

## **Neuropsychological Impairment in Female Patients with Chronic Fatigue**

### **Syndrome: A preliminary study**

#### **Abstract**

This study examines neuropsychological impairments associated with Chronic Fatigue Syndrome (CFS) and explores their association with related clinical factors. Sixty-eight women with CFS were assessed with a neuropsychological battery. Raw scores were adjusted for age and gender and converted to T-scores according to normative data extracted from a local sample of 250 healthy subjects. Neuropsychological dysfunction was calculated using summary impairment indices (proportion of test scores outside normal limits-T-score<40- for each cognitive domain). Finally, a linear regression was calculated to identify predictors of cognitive deficit, including intrinsic factors (level of fatigue and length of illness) and extrinsic factors (emotional factors, age and education) of the disease. Approximately 50% of scores showed impairment in attention and motor functioning, and nearly 40% in speed information processing and executive functioning. Fatigue predicted attention and executive functioning impairment, and emotional factors predicted verbal memory dysfunction. According to our findings, cognitive dysfunction in CFS could be explained by pathophysiological processes of the disease. One implication of this would be the need to identify homogeneous subgroups of CFS patients by taking into account common factors which, in turn, would help to identify more specific cognitive profiles, which could then serve to implement appropriate therapeutic measures accordingly.

*Key words: Cognitive Dysfunction, Chronic Fatigue Syndrome, Neuropsychological assessment*

## **Introduction**

Chronic fatigue syndrome (CFS) is defined by severe and unexplained fatigue for at least 6 months, resulting in a substantial reduction of the patient's quality of life (Fukuda et al., 1994). Cognitive dysfunction is one of the most common symptoms reported by CFS patients. About 89% of people with CFS complain of memory and concentration problems (Jason et al., 1999), and describe their cognitive difficulties as amongst the most disabling and troubling symptoms of their illness (Abbey & Garfinkel, 1991). However, objective measures of neuropsychological performance do not reflect the high magnitude of cognitive complaints.

Cognitive deficits have been identified in the literature, although findings are inconsistent and hindered by methodological irregularities. Some studies show impairments in memory (Claypoole et al., 2007; Daly, Komaroff, Bloomingdale, Wilson, & Albert, 2001; DeLuca, Johnson, Ellis, & Natelson, 1997) and executive functioning (Claypoole, et al., 2007; Dobbs, Dobbs, & Kiss, 2001), whereas other studies do not (Ross, Fantie, Straus, & Grafman, 2001; Short, McCabe, & Tooley, 2002). Busichio et al. (2004), for example, found that CFS patients showed deficits in attention, speed of information processing and motor speed, but not in memory and executive functioning. Other findings suggest that attention could be the primary cognitive dysfunction in CFS (DeLuca et al., 2004; Dickson, Toft, & O'Carroll, 2009), whereas other cognitive deficits, such as memory, could be secondary to this impairment. Overall, recent reviews conclude that the most common CFS related cognitive impairments are attention impairment (working memory and slowed reaction time) and reduced information processing speed (Cockshell & Mathias, 2010; Michiels & Cluydts, 2001).

The etiology of cognitive dysfunction in CFS is uncertain, and may have as its origin a wide spectrum of factors. One possible explanation is the effect of psychopathological factors (e.g. depression, anxiety) on cognitive performance in CFS. Patients with depression and anxiety may experience cognitive dysfunction (Marvel & Paradiso, 2004). Since depressive symptoms and anxiety are frequently observed in patients with CFS (Harvey, Wessely, Kuh, & Hotopf, 2009), the possibility that these may contribute to impaired cognitive performance must be considered. Some studies have found a relationship between cognitive deficits and depression and anxiety in CFS (Michiels & Cluydts, 2001; Tiersky et al., 2001). However, the majority of neuropsychological studies that have examined this relationship conclude that cognitive dysfunction in CFS is not a function of depression or anxiety (Busichio, et al., 2004; Short, et al., 2002). Consistent with this finding, in a recent study we found that cognitive dysfunction in CFS patients was independent of the presence of depression (Santamarina-Perez, Freniche, et al., 2011). Such findings are still preliminary, and, given the disparity of results, further research is still needed.

Fatigue severity is another factor affecting cognitive performance, although there is very little research in this area and the findings are equivocal. The intensity of fatigue may reflect the severity of the disease, which in turn may negatively impact cognitive functioning. Both fatigue and cognitive deficits are present in organic diseases, and are a manifestation of brain dysfunction. In fact, some studies have compared CFS patients to patients with multiple sclerosis (MS), particularly because of the presence of fatigue and cognitive impairments in both disorders (Daly, Komaroff, Bloomingdale, Wilson, & Albert, 2001; DeLuca, Johnson, Beldowicz, & Natelson, 1995). In this respect, Capuron et al. (2006) suggested that the level of fatigue could give an indication of the neural pathways that may underlie cognitive alterations in CFS

patients. However, other studies did not find a relationship between level of fatigue and cognitive performance in CFS (Short, et al., 2002).

The duration of the illness may be another variable to consider. In clinical practice, most patients report a progressive worsening in their cognitive functioning over time which would appear to indicate that cognitive impairment is directly associated with CFS. However, empirical research does not confirm this hypothesis (Cope, Pernet, Kendall, & David, 1995; Tiersky, et al., 2001). In a recent study carried out by our team, we also conclude that there is no progressive cognitive dysfunction in patients with CFS (Santamarina-Perez, Eiroa-Orosa, et al., 2011).

Based on the previous results, the purpose of this study is to identify neuropsychological impairments and their association with basic clinical factors in patients with CFS. As there were not enough male patients being treated for CFS in the hospital where the study took place, only women have been included in order to reduce the potential effect of gender differences on cognitive functioning.

## **Method**

### **Participants**

The study sample consisted of 68 CFS patients who attended the Chronic Fatigue Unit of the Vall d'Hebron University Hospital in Barcelona (Spain), from October 2008 to February 2010. A diagnosis of CFS and being more than 18 years old were the inclusion criteria. As only three men were treated during the data collection, they were excluded from the study in order to reduce possible biases due to gender differences. The exclusion criteria from the study were: 1) current or lifetime diagnosis of schizophrenia, mania, substance abuse or dependence (except nicotine), or an eating disorder; 2) current or lifetime neurological disorder; or 3) organic diseases that involve

cognitive alterations. Two patients were excluded because of eating disorders and one because of substance use disorder.

## **Procedure**

Patients arrived at the Chronic Fatigue Unit of the University Hospital Vall d'Hebron, referred by a primary care physician or other medical services from the Hospital. At the unit, an internist confirmed CFS diagnosis in all patients by carrying out a physical examination and clinical laboratory studies.

All patients who met the 1994 CFS case definition criteria (Fukuda, et al., 1994) were referred to the psychiatry department in order to complete a comprehensive assessment. The evaluation was carried out over two sessions. In the first one, a clinician interviewed the patient, recorded sociodemographic and clinical data, and conducted a clinical interview according to the Diagnostic and Statistical Manual of Mental Disorders (fourth edition, text revision) criteria (American Psychiatric Association, 2000).

At the second assessment session, which took place within 2 weeks of the first, a neuropsychological assessment was carried out. All sessions were performed under standardized conditions and each one lasted 2 hours approximately.

All participants received information about the study, and signed an informed consent form to participate. The study was approved by the Clinical Research Ethics Committee of the Hospital.

## **Assessment**

### **Mood Assessment.**

The Hospital Anxiety and Depression Scale (HAD, Zigmond & Snaith, 1983) was administered to assess the level of anxiety and depression. This scale has been validated for use with CFS patients (Henderson & Tannock, 2005). The HADS does not

include items concerning somatic symptoms including fatigue. A score of 9 or more is the cut off for borderline anxiety or depression.

### **Fatigue Assessment.**

The level of fatigue was evaluated with the Fatigue Impact Scale (FIS, Fisk et al., 1994). Consisting of 40 items, this instrument measures mental, physical, and psychosocial dimensions and yields a total index of fatigue, a score higher than 120 is considered a clinically significant fatigue.

### **Neuropsychological Assessment.**

Neuropsychological tests were administered in a standardized manner. The selection of the battery used was based on previous studies (Busichio, et al., 2004; Claypoole, et al., 2007; Cockshell & Mathias, 2010), with the goal of assessing different cognitive domains. The instruments included were: Mental Control (WMS-III, Wechsler, 1997b), Paced Auditory Serial Addition Test (PASAT, Gronwall, 1977) , Digit Span (WAIS-III, Wechsler, 1997a), and Symbol Digit Modalities Test (SDMT, Smith, 1982); Stroop Test (Golden, 1978), Trail-Making Test (TMT, Reitan & Wofson, 1985), Verbal Fluency Test (FAS, Benton & Hamsher, 1978), and the Tower of London test (Shallice, 1982); Rey Auditory Verbal Learning test (RAVLT, Rey, 1964) and Rey Complex Figure Test (RCFT(Rey, 1964) and Recognition Test (RT,(Meyers & Meyers, 1995); Grooved pegboard (Klove, 1963); and vocabulary subtest of the WAIS-III (Wechsler, 1997a). Neuropsychological tests were translated and culturally adapted. This battery was validated on a general population sample of 250 healthy subjects, confirming no significant differences with the original parameters (please see below, categorization of neuropsychological tests). The sample of healthy subjects was selected from respondents to ads placed in the hospital, hospital staff, and acquaintances of patients. The age range was from 18 years to 65 years, 63% women..

### **Categorization of neuropsychological tests.**

In this study, neuropsychological measures were categorized into 7 specific cognitive domains: Attention, speed of information processing, verbal memory, visual memory, executive functioning, problem solving and motor functioning. Each domain included measures that evaluated similar cognitive skills. This categorization was made taking previous studies as a reference (Busichio, et al., 2004; Claypoole, et al., 2007), and a validation using principal component analysis was carried out (Santamarina-Pérez et al., 2011) in order to assure the unidimensionality of each category. Table 1 shows included tests, range of factor loads and reliability indices (Cronbach's alpha) for each category.

#### ***Attention.***

The attentional domain consisted of the Digit Span forward subtest, the Mental Control, the number of words correct on trials 1 and 2 of the Stroop Color and Word Test, the Symbol Digit Modalities Test (SDMT) and Trail Making Test Part A (TMT). All of these measures are known to evaluate different aspects of attention function (Lezak, 1995).

#### ***Speed of information processing.***

PASAT, a complex task of attention and information-processing ability was used to assess speed of information processing. In this study, we used a version that consists of showing 60 randomized digits to the patient in two blocks, every 3 and 2 seconds respectively. In each task, performance was evaluated in terms of correct responses.

#### ***Verbal memory.***

This dimension was composed of the following measures: immediate recall (trial 1, trial 5, trial 6), delayed recall and recognition from the RAVLT.

Table 1. *Categorization, composition, construct validity\* and reliability of cognitive functions*

<i>Category</i>	<i>Test</i>	<i>Factor weight</i>	<i>%Variance explained*</i>	<i>Cronbach's alpha</i>
<i>Attention</i>	STROOP word	0.926	67.1	.895
	STROOP colour	0.900		
	Mental Control	0.873		
	Digit span forward	0.864		
	TMT A	0.790		
	Symbol Digit	0.478		
<i>Speed of information processing</i>	PASAT-2	0.942	88.8	.874
	PASAT-3	0.942		
<i>Verbal memory</i>	RAVLT immediate recall-trial1	0.544	72.5	.895
	RAVLT immediate recall-trial 5	0.889		
	RAVLT immediate recall-trial 6	0.952		
	RAVLT delayed recall	0.910		
	RAVLT recognition	0.897		
	RCFT delayed recall	0.936		
	RCFT immediate recall	0.630		
<i>Visual memory</i>	RT recognition	0.942	72.0	.794
		0.630		
<i>Executive functioning</i>	COWA	0.782	51.0	.756
	Stroop word-colour	0.764		
	TMT B	0.762		
	Digit span backward	0.671		
	RCFT copy	0.569		
<i>Problem solving</i>	TOL total move score	0.943	88.9	.875
		0.943		
<i>Motor functioning</i>	TOL perfect solutions		92.1	.914
	Grooved Pegboard preferred hand	0.959		
	Grooved Pegboard non preferred hand	0.959		

TMT: Trail Making Test; RT, reaction time; RAVLT indicates Rey Auditory Verbal Learning test; RCFT, Rey Complex Figure Test; RT, recognition trial; COWA Controlled Oral Word Association Test; TOL, Tower of London.

Principal components analyses with Varimax rotations were used to estimate factor weights.

### ***Visual memory.***

Immediate and delayed recall of the RCFT, and the recognition measures of the RT were used to measure visual memory.



### ***Executive functioning.***

Within this domain the Digit Span backwards subtest of the WAIS-III, the TMT Part B, RCFT- copy, the interference trial of the Stroop and the COWA were included. The Digit Span backwards subtest evaluates the executive component of working memory, while the TMT-B is a measure of rapid set shifting and cognitive flexibility. The RCFT-copy assesses visuo-constructional skills and trial 3 of the Stroop test measures the capacity to focus on visual stimuli while filtering out interference or distracting information. Finally, the COWA assesses verbal fluency and cognitive flexibility by requiring the intrinsic generation of responses within a set of constraints. All of these measures have been used to assess executive functioning in previous studies (Busichio, et al., 2004; Claypoole, et al., 2007).

### ***Problem solving***

This domain was assessed using the Tower of London. This test assesses executive planning and problem solving. The number of perfect solutions (problems solved with a minimum of moves), and the number of moves required to solve novel problems were taken as a measure of the subject's planning abilities (Joyce, et al., 1996).

### ***Motor functioning.***

The Grooved pegboard (dominant and non-dominant hand) task is known to evaluate motor speed. The time for the dominant and non-dominant hand were recorded.

## **Design**

A cross-sectional study design was used. The examined variables included sociodemographic data (age, years of education, and work status), disease-related clinical variables (time since diagnosis, patient age at onset of symptoms and degree of fatigue), anxiety and depressive symptoms and scores on the neuropsychological tests.

## **Data analysis**

Test performances were adjusted for age and gender, and transformed to a common metric (T scores) according to local normative data taken from prior studies (Santamarina-Perez, Eiroa-Orosa, et al., 2011). These scores were previously validated using a local healthy population sample of 250 subjects and no significant differences with the original parameters were confirmed. With these scores, a Summary Impairment Index, which represents the proportion of test scores outside normal limits (T score <40, Busichio, et al., 2004), was derived for each subject in each cognitive function. Summary indices reduce the probability of type 1 errors, by limiting the total number of comparisons conducted (Oyegbile et al., 2004).

Pearson's correlations were conducted to measure the relationship between summary impairment indices with sociodemographic and clinical information. Finally, we conducted multiple linear stepwise forward regression analyses to determine which variables could further explain the mentioned deficits. The significance level for all analyses was  $p < .05$ . All the statistical analyses were conducted using SPSS for Windows (version 18.0; SPSS Inc., Chicago).

## Results

As shown in Table 2, the sample was composed of relatively young women, most of whom had completed high school (in Spain at least 12 years of education are required to finish high school). They were mostly unemployed and had been diagnosed with CFS for an average of four years, meaning that they were young at disease onset. The HAD mean score was 11.3 (SD=4.3) for anxiety and 11.1 (SD=4.5) for depression, indicating high levels of both anxiety and depression. 75% of the patients were over the threshold of 9 points for anxiety and 73% for depression. Likewise; the FIS-40 scores (mean 132.9 (SD=21.8) in 75% of the patients exceeded the threshold of 120 proposed for the scale.

Table 2. *Sociodemographic and clinical characteristics of the 68 patients.*

Variable	
Age (years) <sup>a</sup>	46.7 (8.34)
Education (years) <sup>a</sup>	11.1 (3.7)
Any active occupation <sup>b</sup>	16, 23.5
Length of illness (months) <sup>a</sup>	47.3 (39.13)
Age at onset of CFS (years) <sup>a</sup>	36.4 (11.2)
HADS score <sup>a</sup>	22.4 (7.9)
FIS-40 score <sup>a</sup>	132.9 (21.8)

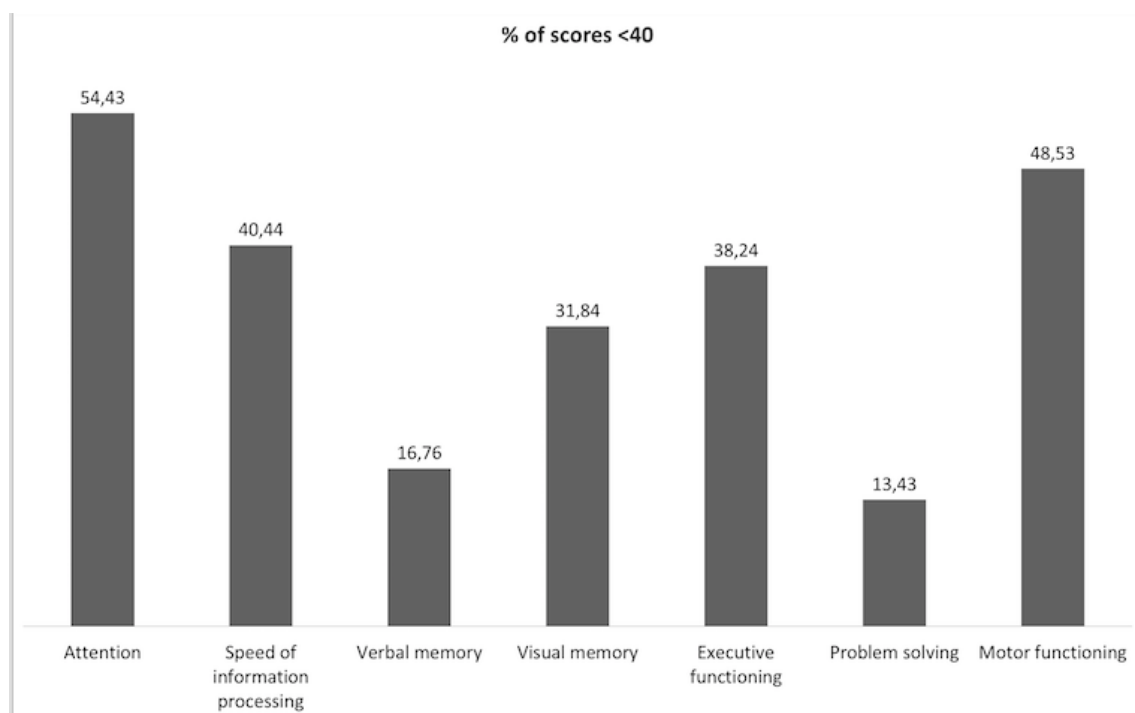
FIS: Fatigue Impact Scale; HADS: Hospital Anxiety and Depression Scale

<sup>a</sup> mean (SD)

<sup>b</sup>Frequency (percentages)

Figure 1 shows the cognitive profile of the sample of CFS patients. Means of the Summary Impairment Index for each cognitive function (representing proportion of test scores outside normal limits, T score <40, i.e. 1SD below the normative mean) obtained by CFS patients are shown. The mean for impaired attention is 54.43 and 48.53 for motor functioning deficit, followed by 40.44 for speed of information processing, and 38.24 for executive functioning.

**Figure 1.** Summary impairment indexes (mean of proportions of abnormal test scores).



As can be seen in Table 3, bivariate Pearson correlations yielded significant results for attention (HAD:  $r=0.309$ ,  $p<0.05$ , FIS:  $p=0.373$ ,  $p<0.001$ ), verbal memory (HAD:  $r=0.407$ ,  $p<0.001$ , FIS:  $p=0.330$ ,  $p<0.01$ ) and executive functioning (HAD:  $r=0.236$ ,  $p=0.056$ , FIS:  $p=0.397$ ,  $p<0.001$ ). Other variables included in our study, such as age, education and length of illness, were not associated with cognitive deficit.

Table 3. *Pearson correlations between sociodemographic and clinical information, and dysfunction index for each cognitive dimension.*

	<i>Attention</i>	<i>Speed of information processing</i>	<i>Verbal memory</i>	<i>Visual memory</i>	<i>Executive functioning</i>	<i>Problem solving</i>	<i>Motor functioning</i>
<i>Age</i>	0.160	0.084	-0.082	-0.058	0.076	0.076	0.111
<i>Education (years)</i>	-0.235	0.095	0.034	-0.154	-0.235	-0.116	-0.008
<i>Length of illness (months)</i>	-0.048	-0.085	-0.129	-0.171	-0.186	-0.029	-0.087
<i>Depression-anxiety (HADS)</i>	0.309*	0.022	0.407***	0.195	0.236 †	-0.211	0.185
<i>Degree of fatigue (FIS-40)</i>	0.373**	-0.044	0.330**	0.066	0.397***	-0.047	0.118

\*p< .05

\*\*<.01

\*\*\*p<.001

† p=.056

Finally, Table 4 shows results of the linear stepwise forward multiple regressions for the factors that had been found to be statistically significant in the correlation analyses. After controlling for all variables correlated with each domain, fatigue was associated with attention and executive functioning deficits. Depression predicted verbal memory dysfunction. Adjusted R2 showed low levels of explained variance (13-15%).

Table 4. *Results of the stepwise linear regression carried out with impaired cognitive functions*

<i>Dimension</i>	<i>R2</i>	<i>Adjusted R2</i>	<i>Variables</i>	<i>Beta</i>	<i>95% CI</i>	<i>p</i>
Attention	0.143	0.127	HAD	0.181	(excluded)	0.228
			FIS	0.378	0.164-0.822	0.004
Verbal memory	0.168	0.153	HAD	0.410	0.573- 20.190	0.001
			FIS	0.161	(excluded)	0.254
Executive functioning	0.158	0.144	HAD	0.079	(excluded)	0.580
			FIS	0.398	0.194-0.791	0.002

## Discussion

In the present study we found individuals diagnosed with CFS showed diverse cognitive impairments, primarily in attention and motor functioning. The levels of attention dysfunction found in this study appear to be consistent with deficits found in other studies (Busichio, et al., 2004; Capuron, et al., 2006; Cockshell & Mathias, 2010; DeLuca, et al., 1997). In addition, attention was the primary impairment in our sample. This result suggest that attention deficit could be the primary cognitive dysfunction in CFS, and other cognitive deficits could be secondary to this dysfunction, in as found by Deluca et al (2006).

Participants showed poor performance in motor functioning, consistent with some studies (Busichio et al., 2004; Claypoole et al., 2007) but not others (Cockshell & Mathias, 2010). These inconsistencies may be the result of instrument heterogeneity in the assessment of this function. For instance, reaction time has been assessed using a reaction time test, (Majer et al., 2008), Finger Tapping (Mahurin et al., 2004), and Grooved Pegboard (Claypoole, et al., 2007), which may not measure the exact same construct. Another explanation of this poor motor functioning could be the possible effect of drug treatment. Grooved Pegboard is a sensitive instrument for measuring

general slowing due to medication (Lezak, 1995). The possible effects of medication on cognitive functioning was not controlled for in our study, which may not be a concern as Dickson et al. (2009) found no differences on any dependent variable when comparing groups of patients with and without medication. However, Dickson et al. did not include measures of motor functioning. We suggest the assessment of this function in future studies, while controlling for the effect of drugs.

Patients with CFS showed poor results on tests that assess speed of information processing and executive functioning. These results are consistent with previous studies (Busichio, et al., 2004; Claypoole, et al., 2007; Dobbs, Dobbs, & Kiss, 2001), providing more evidence of cognitive deficits in people with CFS.

As in previous studies, our data show memory being one of the less impaired dimensions among patients diagnosed with CFS (Busichio, et al., 2004; Lawrie, MacHale, Cavanagh, O'Carroll, & Goodwin, 2000; Ross, et al., 2001). Curiously, even though one of the major explicit complaints in patients with CFS is memory problems (Wearden & Appleby, 1996), little in the way empirical support for such memory complaints has been found in previous studies. Some studies suggest that memory problems could be the result of a general dysfunction in information processing and attention (DeLuca et al., 2004; Dickson, et al., 2009) an idea supported by our findings that although memory scores were generally not low in our study, attention impairment was elevated. Consequently, memory problems experienced by CFS patients could be result of deficient acquisition secondary to impaired attention functions.

In this study, we also analyzed the influence of clinical factors on cognitive dysfunction in CFS. An interesting result is that the level of fatigue would appear to be one of the main reasons for cognitive deficits in CFS. In fact, the level of fatigue could

be a manifestation of the disease severity, and cognitive deficits may be secondary to the pathophysiological processes of the disease itself, in agreement with Capuron et al. (2006).

Anxiety and depression partially explained memory deficit, although were not involved in other cognitive impairments. In a study carried out by Dickson et al. (2009), patients with CFS showed elevated dysfunction on measures of memory, attention and visuo-constructional ability. After controlling for the effects of mood, patients showed dysfunction only in attention. Consequently, the memory complaints among CFS patients could be associated with mood and anxiety, and therefore be secondary to exogenous factors of the disease. In addition, impairments in memory functions have been found in depressed patients (Marvel & Paradiso, 2004).

Our study was subject to some limitations. For instance, the exclusion of males could hamper the generalization of our results. As indicated in the methods section, this was done in order to homogenize the sample. Gender not only is related to cognitive function (Lezak, 1995), but also CFS prevalence (Jason, et al., 1999). This means that controlled studies that include men should be carried out. More factors such as personality traits, acute or progressive onset of the illness, sleep disturbances, possible effects of drugs and level of daily activity should be included in future studies in order to develop a more comprehensive model. In conclusion, our sample of patients with CFS showed cognitive dysfunction primarily in attention and motor functioning. The attention deficits could be explained by the level of fatigue, which may be a manifestation of alterations in neural pathways underlying cognitive dysfunctions in CFS. Emotional factors appeared only to explain memory complaints.

One of the possible explanations for the inconsistency of results from neuropsychological studies with CFS patients is the inclusion of heterogeneous samples.



Consequently, the main implication of this study may be the need to stratify patient groups taking into account common characteristics. We suggest that the sample is stratified depending on the presence of depression as assessed by an internationally recognized clinical interview. We also suggest that future studies identify patient groups according to the level of fatigue, which could be assessed through scales such as the FIS. This could help to identify specific cognitive profiles of each subgroup and, consequently, differential treatment approaches. Specifically, CFS patients with emotional disorders may benefit from psychotherapy and psychopharmacological interventions which could serve to improve the cognitive deficits associated with anxiety or depression. Those CFS patients with higher levels of fatigue may benefit from cognitive rehabilitation in order to compensate for associated cognitive deficits. Implementing therapeutic physiotherapy programs, with the objective of improving the functional impairment usually associated with higher levels of fatigue, could also be of great interest.

### **Conflict of Interest**

The authors declare that they have no conflict of interest regarding this study.

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