

SHORT REPORT

Cognitive impairment in patients with chronic fatigue: a preliminary study

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Abstract

Subjective impairment of memory and concentration is a frequent complaint in sufferers from chronic fatigue. To study this, 65 general practice attenders identified as having chronic fatigue were administered a structured psychiatric interview and a brief screening battery of cognitive tests. Subjective cognitive impairment was strongly related to psychiatric disorder, especially depressed mood, but not fatigue, anxiety, or objective performance. Simple tests of attention and concentration showed some impairment but this was influenced by both fatigue and depression. Subjects with high levels of fatigue performed less well on a memory task requiring cognitive effort, even in the absence of depression. There was no evidence for mental fatigability. The relationship between depression, fatigue, and cognitive function requires further research.

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The current definition of the chronic fatigue syndrome (CFS)¹ states that the fatigue is "severe, disabling and affects physical and mental functioning" (italics added). United States criteria² include neuropsychological complaints, such as difficulty in thinking and inability to concentrate, as "minor criteria". These definitions reflect accurately the emphasis given to cognitive difficulties by patients with a presenting complaint of severe and persistent fatigue.³ Some sufferers are so impressed by the severity of such symptoms as to regard them as evidence for an encephalitic process, although this is unsupported by research.

The most familiar complaints range from forgetfulness and anomia, to difficulty in carrying out a complex task.⁴ Concentration difficulties seem to be the most common problem in patients with chronic fatigue. A hospital based study reported just over 50% of cases had impairment in concentration and attention and over a quarter complained of problems with memory.⁵ The overall prevalence of self-reported cognitive impairments in chronic fatigue has been estimated at approximately 50-70%.⁶

These neuropsychological symptoms are a cause of considerable morbidity and are frequently implicated in occupational failure.

Study of these phenomena is therefore of obvious clinical relevance. Moreover, the presence of cognitive difficulties also provides avenues which may lead to further understanding of the nature of chronic fatigue. It has been pointed out⁷ that the prominence given to mental fatigue in most subjective accounts of the syndrome is, in itself, strong evidence against the view that CFS is a purely neuromuscular as opposed to a "central" disorder. This view is supported by Wessely and Powell⁸ who showed that questions on mental fatigue including items on concentration, memory, and word finding, clearly discriminated between hospitalised CFS patients, and controls with neuromuscular disease. CFS cases who were, in addition, depressed had the highest mental fatigue scores although interestingly, a number of non-depressed cases also scored highly.

The effect of depressed mood on cognitive function has been well studied.⁹ This is relevant to CFS since epidemiological, primary care, and hospital based studies^{5,8,10-12} all show a strong association with affective disorder as well as other psychiatric conditions.¹³ Hence some degree of cognitive impairment in chronically fatigued patients is to be expected.

Four studies have been published to date which carried out psychometric testing on CFS patients. Millon *et al*¹⁴ studied 24 fatigued patients with serological evidence of Epstein Barr virus exposure. They showed no impairment on the Mini-Mental State Examination, or overall memory deficit on the Weschler Memory Scale (WMS).¹⁵ More striking was the high level of psychological symptomatology. Atlay *et al*¹⁶ published a preliminary report on 21 subjects and found no impairment in a timed test of attention, coupled with scores in the superior range on two subtests of the Weschler Adult Intelligence Scale (WAIS-R) and other measures of language and abstraction. This curious result is best explained by the selection of cases being biased towards those of high occupational status. The authors made an interesting observation that there was a discrepancy between the patients' subjective complaints and assessment of their abilities, and the test results. Smith,⁴ carried out a questionnaire survey on patients from a self-help group of CFS patients. Cognitive failures were reported more often in comparison with controls but this was explained by the presence of anxiety and depression. Detailed assessment was carried out on 18 polysymptomatic patients who were found to

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have slowed reaction time and impaired performance on tests of visual attention and memory, in relation to nine normal controls. Recognition and digit span were unaffected. The influence of psychological symptoms in the second phase of the study was not addressed. Finally, Riccio *et al.*¹⁷ report neuropsychological test scores on nine hospital outpatients with postviral fatigue and found impairment on the WMS in comparison with healthy controls. The patients also reported significantly more symptoms of depression yet no measurement of the effect of this on cognition was attempted.

One concern about the work reviewed above is that it was based on biased samples, either through self-referral, unusual disability, or because of suspected viral infection. A recent study¹⁸ attempted to avoid this problem by surveying a random sample of general practice attenders with a variety of physical and psychosocial complaints, and selecting those suffering from severe, recurring fatigue, defined according to a specially designed fatigue questionnaire. The authors confirmed the high prevalence of psychiatric illness. In addition, preliminary information was gathered on neurological signs and both objective and subjective cognitive impairment.

The aims of the study were:

- (1) to determine the prevalence of subjective impairment of cognitive functioning in an unselected sample of patients with chronic fatigue
- (2) to screen for the presence of objective impairment of cognitive functioning
- (3) to examine the relationship between psychiatric morbidity—especially depressed mood and anxiety—and cognitive dysfunction, both subjective and objective.

Methods

SAMPLE

The sample was drawn from general practice attenders aged between 18 and 45 years, with 'chronic fatigue', defined as those scoring nine or more on a questionnaire (range 0–27) designed to assess fatigue, who had suffered symptoms for six months or more, although a minority were persistently disabled. The cut off separated the most fatigued 10% from an original cohort of 686 attenders and has been found to be specific and sensitive to a chronic fatigue syndrome.¹⁸ There were 77 eligible patients of whom 65 were contactable and agreed to be interviewed. Of these, 50 were women, reflecting the sex ratio of practice attenders, Mean age (SD) was 32.5 (6.4). Some 26% had received education beyond high school; 18% left with no qualifications. The remainder had O or A levels.

ASSESSMENTS

Psychiatric assessment

A variety of medical, psychiatric, and social assessments were carried out. These included a standardised psychiatric interview, the revised Clinical Interview Schedule (CIS-R),¹⁹ which was used to elicit and quantify current (during the past week) symptoms of minor psychiatric disorder. There are 14 items including depression, concentration,

worry, anxiety, somatic symptoms, fatigue, etc. Each section is scored on a 0–4 scale (except depressive ideas; 0–5) depending on the symptom's severity and frequency. Individual symptom ratings can be summed to yield an overall score. A cut off of ≥ 12 indicates a level of significant psychiatric morbidity. The CIS-R overall score can be adjusted to remove the symptom of fatigue (CIS-f) lowering the cut off to ≥ 11 .¹⁹

Neuropsychological evaluation

*The Quantitative Neurological Examination (QNE)*²⁰. This is a structured clinical examination with emphasis on the motor system.

Subjective cognitive impairment. The CIS-R includes an item on concentration and forgetfulness. A problem in this domain noticed by the subject in the past week scores 1. Further questions probe ability to concentrate on a newspaper article, etc, whether anything important has been forgotten, and whether the subject has given up anything through lack of concentration. A positive response to each probe scores an additional point.

Cognitive tests. A brief screening battery was used. Concentration was tested with serial 7s (subtracting 7 from 100), and digit span (DS) forwards and backwards.¹⁵ Visual attention was examined with the star cancellation test.²¹ The paired associate learning test from the WMS was used to test memory. Ten pairs of words are presented, some of which are commonly associated (for example, fruit—apple) and others which are not (for example, crush—dark). Easy and difficult pairs are mixed together. There are three presentations of all pairs; after each, one word is said to the subject who then attempts to recall its companion. The forwards DS, easy paired associates, and star cancellation allow for relatively automatic processes to be examined while the remainder require more cognitive effort.

Results

No neurological abnormalities were detected on the QNE, except in one patient who had old poliomyelitis. Power, praxis and coordination were normal and there was no imper-sistence.

The mean CIS-R score was 17.1 (SD 7.1); the mean after adjustment to remove fatigue (CIS-f) was 13.9 (SD 6.8). Forty nine (75%) met the criterion for caseness on the CIS-R and 42 on the CIS-f. Forty seven subjects (72%) were given an ICD-9 diagnosis, 24 of whom had neurotic depression and 8 an anxiety state, the rest receiving miscellaneous diagnoses.

The items for anxiety and worry were combined (mean 2.9; SD 2.3; range: 0–8) and depression and depressive ideas (mean 2.25; SD 2.1; range 0–9). Forty five (69%) and 53 (81.5%) scored ≥ 1 on the depression and anxiety totals, respectively. The mean score on the fatigue questionnaire was 12.14 (SD 6.5); 70% scored 9 or above. Fatigue correlated with CIS-R and CIS-f; $r = 0.43$ and 0.39 , respectively ($p < 0.001$).

Subjective cognitive impairment

Forty seven (72.3%) scored on this item;

Table 1 Relationship between positive scores on depression and concentration items of the CIS-R

		Depression item score		Total
		No	Yes	
Concentration item score	No	13	5	18
	Yes	12	35	47
	Total	25	40	

$\chi^2 = 10.1$; $p = 0.002$ (with Yates' correction)

mean (SD) 1.59 (1.2). There was a significant relationship between subjective cognitive impairment and the presence of depression (see table 1). There was also a relationship with somatic complaints ($p = 0.005$) but not anxiety ($p = 0.5$), or any other symptom including fatigue. Those scoring on the concentration item had higher total CIS-R (and CIS-f) scores (Mann-Whitney U test; $p < 0.001$) but not fatigue questionnaire scores ($p = 0.13$). There was no relationship between subjective concentration and performance on serial 7s, star cancellation, DS, or tests of memory.

Serial 7s. Forty eight (74%) performed six subtractions without error; 14% produced one error and the remainder gave between two and nine errors. Many subjects required encouragement to persist with the task.

Star cancellation. Forty four (68%) performed without error; 23% omitted 1 star and the remainder missed between 2 and 9. Those failing on these tests were not significantly more fatigued nor did they have greater psychiatric morbidity.

Healthy controls would be expected to perform without error.

Digit span (forwards). Mean (SD) 7.1 (1.1); range 4–9. **Digit span (backwards).** Mean (SD) 4.9 (1.5); range 0–9.

Paired associates. Easy: mean No recalled (SD) 15.6 (2.3). Hard: mean No recalled (SD) 7.2 (3.2).

The DS and paired associate scores were well within the normal range. The relationship between fatigue, psychiatric morbidity and cognitive performance was examined using Pearson's correlation (see table 2).

As shown in table 2, CIS total influenced performance on backward DS but no other cognitive test. This effect was seen with CIS depression scores but not anxiety which, in general, did not correlate with performance. Fatigue showed a different pattern of influence. Both forward and backward DS were reduced with increasing fatigue while there was a suggestion that the memory tests may be adversely affected. Age exerted minimal effects on performance.

Further analyses were carried out to exam-

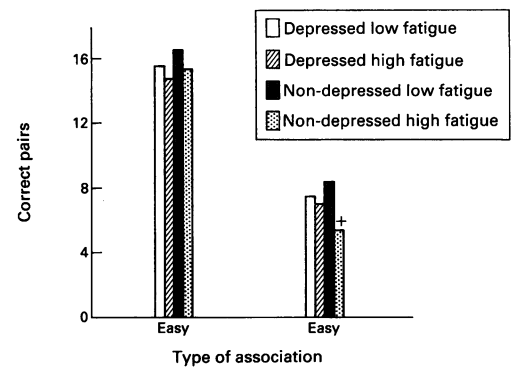


Figure 1 Performance on paired associates in high and low fatigue patients, with and without depressed mood. (+ $p = 0.03$, t test, two tailed.)

ine the effects of fatigue and psychological symptoms on performance. The sample was divided about the median score of 11 on the fatigue questionnaire and test scores compared. The high fatigue group did not differ significantly from the low fatigue group on DS, although the tendency was for the more fatigued to do worse. However, the high and low fatigue groups, while showing almost identical scores on easy paired associates, showed a near significant difference on hard pairings (high fatigue, 6.5 versus low fatigue, 8.0; $t = 1.8$, $p = 0.08$). Additionally, they gave poorer scores on trial 1 ($p = 0.08$) and trial 2 ($p < 0.05$), but not trial 3 ($p = 0.3$)—that is, there was no decrement in performance with successive trials in the high fatigue group.

Analyses were repeated with those scoring on the depression item of the CIS-R being separated from those not scoring. Results are illustrated in figure 1.

It can be seen that the effect of fatigue on hard paired associates was more striking in the non-depressed group, with the presence of depression on its own exerting little effect. The greatest difference between low and high fatigued groups in the absence of depression was on the first two trials (trial 1 $p = 0.08$; trial 2 $p = 0.047$; trial 3 $p = 0.09$).

Discussion

The current study reports on patients with CFS identified within a primary care setting so is less liable to selection bias which may influence the results. The main findings are:

(1) Subjective complaints of poor concentration and forgetfulness are common in these patients, affecting nearly three quarters, a rate comparable to previous studies.⁶

(2) Objective evidence for impaired cognitive function comes from two simple "bed-

Table 2 Correlation matrix showing the strength of association between overall psychiatric morbidity, fatigue score, depression, and anxiety with neuropsychological performance

	Digit forward	Span backward	Associates		Trials		
			Easy	Hard	T1	T2	T3
CIS-R	-0.09	-0.31**	-0.02	-0.04	-0.05	-0.09	-0.06
CIS-f	-0.08	-0.29**	0.01	-0.01	0.00	-0.06	-0.02
Fatigue Q	-0.29**	-0.33***	0.00	-0.14	-0.19	-0.21*	-0.13
Depression (total)	-0.10	-0.35***	-0.24*	-0.13	-0.07	-0.10	-0.07
Anxiety (total)	-0.08	-0.13	0.11	0.00	-0.07	-0.04	0.02

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.005$; (one tailed significance).

side" tests: the serial 7s and star cancellation. Over one quarter of the sample made errors on these, indicating impairment in attention and concentration. Scores on DS and memory were in the normal range (see also Smith).⁴

(3) There exists a complicated relationship between fatigue and psychiatric disturbance on the one hand, and cognitive impairment, both subjective and objective, on the other.

Psychiatric morbidity correlated moderately with backward but not forward DS. This might be thought to indicate a relationship with tasks requiring cognitive effort. However, performance on both easy and difficult paired associates did not appear to be related. By separating anxiety and depression from overall psychiatric scores it emerged that depression is more influential. Anxiety, though common in the sample, may not have been severe enough to interfere with performance. A clear relationship was found between subjective complaints of poor concentration and depression. However, as noted by Atlay *et al*¹⁶ subjective impairment bore little relation to objective impairment. This discrepancy is analogous to that found between self-perceived and observer-rated physical capacity in CFS.²²

Can fatigue be considered separate from other psychological symptoms? From table 2, there are hints that this is justifiable, while acknowledging that fatigue and CIS-R scores are themselves correlated. Fatigue adversely affects performance on span tasks, and appears to have quite a specific effect on memory (see also¹⁷). This cannot easily be explained by the co-occurrence of depression (see figure). Conversely, depressed mood reduced recall of easy paired associates but only affected backward DS, a result consistent with previous research.⁹

The nature of the memory impairment in chronic fatigue is clearly complex. In absolute terms it is slight but a pattern emerged whereby patients with severe fatigue had most trouble with hard associates. However, their performance seemed to "catch up" to those with less fatigue, over successive trials. This is quite contrary to the notion of true mental fatigue or fatiguability, whereby performance would be expected to decline over repeated trials diverging from the more normal comparison group, a pattern seen in true amnesic syndromes²³ and severe depression.²⁴ This may in part explain the DS results in that patients with marked fatigue may find any task, no matter how simple, difficult to embark upon. However, once started, they may discover that performance improves. This has implications for rehabilitation²⁵ which should aim to encourage the subject to persist beyond the initial phase so experiencing a degree of recovery of ability. This is again analogous to the management of physical fatigue.

Finally, the results obtained were based on only a few brief tests designed to screen for

neuropsychological deficits, so must be regarded as tentative. A more detailed assessment, particularly with regard to memory, is required before any firm conclusions can be drawn. In the meantime it can be stated that relative cognitive impairment is indeed found in patients with chronic fatigue. Further research should focus on the specificity of the effects of fatigue syndromes for different cognitive processes and the suggestion that the impairment may not be entirely explicable by the presence of depression.

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