

Cognitive functioning is impaired in patients with chronic fatigue syndrome devoid of psychiatric disease

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Abstract

Objective—To examine the effect of the presence or absence of psychiatric disease on cognitive functioning in chronic fatigue syndrome.

Methods—Thirty six patients with chronic fatigue syndrome and 31 healthy controls who did not exercise regularly were studied. Subgroups within the chronic fatigue syndrome sample were formed based on the presence or absence of comorbid axis I psychiatric disorders. Patients with psychiatric disorders preceding the onset chronic fatigue syndrome were excluded. Subjects were administered a battery of standardised neuropsychological tests as well as a structured psychiatric interview.

Results—Patients with chronic fatigue syndrome without psychiatric comorbidity were impaired relative to controls and patients with chronic fatigue syndrome with concurrent psychiatric disease on tests of memory, attention, and information processing.

Conclusion—Impaired cognition in chronic fatigue syndrome cannot be explained solely by the presence of a psychiatric condition.

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Keywords: chronic fatigue syndrome; cognition; psychiatric illness

Chronic fatigue syndrome is a disease which is characterised by persistent and debilitating fatigue, as well as neuropsychiatric, infectious, and rheumatological symptoms. No single pathogenic mechanism has been consistently identified using physical or laboratory tests, thus making the diagnosis of chronic fatigue syndrome one of exclusion. Although a case definition has been established by the Centers for Disease Control (CDC),^{1,2} the heterogeneity of the case defined chronic fatigue syndrome population may be one major contributing factor accounting for the lack of consistent medical findings. Thus seeking critical variables which may identify more homogeneous subgroups may not only increase the diagnostic accuracy in chronic fatigue syndrome but may help in the identification of potential causative agents.² One such critical variable is psychiatric disease. Some studies have reported a relatively high frequency of psychiatric disorders (primarily depression) in

those with chronic fatigue (not necessarily chronic fatigue syndrome).³⁻⁶ This, coupled with the fact that many symptoms of chronic fatigue syndrome resemble those of depression, has led to the notion that chronic fatigue syndrome is a primary psychiatric disorder. The purpose of the present study was to examine the effect of the presence or absence of psychiatric disease on cognitive functioning in chronic fatigue syndrome.

Cognitive difficulties can be the most disabling and troublesome aspects of chronic fatigue syndrome,⁵ with such complaints reported in up to 85% of patients.⁶ Several groups have reported cognitive impairment on objective neuropsychological testing.⁷⁻¹³ When detected, these impairments are generally subtle, and primarily in the area of attention and concentration, memory, and information processing efficiency. Because of the high rate of psychiatric disorders in patients with chronic fatigue syndrome, some research groups have indicated the need to clarify the role of depression in producing cognitive impairment.^{5, 13-16} A similar recommendation was made by an international NIH/CDC study group, which further recommended the use of stratification techniques to consider this issue.²

To study the influence of psychiatric disease on cognitive functions in chronic fatigue syndrome, we examined two groups of patients: (1) those without psychiatric disorder(s) in their lifetime or concurrent with chronic fatigue syndrome: (CFS-nopsych group); and (2) those with a concurrent axis I psychiatric disorder, (CFS-psych group). If psychiatric disease is the primary reason for impaired cognitive functioning in chronic fatigue syndrome, the CFS-psych group should be more impaired relative to controls on neuropsychological testing than the CFS-nopsych group. By contrast, greater impairment in the CFS-nopsych group than the CFS-psych group relative to controls would lend support to the claim by some that impaired cognition is due to cerebral dysfunction.¹¹⁻¹³

Methods

SUBJECTS

We studied 36 patients with chronic fatigue syndrome and 31 healthy subjects who did not exercise regularly (controls). The groups did not differ statistically in mean age, sex distribution, or years of education (table 1). Patients with chronic fatigue syndrome were recruited via self referral based on media reports about the centre and by physician referral. Inclusion

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Table 1 Mean (SD) demographic and clinical characteristics

	No of patients	Age (y)	Sex (% female)	Education (y)	Fatigue‡	BDI
CFS	36	33.6 (8.7)	86%	14.7 (2.5)	57.7 (4.6)*	14.0 (7.7)*
CFS-psych	15	31.9 (9.5)	86%	14.8 (2.3)	58.5 (4.2)*	18.6 (8.1)*†
CFS-nopsych	21	34.8 (8.1)	87%	14.7 (2.7)	57.2 (4.8)*	10.8 (5.6)*
Controls	31	37.3 (10.2)	90%	15.8 (2.6)	18.9 (10.8)	1.8 (2.4)

*Significantly different from controls.

†Significantly different from CFS-nopsych group.

‡Sample size as follows: CFS-psych = 12, CFS-nopsych = 21, Controls = 28.

BDI = Beck depression inventory.

of patients with chronic fatigue syndrome was based on a careful history, physical examination, elimination of possible medical causes of fatigue, and fulfillment of the published case definition for chronic fatigue syndrome.^{1,17}

Additional exclusion criteria were: (1) illness onset longer than four years; (2) symptoms of less than moderate severity at the time of intake; and (3) a history of a psychiatric disorder in the five years before the onset of chronic fatigue syndrome. This last criterion effectively eliminated all patients with chronic fatigue syndrome with prior psychiatric histories with the exception of one patient in the CFS-psych group who had had a major depressive episode many years earlier. Based on our experience, we exclude about 10% of our patients with chronic fatigue syndrome at intake (psychiatric interview) due to an axis I disorder in the five years before diagnosis. Healthy subjects were recruited by advertising in the local community, and were paid for their participation. Only those who reported no medical problems, no psychiatric history, and were not taking medication other than birth control pills were included as subjects.

Psychiatric history (DSM III-R axis I disorders) was obtained in all subjects using a structured psychiatric interview, the computerised version of the diagnostic interview schedule (DIS)¹⁸ administered by a psychologist or neuropsychology technician trained in its use. Additional exclusions included a history of loss of consciousness for greater than five minutes, substance misuse, eating disorders, schizophrenia, or bipolar disorder.

PROCEDURE

The patients with chronic fatigue syndrome were divided into those who had a DSM III-R axis I psychiatric diagnosis occurring since their diagnosis (but not in the five years before diagnosis) (CFS-psych: $n = 15$) and those without a psychiatric diagnosis, either concurrently or historically; (CFS-nopsych: $n = 21$). The primary axis I diagnosis was major depression, found in 73% of the CFS-psych group. Other axis I disorders included dysthymia (13%), phobia (26%), panic disorder (26%), generalised anxiety disorder (20%), and somatoform disorder (6%) (percentages do not add up to 100% because patients may have had more than one diagnosis). There were no significant differences between the two chronic fatigue syndrome subgroups with respect to age, sex distribution, and education. Mean level of depression (Beck depression

inventory) was significantly raised in the two chronic fatigue syndrome groups relative to controls ($F(2,64) = 56.81$, $P = 0.0001$). Mean level of depression was also significantly higher in the CFS-psych group than in the CFS-nopsych group ($P = 0.0035$). As expected, fatigue was significantly greater in the two chronic fatigue syndrome groups than in controls ($F(2,57) = 168.8$, $P = 0.0001$), but the CFS-psych group and the CFS-nopsych group did not differ from each other (table 1).

All subjects were given a battery of standard neuropsychological tests, administered and scored in accordance with published procedures. The tests consisted of the paced auditory serial addition test (PASAT), assessing complex information processing efficiency; vocabulary, arithmetic, and digit span subtests of the WAIS-R,¹⁹ assessing intellectual and attentional skills; the Rey-Osterreith complex figure test (ROCF), assessing visual memory and visual-constructional ability; and the California verbal learning test (CVLT),²⁰ measuring verbal memory. The Beck depression inventory (BDI)²¹ and the fatigue severity scale²² were also administered.

DATA ANALYSIS

The 12 dependent variables of the neuropsychological data were analysed by multiple analysis of covariance (MANCOVA) with subject condition (CFS-nopsych, CFS-psych, controls) as the between group factor, and age, sex, and education as covariates. If the subject condition factor on the MANCOVA was significant, subsequent analyses consisted of separate one way analyses of covariance (ANCOVAs) for each neuropsychological variable, with group (CFS-psych, CFS-nopsych, and controls) as the between group factor and age, education, and sex as covariates. Post-hoc analyses were conducted using the Welch modified t test.²³

Results

The overall MANCOVA showed that the factor of subject condition was significantly different for overall neuropsychological performance ($F(24,102) = 2.13$, $P = 0.005$). Post hoc MANCOVAs showed that both the CFS-nopsych ($P = 0.003$) and CFS-psych groups ($P = 0.049$) differed from the control group, but not from each other.

To examine which of the specific tests were influenced across the three groups, the

Table 2 Mean (SEM) neuropsychological performance for the CFS-nopsych group, CFS-psych group, and controls

	CFS-nopsych (n = 21)	CFS-psych (n = 15)	Controls (n = 31)	F value	P value
Rey figure:					
Copy	67.4 (1.2)	68.2 (1.1)	68.9 (0.5)	0.89	NS
Immediate recall	33.2 (2.8)†*	42.3 (3.0)	44.8 (1.6)	7.68	0.001
Delayed recall	32.5 (2.9)‡*	43.3 (2.8)	41.4 (2.0)	4.90	0.01
CVLT:					
T score	32.3 (3.6)*	41.4 (3.8)	48.2 (1.8)	8.70	0.0005
Short free recall	9.3 (0.8)*†	11.7 (0.7)	12.3 (0.5)	6.49	0.0028
Long free recall	10.2 (0.8)*	11.7 (0.7)	12.9 (0.5)	5.12	0.009
PASAT (total)	125.8 (8.2)*	135.4 (4.7)	147.4 (4.0)	4.74	0.012
Digit span:					
Forward	9.0 (0.6)	9.9 (0.8)	9.9 (0.3)	1.51	NS
Backward	7.0 (0.5)*†	9.1 (0.7)	8.8 (0.4)	4.82	0.011
Arithmetic (ss)	12.4 (0.8)	14.3 (0.8)	13.5 (0.6)	2.00	NS
Block design	32.6 (1.6)	35.5 (2.1)	33.2 (1.3)	0.74	NS
Vocabulary	51.1 (2.1)	54.5 (2.2)	53.5 (1.5)	0.39	NS

*P ≤ 0.01 v controls.

†P ≤ 0.05 v CFS-psych.

‡P ≤ 0.012 v CFS-psych.

Age, sex, and education were included as covariates in the statistical analysis, ss = standard score (age corrected).

neuropsychological variables were analysed individually. Table 2 presents the results. The groups differed significantly in immediate recall on the ROCFT ($F(2,61) = 7.68$), with the CFS-nopsych group performing significantly below both the control ($P = 0.0004$) and CFS-psych ($P = 0.04$) groups. Group differences were also found on delayed recall of the ROCFT ($F(2,61) = 4.90$). Delayed recall on the ROCFT was significantly reduced in the CFS-nopsych group relative to both the healthy control ($P = 0.01$) and CFS-psych groups ($P = 0.01$). On the CVLT, significant group effects were found for all three variables examined: trials 1–5 ($F(2,61) = 8.70$), short delay free recall ($F(2,61) = 6.49$), and long delay free recall ($F(2,61) = 5.12$). In all cases, the CFS-nopsych group performed significantly worse than controls ($P = 0.0006$, $P = 0.0061$, and $P = 0.009$ respectively). Additionally, the CFS-nopsych group performed worse than the CFS-psych group on short delay free recall ($P = 0.028$).

Whereas no group differences were seen on digit span forward, the groups did differ on digit span backwards ($F(2,61) = 4.82$). Once again, post hoc analysis showed that the CFS-nopsych group performed significantly below both controls ($P = 0.0053$) and the CFS-psych group ($P = 0.023$). Significant group differences were also found on the PASAT ($F(2,61) = 4.74$), with the CFS-nopsych group differing from controls ($P = 0.01$). There were no significant group differences on block design, arithmetic, copy of the ROCFT, or vocabulary.

Because two of the 15 patients in the CFS-psych group had an axis I diagnosis other than depression, we were interested in comparing only patients with chronic fatigue syndrome with comorbid depression with controls. Deletion of these two patients had no effect on overall neuropsychological performance compared with the larger analysis.

Discussion

The purpose of the present study was to use stratification techniques to examine whether impaired cognition in chronic fatigue syn-

drome is influenced by the presence or absence of an axis I psychiatric diagnosis (primarily major depression). The results clearly showed the existence of important subgroups within a sample of patients who met the case definition for a diagnosis of chronic fatigue syndrome. The overall result showed that, relative to healthy controls, cognition was impaired in the CFS-nopsych group (chronic fatigue syndrome subjects without a lifetime or concurrent psychiatric disorder). Patients with chronic fatigue syndrome with a concurrent axis I psychiatric diagnosis (CFS-psych group) did not differ from controls on individual neuropsychological tests. Further, the CFS-nopsych group also performed significantly below the CFS-psych group on several measures of memory and concentration. These data suggest that cognitive impairment in chronic fatigue syndrome cannot simply be explained by the presence of psychiatric state, and are contrary to expectations based on a model of depression induced cognitive impairment in chronic fatigue syndrome.

It should be noted that whereas the CFS-psych group did not differ significantly from controls on individual tests of cognition, when the neuropsychological tests were analysed as a whole (by MANCOVA), a statistical difference did emerge. This suggests that although the CFS-psych group may show a small decrement in "overall" cognitive functioning, this effect is very subtle and unlikely to be seen in individual patients undergoing clinical testing.

The results of the present study are particularly important in the light of the recommendations by an international NIH/CDC study group,² which outlined the need to clarify the role of comorbid psychiatric conditions in symptoms of chronic fatigue syndrome. Previous researchers have specifically emphasised the need to clarify the role of psychiatric disorders on cognitive functioning in chronic fatigue syndrome.^{5,13–15} The technique of using statistical measures to adjust for the presence of depression on cognitive performance has provided no clear solution; although several studies^{7,8,11–13} have found no relation between depression and cognitive performance, others^{14,16} have. To our knowledge, the present study is the first to report significant differences in cognitive performance in patients with chronic fatigue syndrome with and without comorbid psychiatric disorders. The only other study comparing patients with chronic fatigue syndrome with and without "significant depression" did not find impaired neuropsychological performance in either group compared with healthy and depressed controls.²⁴ However, there are some important differences between the two studies which may account for the discrepant findings. The study of Cope *et al*²⁴ (1) did not exclude subjects with concurrent psychiatric disorders (other than "significant depression") in their chronic fatigue group without depression; (2) did not exclude subjects with prior psychiatric disorders; and (3) did not require patients to meet the more stringent CDC case definition^{1,17} for chronic fatigue syndrome.

At first glance, the finding that patients with chronic fatigue syndrome with comorbid psychiatric disturbance were not impaired on tests of cognition seems counterintuitive. This is because of the common belief that psychopathology (primarily depression) itself results in cognitive impairment. However, little convincing evidence to support this belief exists with some²⁵⁻²⁷ but not all studies^{24,28-30} showing impaired cognitive functioning in depressed patients on effortful tasks. On the contrary, studies in several medical populations³¹⁻³⁴ and even among currently healthy subjects (with personal or family psychiatric history)³⁵ show no adverse effects of depression on cognitive functioning.

The results of the present study have important implications for treatment. That is, patients with chronic fatigue syndrome with psychiatric complications may benefit more from psychotherapy in conjunction with psychopharmacological interventions. By contrast, patients without psychiatric comorbidity may benefit more from a psychoeducational approach to symptom management or cognitive rehabilitation.

The present results can be added to a growing body of literature suggesting that at least some patients with chronic fatigue syndrome differ from patients with major depression.³⁶⁻⁴¹ Taken together, the results of the present study suggest that at least in a subgroup of patients, chronic fatigue syndrome is not simply a manifestation of a primary psychiatric disorder such as major depression. Although the results of the present study do not provide direct evidence for an encephalitic process as suggested by others,⁴²⁻⁴⁵ our working hypothesis is that patients with chronic fatigue syndrome without concurrent or history of psychopathology is the subgroup with the highest probability of finding reproducible biomedical markers.

In the present study, stratification of patients with chronic fatigue syndrome by the presence of comorbid psychiatric disorder clearly reduced the heterogeneity of the chronic fatigue syndrome population, which had important consequences on measures of cognitive functioning. Employing a stratification methodology contrasts with another recently suggested approach to studying chronic fatigue syndrome. Katon and Russo⁴⁶ noted that patients with chronic fatigue syndrome reporting many symptoms also had a high lifetime prevalence of psychiatric disorders. Their approach to considering this problem was to redefine chronic fatigue syndrome by reducing the number of required symptoms. However, the net effect of doing this would be to increase population heterogeneity. The present data argue for accepting patients with many symptoms but stratifying the sample for lifetime and concurrent psychiatric diagnoses.

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