with MDD. Particular attention was paid to the evaluation of the quantitative dimension of depressive symptoms in the patients with CFS. Investigation of attention and memory functions was chosen because these are the functions most often reported as impaired in CFS but also in MDD. Our primary hypothesis was that patients with CFS would have cognitive impairments that were only partially correlated with the depressive dimension of the condition, suggesting that some cognitive impairments may be present independent of the depressive dimension. The partial relationship between cognitive and depressive symptomatology could be confirmed by direct comparison with the MDD group.

In addition to these primary objectives, we wanted to investigate the possible gap between the subjective and objective dimensions of cognition, as some studies have reported more subjective complaints than objective impairments. Our secondary objectives were, therefore, to examine the subjects' reactions to suggestibility. Some authors [29] have argued that subjects with CFS are more suggestible than healthy persons using a measure of general suggestibility and the hypnotic induction profile (HIP) [30]. Another way to approach this question would be to investigate task involvement in order to exclude deficit feigning and the attribution of cognitive deficits to the possibility that CFS patients may be less than optimally motivated in the tasks (thus expending less effort because of a metacognitive belief of cognitive impairment).

2. Materials and methods

2.1. Subjects

We studied 25 patients with CFS, 25 patients with MDD, and 25 healthy control subjects (see Table 1 for demographic parameters of these three groups). All of the participants were right-handed. There was no significant among-group difference for age [$F(2,72) = .64$; $p = .52$]. There was a significant difference in degree of education among the three groups [$F(2,72) = 10.41$; $p < .01$], with the MDD group having fewer years of education than the CFS and control groups (both $p < .01$). The groups were comparable for gender [$\chi^2(2, 75) = 3.86$, $p > .10$].

All the CFS patients met the diagnostic criterion for CFS, i.e., at least six months of unexplained disabling fatigue [1,2]. CFS subjects were recruited from the Referral Centre for CFS and MDD patients from the outpatient psychiatric unit of the Cliniques Universitaires Saint-Luc, Brussels. The healthy controls were recruited from the care staff and volunteers of the Cliniques Universitaires Saint-Luc and from volunteer associations. Before entering the study, patients and controls gave their informed consent to a protocol approved by the Medical Ethics Committee of the School of Medicine of the Université catholique de Louvain. The patients and the control subjects underwent a psychiatric interview supplemented by the Structural Clinical Interview for DSM-IV Axis I Disorders (SCID) [31] to confirm the diagnosis of unipolar major depressive episodes in the patients with MDD and the absence of any Axis I psychiatric disorder in the controls and the patients with CFS (in particular the absence of MDD). Exclusion criteria for the control subjects were unexplained fatigue, an organic condition that causes fatigue, an unstable medical condition, an organic brain disorder, the use of psychotropic drugs, and a current or past mental disorder on the basis of the SCID I interview.

2.2. Procedure

2.2.1. Self-questionnaires

Several scales were used to assess anxiety, depression, and fatigue. The 40-item State Trait Anxiety Inventory Scale (STAI A & B) [32] assesses anxiety symptoms. The first sub-scale indicates the state of anxiety at the moment of the session (STAI-A); the second sub-scale indicates the subject's anxiety traits (STAI-B). The results are converted into T-scores. A French version of the 21-item Beck Depression Inventory (BDI) [33] assesses depression in adults [34]. The scores range from 0 to 63. A score of 13 or less indicates a non-depressed state; a score from 14 to 19 corresponds to "mildly depressed"; and a score over 20 indicates clinical depression. The geriatric depression scale (GDS) [35] is a 30-item instrument for assessing depression. The value of this questionnaire is that physical symptoms are excluded, whereas other instruments of depression assessment are too rich in somatic symptoms and too poor in cognitive symptoms. Scores range from 0 to 30. A score of 10 or less is considered to indicate the absence of depressive symptoms, and a score over 11 reflects the presence of depressive symptoms. The fatigue severity scale (FSS) [36] is a 9-item scale assessing "disabling fatigue". Total scores range from 9 to 63. The higher the score, the more the fatigue is disabling.

2.2.2. Cognitive tasks

Attention was assessed with one computerized reaction time test: the Phasic Alertness Task of the TEA1.5 battery [37]. In this task, the subject is instructed to press a button as quickly as possible as soon as a cross appears in the centre of the screen. In one condition, the cross is preceded by a warning signal (i.e., a beep) while in the other condition there is no warning signal. The median reaction time for correctly detected crosses is calculated for each of the two conditions (i.e., with and without an audible warning signal). Phasic alertness reflects optimization of the state of preparation or reactivity of a subject when the information he/she has to deal with is preceded by a signal warning of its imminent appearance.

In addition to this reaction time task, two working memory tasks were administered. The first was the computerized working memory task of the TEA1.5 battery [37] where the subject has to press on a button when a given stimulus (a digit which appears in the centre of the screen) is identical to a stimulus shown previously (the next to last digit shown on the screen). A hundred digits from 1 to 9 were presented in succession at 3-s inter-stimulus intervals. The median reaction time for correct responses and the numbers of correct responses and errors are recorded. The second working memory task was the computerized paced auditory serial attention test (PASAT) [38] where single digits are presented auditorily. Subjects were instructed to add each new digit to the one immediately prior to it. The test score is the total number of correct sums given in each trial.

Finally, two episodic memory tasks (one verbal and the other visual) were also administered. The verbal task was the word memory test (WMT) [39]. This computerized memory test measures the ability to learn a list of 20 pairs of words displayed on the screen, e.g., pig/bacon. There are then six sub-tests: immediate recognition (IR), delayed recognition (DR), multiple choice (MC), paired associates (PA), free recall (FR), and long delayed free recall (LDFR). Visual episodic memory was assessed using the "Doors test" [40] in which subjects are instructed to memorize two series of 12 pictures of doors (garage doors, front doors, etc.). Each door is shown for 3 s and then the subject is asked to recognize the door (target items) from a choice of four pictures of doors (score ranging between 0 and 24).

2.2.3. Cognitive fatigue assessment

In addition to the subjective assessment of fatigue using the fatigue severity scale, we assessed fatigue more objectively by administering the phasic alertness part of the TEA again at the end of the testing session (which took approximately an hour and a half). A fatigue index (total reaction times of Alertness test 2 minus total reaction times of Alertness test 1) was calculated and compared among groups using an ANOVA. A higher fatigue index indicated a stronger effect of fatigue on phasic alertness.

2.2.4. Suggestibility and lack of effort (simulation)

We also added some tasks and/or indexes assessing suggestibility and lack of effort. Suggestibility is defined as the tendency to respond to suggestions. The effect of suggestibility was assessed by dividing the PASAT into two equal parts. Half-way through the test there was a pause, and the investigator said: "Now, after this first part of the test, you probably feel a certain degree of fatigue, which we will investigate before going on with the task". The subject had to assess his/her subjective fatigue on a 7-point Likert scale (fatigue severity scale, FSS, ranging from "no fatigue" to "extreme fatigue"). A suggestibility index (total score of PASAT 2 minus total score of PASAT 1) was calculated and compared among the groups using an ANOVA. A higher negative index indicated a greater deterioration of scores on PASAT 2 and thus a greater response to suggestibility.

For the assessment of simulation (or lack of effort), we used a specific task: the Amsterdam Short Memory Test (short version) [41]. This task comprises 45 items. Each item involves the presentation of five words from a common semantic category (e.g., x, y, z, w, v). Subjects have to read the words aloud and memorize them. They are then distracted with a simple addition or subtraction task. After this short interference task, five words from the original semantic category are presented (e.g., x, y, z, a, b). Three words are the same as in the previous trial, and two are new and less frequent for that category. Subjects have to indicate which three words were present in the first series (no time limit). The test score is the number of correct responses; the maximum score is 45 (3 points for each 15 items). In a preliminary study, we showed that a cut-off score of 40/45 (the lowest score obtained by a group of patients with marked cerebral damage and severe amnesia) was the best threshold to detect subjects asked to feign a memory deficit (these subjects having a weaker score).

In addition to this specific task, some index of simulation can also be extracted from the WMT and the Doors tests. Indeed, IR and DR sub-tests from the WMT are particularly sensitive to lack of effort. The consistency of the responses from IR to DR is calculated. This score allows investigation of lack of effort or simulation. The person receives a point if the correct response was chosen in the two sub-tests or if the incorrect response was chosen in the two sub-tests and receives a score of zero if responses were inconsistent for a given item, scoring "correctly" with some trials and "incorrectly" with others. The cut off score is <70%. Using this score, the performance of the subject can be questioned [42]. In the Doors test, the subject's score is compared to chance performance. Indeed, it is widely recognized that amnesic patients use implicit memory (or familiarity) to recognize the target item, and perform better than chance in most recognition tasks. Hence, if the subject's performance is significantly near to or less than that of chance (here 25% correct which is a score of 6/24), the examiner may conclude that the examinee has intentionally chosen incorrect responses and may have been motivated to perform inadequately [43].

2.3. Data analysis

Data were analyzed with Statistica 5.0. The groups were compared using a univariate analysis of variance (ANOVA). The LSD test or planned comparisons (post hoc comparisons) were calculated. The statistical significance for all of the analyses was set at $\alpha = .05$.

3. Results

3.1. Depression, anxiety and subjective fatigue

First analyses of the questionnaires (see Table 2) showed a significant main effect for each index. Post hoc analysis suggested that patients with CFS were more depressed than controls on the BDI and GDS questionnaires, but less depressed than the MDD group. The same pattern was observed for anxiety with patients with CFS being more anxious than the control subjects, but less anxious than the patients with MDD. Concerning subjective fatigue, patients with CFS were significantly more tired than the depressed and control groups. Moreover, the patients with MDD had a higher fatigue score than the control group.

3.2. Do patients with CFS have cognitive deficits?

Our first question was to verify whether patients with CFS had cognitive impairments compared to control subjects. Results for the CFS and control groups are presented in Table 3. Compared with normal controls, patients with CFS subjects had slower total median RT and median RT without signal on the first alertness subtest (TEA) but not median RT with signal. There was no significant

Table 2
Results on depression, anxiety and fatigue questionnaires.

	CFS Mean (*SD*)	DG Mean (*SD*)	CG Mean (*SD*)	ANOVA	CG/DG	CG/CFS	DG/CFS
Anxiety							
STAI							
STAI-A	56.6 (*14.2*)	65.9 (*14.3*)	41.4 (*6.9*)	$F(2,72) = 25.32$; $p < .01$	**	**	**
STAI-B	55.2 (*9.4*)	65.2 (*6.7*)	40.4 (*8.5*)	$F(2,72) = 56.63$; $p < .01$	**	**	**
Depression							
BDI	16.1 (*6.5*)	25.6 (*8.6*)	2.4 (*3.2*)	$F(2,72) = 80.3$; $p < .001$	***	***	***
GDS	17.8 (*6.2*)	22.0 (*5.8*)	4.0 (*3.3*)	$F(2,72) = 79.29$; $p < .001$	***	***	**
Fatigue							
FSS	57.8 (*5.1*)	51.4 (*9.8*)	23.1 (*11.7*)	$F(2,72) = 59.44$; $p < .001$	***	***	*

Note. CFS: chronic fatigue group; DG: depressed group; CG: control group; ANOVA: results of univariate ANOVA on groups; x vs x: results of the post hoc comparisons; *p* value is indicated when >.05.
* $p = <.05$.
** $p = <.01$.
*** $p = <.001$.

Table 3
Results on cognitive tests.

Tasks	CFS Mean (*SD*)	DG Mean (*SD*)	CG Mean (*SD*)	ANOVA	CG DG	CG CFS	DG CFS
Reaction time							
Alertness 1 (TEA)[a]							
Median time total	392.97 (*147.55*)	395.26 (*14.3*)	392.97 (*6.9*)	$F(2,72) = 4.24$*	*	*	=.96
Median time without signal	427.10 (*165.14*)	433.10 (*254.45*)	300.20 (*46.17*)	$F(2,72) = 4.63$*	**	*	=.91
Median time with signal	368.42 (*140.78*)	373.86 (*210.23*)	280.87 (*58.02*)	$F(2,72) = 2.98$≈			
Alertness 2 (TEA)[a]							
Median time total	435.72 (*121.12*)	470.58 (*327.20*)	295.42 (*72.64*)	$F(2,66) = 5.63$**	**	*	=.55
Median time without signal	473.26 (*179.54*)	515.90 (*355.35*)	310.12 (*85.21*)	$F(2,68) = 6.13$**	**	**	=.65
Median time with signal	415.92 (*118.55*)	435.85 (*276.36*)	284.88 (*59.28*)	$F(2,67) = 5.88$**	**	**	=.69
Working memory							
PASAT							
Score total	48.6 (*7.49*)	41.08 (*13.76*)	53.72 (*6.96*)	$F(2,72) = 10.3$***	***	≈	**
Score total (*Part A*)	24.52 (*3.80*)	21.84 (*6.41*)	27.48 (*3.49*)	$F(2,72) = 8.8$***	***	*	*
Score total (*Part B*)	24.08 (*4.73*)	19.24 (*7.69*)	26.24 (*3.74*)	$F(2,72) = 10.1$***	***	=.18	**
Working memory (TEA)							
Median time	798.52 (*254.35*)	608.74 (*385.15*)	547.98 (*186.95*)	$F(2,72) = 5.2$**	=.46	**	*
Correct response	9.16 (*3.52*)	7.72 (*4.86*)	12.72 (*2.35*)	$F(2,72) = 12.0$***	***	**	=.18
Episodic memory							
WMT							
Immediate recognition (*IR*)	95.84 (*8.60*)	94.40 (*10.83*)	98.60 (*2.29*)	$F(2,72) = 1.7$	–	–	–
Delayed recognition (*DR*)	94.40 (*10.34*)	95.36 (*8.93*)	100.00 (*0.0*)	$F(2,72) = 3.6$*	*	*	=.69
Multiple choice (*MC*)	92.60 (*11.82*)	91.00 (*15.41*)	98.60 (*2.29*)	$F(2,72) = 3.1$*	*	≈	=.62
Paired associates (*PA*)	89.40 (*14.53*)	96.20 (*46.28*)	97.60 (*3.85*)	$F(2,72) = .6$	–	–	–
Free recall (*FR*)	71.08 (*12.57*)	77.24 (*19.70*)	86.60 (*9.18*)	$F(2,72) = 7.3$**	*	***	=.14
Long delayed free recall (*LDFR*)	70.84 (*16.84*)	79.80 (*19.69*)	86.52 (*9.93*)	$F(2,72) = 6.0$**	=.14	***	≈
Doors test—total score (/24)	16.76 (*2.55*)	16.80 (*3.08*)	19.52 (*1.98*)	$F(2,72) = 9.4$***	***	***	=.96
Fatigue index	42.75 (137.63)	71.85 (142.41)	10.63 (93.9)	$F(2,66) = 1.3$			
Suggestibility index	−.44 (4.18)	−2.6 (3.30)	−1.24 (1.9)	$F(2,72) = 2.8$≈	=.15	=.39	*

Note. CFS: chronic fatigue group; DG: depressed group; CG: control group; ANOVA: results of univariate ANOVA on groups; x vs x: results of the post hoc comparisons; ≈: <1.0 and >.05; *: <.05; **: <.01; ***: <.001.
[a] Alertness 1 corresponds to the administration of the task at the beginning of the session while Alertness 2 corresponds to the administration of the task at the end of the testing session.

difference in the alertness index [$F(2,72) = .59$; $p = .55$] suggesting that CFS patients gained the same benefit from the warning signal as the control subjects did. For the working memory tasks, CFS patients had longer median times and fewer correct responses than controls on the working memory (TEA) and a tendency for lower total scores on the PASAT. It is also interesting to note that for the working memory (TEA) there was a negative correlation between median time and length of illness ($r = -.4563$; $p = .022$) and between correct responses and length of illness ($r = -.4331$; $p = .031$), suggesting that the longer the duration of the CFS, the more impaired the patients were on this cognitive test. For the visual memory task (Doors test), patients with CFS had lower total scores than did control subjects. For verbal episodic memory (WMT), CFS patients had lower scores on DR, FR and LDFR and a tendency to lower scores on MC.

3.3. Comparison of the cognitive performance of patients with CFS and those with MDD

A univariate ANOVA on reaction times for the first administration of the alertness subtest (TEA) showed a significant main effect on *total median RT*. There was no significant difference between the MDD and the CFS groups, but both differed from the control group, which responded faster. The same significant main effect for group was observed for the *median RT without signal* but not (almost significant) for the *median RT with signal*. All three groups benefited from the warning signal in the same way.

For the two working memory tasks, a univariate ANOVA revealed a significant main effect on the total score of the working memory (TEA) and PASAT. There was no significant difference in the quality of responses to the working memory subtest between

Table 4
Correlations between cognitive scores and depression and subjective fatigue measures.

Cognitive scores	CFS			DG		
	BDI	GDS	FSS	BDI	GDS	FSS
Median time total Alertness 1 (TEA)	.16	.25	.07	.70***	.57*	.5084*
Median time total Alertness 2 (TEA)	.07	.16	−.15	.75***	.55*	.5706*
PASAT—Part 1	−.46*	−.15	−.09	−.55**	−.09	−.5130**
PASAT—Part 2	−.41*	−.20	−.3154	−.57**	−.13	−.5699**
PASAT—Total	−.49*	−.20	−.2442	−.58**	−.12	−.5572**
Working memory TEA—median time	.34	.40*	.2362	−.20	.24	.0550
Working memory TEA—correct response	−.15	−.18	−.1437	−47*	−.06	−.2956
Word memory test—IR	−.03	.17	−.0509	−.62***	−.41*	−.3691
Word memory test—DR	.00	.11	−.0362	−.65***	−.45*	−.3698
Word memory test—MC	.04	.20	.0296	−.74***	−.49*	−.4172*
Word memory test—PA	.02	.12	−.0325	−.55**	−.47*	−.1304
Word memory test—FR	−.03	−.13	−.0638	−.66***	−.47*	−.5643**
Word memory test—LDFR	−.06	−.21	−.0424	−.61***	−.41*	−.5265**
Doors test—total score (/24)	−.06	−.15	.0599	−.67***	−.43*	−.4013*
Cognitive fatigue index	−.02	.16	−.2035	.51*	.28	.4357
Suggestibility index	−.01	.12	−.2764	−.26	−.10	−.3313

Note. CFS: chronic fatigue group; DG: depressed group; CG: control group.
* $p = <.05$.
** $p = <.01$.
*** $p = <.001$.

the MDD and CFS groups, but both differed from the control group, which was more effective. Moreover, a univariate ANOVA on the groups showed a significant main effect for group on the median RT of response. There was no significant difference between the MDD group and the controls, but both differed from the patients with CFS who were slower. For the total PASAT scores, there was a tendency for lower scores in CFS patients compared with controls, and both differed from the patients with MDD depressed who were less effective.

For the memory tasks, a univariate ANOVA on the visual memory task (Doors) revealed a significant main effect for group. There was no significant difference in the quality of responses between the MDD and CFS groups, but both differed from the control group, which was more effective. A univariate ANOVA on the WMT revealed a significant main effect for group for DR, MC, FR, LDFR. For DR, MC and FR, patients with MDD and those with CFS had lower scores than controls with no difference between MDD and CFS patients. However, and notably, patients with CFS showed worse performances for the LDFR compared to controls and patients with MDD, but these latter groups did not differ from each other.

3.4. Effect of fatigue

Regarding the impact of objective fatigue, a univariate ANOVA on the fatigue index (total reaction times of Alertness test 2 minus total reaction times of Alertness test 1), showed no significant group effect suggesting that all groups were influenced equally by the effect of fatigue.

3.5. Subject's response to suggestibility

Concerning suggestibility, a univariate ANOVA on the suggestibility index revealed a tendency for a significant main group effect; post hoc analysis showed only a tendency for patients with MDD to be more suggestible than patients with CFS. Within the CFS group now, we also observed a positive correlation between length of illness and the suggestibility index ($r = .4518$; $p = .023$); suggesting that the longer these patients had had CFS, the more open they were to suggestion.

3.6. Lack of effort/simulation

Globally, the majority of controls and patients obtained good scores, excluding a global lack of effort or simulation. At the individual level and considering the cut-off scores for each task: (1) no patients obtained a score near or below chance on the Doors test; (2) only one patients with CFS and one with MDD obtained a result under the threshold on the ASTM (40/45); and (3) two patients with CFS and two with MDD obtained a consistency result under the threshold on the WMT (70%).However, removing these four subjects from our database did not change the results for the different cognitive tests presented earlier.

3.7. Correlations between cognition and measures of depression and subjective fatigue

Are the cognitive impairments in patients with CFS associated with depressive symptomatology or subjective fatigue, and are these potential associations the same as those present in patients with MDD? To answer these questions, we evaluated correlations between the main cognitive scores and BDI and GDS scores for depression, and FSS scores for subjective fatigue (Table 4). Our results clearly demonstrate that, for patients with CFS, surprisingly, there were no correlations between cognitive scores and subjective fatigue, and only a few correlations between the working memory dimension (measured by PASAT and WMT) and depression, with no correlations at all for other cognitive dimensions. These results contrast with those of patients with MDD, for whom there were strong correlations between most cognitive scores and not only the depression dimension but also subjective fatigue. We also analyzed for CFS patients whether scores on cognitive measures differed between the CFS patients with significant depressive symptoms (GDS ≥ 11; BDI ≥ 14) and those CFS patients without the presence of depressive symptoms (GDS < 11; BDI < 14). We did not observe any significant difference between the two groups.

4. Discussion

In this study, we examined the performance of patients with CFS during different cognitive tasks because there is still debate concerning the presence and interpretation of cognitive impairments in patients with CFS, with some studies showing cognitive impairment and others not. If there are cognitive deficits in CFS patients,

the question is then to know whether these are core features of the condition or an indirect consequence of other aspects of associated comorbitities, one of the most important being depression. In this context, the cognitive performances of patients with CFS were compared with those of healthy controls.

Our results clearly demonstrate cognitive impairment in patients with CFS and, more importantly, that it cannot be explained by a lack of effort. Indeed, in terms of the subjects' involvement in the task, we observed very good global performances not only for patients with MDD but also for those with CFS. Also, importantly, the cognitive impairments remained significant after the few patients who showed a lack of effort ($n = 4$ among a total of 50 patients) were removed from our database.

The patients with CFS differed from the control group in several aspects. We observed that the patients with CFS were significantly more anxious, more depressed, and more tired than the healthy controls. The overall results of the cognitive tests showed that, relative to healthy controls, cognition was weaker among the patients with CFS. Analyses based on the group comparisons lead to the conclusion that the patients with CFS showed an impaired or markedly decreased ability to maintain attention and alertness. The patients with CFS had slower phasic alertness. They also showed impairments in one working memory test (TEA) and a tendency to impairments in another (PASAT) and in long-term memory (visual and verbal), compared with the controls.

How can we interpret these cognitive impairments? Are they directly linked to the pathophysiological mechanism of CFS or do they reflect an indirect consequence of the depressive symptoms often observed in this condition? Two arguments suggest that the cognitive deficits in CFS are core symptoms of the condition and are not the consequence of the depression dimension of the disorder. First, when we compared the performances of patients with CFS and those with MDD, there were several differences: the patients with CFS were significantly less anxious and less depressed, but more fatigued than the patients with MDD. These results are in line with other papers. Using the BDI, Short et al. [25] and DeLuca et al. [44] reported that subjects with CFS were more depressed than controls. Cope et al. [3] and DeLuca et al. [10], on the other hand, found that subjects with CFS were less depressed than depressed patients. Using the STAI, Riccio et al. [8] and Cope et al. [3] reported that there were no differences between patients with CFS and controls. However, DeLuca et al. [10] found that patients with CFS were more anxious than controls but less anxious than depressed subjects, similar to the results of the present study. Finally, the literature also reports that subjects with CFS are more tired than controls [44,45] and more tired than depressed subjects [10]. For the cognitive tests, patients with CFS and those with MDD also differed in several aspects. There were three differences for the reaction time and accuracy measures we used: the patients with CFS were slower in the TEA working memory test and obtained a better accuracy score on the PASAT test than the patients with MDD. It is also very interesting to note that patients with CFS were more impaired on the long delay free recall of the WMT than patients with MDD. This index is probably the most sensitive for the detection of memory difficulties.

The second argument for considering that cognitive deficits are core symptoms of CFS comes from the correlation analyses. Although, as expected, cognitive impairments in patients with MDD were strongly associated with depression and subjective fatigue, in patients with CFS we only observed: (1) a weak correlation between working memory index and depression; (2) no correlation at all for the other cognitive dimensions and depression; and (3) no correlation between cognitive measures and subjective fatigue. Our results are in line with those of several authors [3–5,13,15,22–25] who have shown that symptoms of depression do not correlate significantly with a variety of neuropsychological measures, although other studies [6,7,11,17,21] have reported such a correlation. As discussed by others [23], the fact that, in this study, MDD and CFS patients differed in several aspects is not surprising. From a neurobiological point of view, there are also differences: hypoactivity of the hypothalamic-pituitary-adrenal axis is usually observed in CFS, in contrast to the hyperactivity of this axis in MDD [46–48]. Interestingly, in an atypical subtype of MDD (with hypersomnia, leaden paralysis, mood reactivity, interpersonal rejection sensitivity), hypoactivity of this axis is also observed [46,47].

Our results show that globally the patients with CFS were no more sensitive to suggestibility than the other two groups and, in fact, were less suggestible than the patients with MDD. Our results do not replicate the findings of DiClementi et al. [29], who observed that patients with CFS were more suggestible than controls on a measure of general suggestibility (recall task of history) and on the hypnotic induction profile (HIP) [30]. The HIP is a brief structured technique that measures behavioural, perceptual, and cognitive responses to suggestions. Subjects are asked to perform an eye roll and then, once their eyelids are closed, the hypnotic induction involves suggestions by the examiner of floating and arm levitation. In that study, induction scores for the CFS group were higher than those for controls. It is important here to specify that suggestibility is not synonymous with gullibility. Suggestibility refers to a type of information processing that is selective and distorted in that relevant information cannot be handled in a balanced fashion. According to DiClementi et al. [29], "suggestible persons with CFS do experience the symptoms they report. However, a tendency to focus on symptoms, perhaps to the exclusion of other information, may be related to CFS patients' difficulties in processing complex cognitive information, and difficulties with divided attention" (pp. 684–685). In line with this argument, it is important to note that although, in our study, patients with CFS were not more suggestible than the two other groups, there was a positive correlation between length of illness and the suggestibility index. This may mean that the longer the CFS illness, the more patients focus on their symptoms and if someone else focuses their attention on their symptoms, they will show a greater response to that suggestion and this process will impair the realization of the cognitive task in which they are involved.

As regards the impact of fatigue, there were no significant differences among the three groups on the fatigue index. These results are in line with the observations of most other authors [5,6,25–27] who found no relationship between the level of fatigue in patients with CFS and their performance on cognitive tests. However, Joyce et al. [13] did find one relationship between these parameters. It is interesting to note that in another condition, the post-polio syndrome, Ostlund et al. [28] also found no relationship between general fatigue and cognitive deficits. However, it is important to remember that the fact that we did not observe a direct effect of fatigue on cognitive variables does not mean that, at the brain level, the mental fatigue induced by our task did not have different consequences on brain activity in our three study populations. In a functional neuroimaging study, Cook et al. [49] observed that, compared with normal controls, patients with CFS did not differ in finger tapping or auditory monitoring tasks (PASAT), but exhibited significantly greater activity in several cortical and subcortical regions during the fatiguing cognitive task (PASAT). In particular, compared to controls, patients with CFS exhibited greater utilization of brain regions within the working memory system in order to successfully complete the PASAT. These results, therefore, suggest an association between subjective feelings of mental fatigue and brain responses during a fatiguing cognition. Moreover, the fact that, in this study, the objective effect of fatigue on cognition was not larger than in the two other groups does not mean that the subjective impression of fatigue would not be higher in patients with CFS. Grafman et al. [5] investigated the relationship between

the subjective memory complaints of patients with CFS and their level of fatigue and found that there was evidence of a positive relationship.

Finally, the present study has methodological issues that need to be addressed. First, the MDD group did not strictly match the other groups in years of education. However, we believe that this cannot explain the results observed in the cognitive tests. After adjusting for years of education as covariates, we observed the same results in the different cognitive tests. Second, maximum age in the CFS group was 55, in the MDD group 68, and in the control group 64. Especially for the MDD and control group there were some older persons included. We know that aging has also a deteriorating effect on cognitive functioning although we do not think it would have impacted substantially the current outcomes. Third, the patients with MDD were typically outpatients without atypical depression or melancholic depression, so the results of the present study cannot be extended to all types of patients with MDD. Moreover, it could have been their first major depressive episode or a recurrent one. Some may argue that patients with recurrent depressive episodes are more at risk of cognitive impairments. Fourth, we used two self-administered questionnaires (BDI and GDS) to investigate depression and not the Hamilton depression rating scale (HDRS) administered by a clinician. Some may argue that subjectivity is more often reflected in the BDI scores than in the HDRS. We chose to use self-administered questionnaires because two psychologists participated in the evaluation of the patients and we wanted to avoid interjudge variability. Moreover, in the GDS, physical symptoms are excluded, which is important for the assessment of the depressive dimension in patients with CFS. Fifth, although the controls were not included if they were taking psychotropic drugs, this was not the case for the patients with MDD or CFS, and psychotropic drugs may influence cognition. Nevertheless, it is almost impossible to conduct such a study in drug naive patients and we can argue that our patients are at least highly representative of patients seen in daily practice. Finally, it would have been interesting to investigate the suggestibility and fatigue dimensions with more than one cognitive test. It would have been interesting also to investigate other types of executive functions. Future research in this field should also compare cognition in subgroups with similar neurobiological findings, for example, patients with atypical MDD or CFS.

In conclusion, the present study confirms the presence of objective impairment in attention and memory in patients with CFS but with good mobilization of effort and without exaggerated suggestibility.

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Conflicts of interest

There are no conflicts of interest.

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