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Acute fatigue in chronic fatigue syndrome patients

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ABSTRACT

Background. Chronic fatigue syndrome (CFS) patients often complain that they are more susceptible to acute mental fatigue. It is important to determine whether this is observed using objective tests of sustained attention and responding.

Methods. Sixty-seven patients who fulfilled the criteria for CFS proposed by Sharpe *et al.* (1991) were compared with 126 matched healthy controls. Acute fatigue was assessed by comparing performance at the start and end of a lengthy test session and by examining changes over the course of individual tasks.

Results. CFS patients showed impaired performance compared to the controls and these differences increased as the volunteers developed acute fatigue. In addition, differences between the two groups were larger at the end of the test session.

Conclusions. The present results show that CFS patients are more susceptible to acute fatigue than healthy controls. This could reflect motor fatigue or an inability to compensate for fatigue with increased effort. This profile is consistent with previous research on fatigue and suggests that interpretation of certain aspects of CFS may be helped by considering it as the end point of a continuum of fatigue rather than a distinct disease.

INTRODUCTION

A number of syndromes have been described that refer to patients who present with the principal complaint of disabling fatigue. The term 'chronic fatigue syndrome' (CFS) is the most frequent name used for these conditions, largely because it is descriptive and free from aetiological implications. Behavioural abnormalities are a common feature of CFS, with patients often reporting the following problems: mental fatigue; psychiatric symptoms such as depression; sleep disturbance; and impairments of attention, memory and psychomotor functioning.

There is a general consensus that CFS patients do report more cognitive problems than controls. Smith (1991) compared 200 patients and 100 healthy controls and found that the CFS patients reported more cognitive failures (measured using the cognitive failures questionnaire, Broadbent *et al.* 1982). Similarly, Smith *et al.* (1993*a*) found that 84% of their sample of CFS patients complained of loss of concentration and 68% of memory problems. These results have been confirmed by considering problems associated with specific tasks (e.g. reading – Wearden & Appleby, 1997) and by asking about the extent to which the patients had to cease activities involving mental work (Wood *et al.* 1994).

A different picture emerges when one considers results from studies using objective tests of mental functioning. Several studies have found subjective reports of cognitive impairments but little (if any) decrement on objective tests (Altay *et al.* 1990; Grafman *et al.* 1993; Ray *et al.* 1993; Wood *et al.* 1994). Other studies have found significant impairments, although

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the precise nature of these has been variable (Deluca *et al.* 1993, 1995; Sandman *et al.* 1993; Smith *et al.* 1993*a*). These conflicting results probably reflect several things. First, patient selection has varied considerably as has the choice of control groups. Secondly, important variables, such as pre-morbid intelligence have not been controlled for in some studies. Thirdly, some studies have lacked experimental power and others have not considered possible confounders in the analyses. Finally, tasks used have varied from those sensitive to structural changes to those which are known to be sensitive to changes in physiological state. One possibility is that at least some of the impairments seen in CFS patients are similar to those observed in healthy individuals who are suffering from acute fatigue. This view suggests that tests known to be sensitive to low arousal states (e.g. sleep deprivation) should also be impaired in CFS patients. Indeed, such results would be consistent with the view that CFS represents the end point of a fatigue continuum (from acute to chronic fatigue to CFS) rather than a distinct condition.

Evidence for the above view comes from two types of study. First, Smith *et al.* (1996) examined the role of sleep disorder in CFS. They found that the problems of memory and attention seen in CFS were restricted to those with sleep disorder (and that similar impairments were seen in the controls with sleep problems). Given that sleep disorders are frequently observed in CFS patients (Moldovsky, 1993; Farmer *et al.* 1995) it is clearly worthwhile considering the extent to which performance impairments in CFS resemble those induced by sleep deprivation.

Acute fatigue may also be induced by viral infections and following some types of infection (e.g. influenza, glandular fever) this fatigue may persist for weeks or even months (White *et al.* 1995). Smith (1992) reports a study comparing 25 CFS patients, 32 healthy controls and 10 patients with fatigue following confirmed influenza illnesses in the previous month. These groups were well-matched for age and pre-morbid intelligence and the results showed that both CFS and influenza groups were impaired on free recall, recognition memory and selective and sustained attention tasks compared to the control group. Hall & Smith (1996) used similar tests to examine after-effects of infectious mononucleosis. The results showed that selective impairments of memory and attention were apparent 6 months after the original illness. This again suggests that performance impairments seen in CFS may be similar to those produced by short-term or chronic fatigue.

There is considerable evidence that when a person is fatigued they are more sensitive to other factors which lower arousal (see Tilley & Brown, 1992, for a review). For example, sleep deprived individuals show greater decrements when tasks are long and monotonous than the non-deprived people. Similarly, if a task requires a great deal of effort fatigued individuals will not be able to compensate for their lowered alertness for long periods and impairments will start to show. The main aim of the present study was to determine whether CFS patients are more susceptible to acute fatigue than controls. If this is the case it may be extremely useful to view CFS as an end point on a fatigue continuum.

It should be pointed out at this stage that the conceptualization of CFS described above cannot account for all features of the disease. Indeed, the results from the studies described in the previous section (Smith, 1992; Hall & Smith, 1996; Smith *et al.* 1996) all showed that CFS patients had a motor slowing that could not be accounted for by sleep problems and which was not observed in short-term post-viral groups. This motor slowing could reflect physical deconditioning and this problem probably needs to be considered separately from the cognitive aspects of the syndrome.

Prolonged work leads to identical problems to those induced by sleep disturbance or other methods of producing acute fatigue. The vast literature on sleep deprivation and fatigue is, therefore, highly relevant to cognitive impairments in CFS. Acute fatigue may be indicated by lapses of attention but with more complex skilled performance the effect of fatigue is to disturb the essential timing, to impair memory for recently acquired information and influence selective attention (Craig & Cooper, 1992). Observed effects may depend on the personality or coping style of the person and also on task demands. The effects of fatigue become accentuated with time on task and in tasks which require continuous effort. One might predict, therefore, that CFS patients will show greater impairments as tasks progress especially if they involve continuous responding. The following study was designed to test this view.

METHOD

Participants

Chronic fatigue syndrome patients

The study examined patients with CFS, as defined by the Oxford criteria (Sharpe *et al.* 1991). Patients were recruited from the primary health care setting by standard NHS referral. All subjects attending the clinic were invited to attend the Health Psychology Research Unit (HPRU) based at the University of Wales College of Cardiff for a testing session. Subjects were aware that their participation was entirely voluntary. Of the first 100 patients attending the clinic, 67 agreed to make part in the present study and details about them are given in the first part of the Results section. Non-participation usually reflected the fact that the patients lived too far from Cardiff. Indeed, only six of the 100 actually refused to participate in any research. Questionnaire measures (see later section) showed no differences between patients who did and did not take part in the study.

Control group

One hundred and twenty-six members of the general population were recruited to take part in the study as control subjects for a chronic fatigue sample. These subjects were recruited from an advertisement in the local press and selected to participate on the basis of age and occupational status.

Procedure

Information about the patients and controls was initially collected by questionnaire. The information ranged from standard demographic details to measures of physical and mental health and cognitive functioning. These questionnaires are listed in Table 3.

The volunteers then attended for a single session in the laboratory. Performance was assessed over a period of about 2 h and the volunteers carried out computerized tests measuring a variety of aspects of memory, attention and psychomotor function.

Acute fatigue was assessed in two ways. First, two tasks were completed at the start and then again at the end of the test session. Differences between the start and end tests would act as a general indicator of fatigue over the session. Secondly, it was possible to analyse some tasks minute by minute, which meant that one could look at the build up of fatigue over specific tasks. The tasks selected were those which have been shown to be sensitive to sleep loss and other forms of acute fatigue (see Craig & Cooper, 1992; Smith & Maben, 1993) and to be impaired in CFS patients (Smith, 1992; Smith *et al.* 1993*b*).

All computer tasks were performed using an Amstrad PC1640 computer. Responses were measured using a Cologic response box connected to a timer card allowing measurement of reaction times to the nearest millisecond. The box was designed to offer all the keys required to complete the tasks. These keys comprised three white square buttons, the central one being used in the simple reaction time tests, and the buttons either side were used when subjects performed forced-choice tasks. These keys facilitated measurement of responses and reaction times. There were also a set of red keys which could be illuminated and were used in the five-choice task.

Details of the tasks

Variable force-period simple reaction time task

In this task a box was displayed on the screen and this was followed after a period of 1–8 s by a square (the target) being presented in the middle of the box. The subject had to press a key as soon as the square was detected and, following this, another box was presented. This task lasted for 3 min.

Fixed fore-period simple reaction time task

This was identical to the above task except that the time between the box being displayed and the square appearing was always 2 s.

Five-choice serial response task

Five key-lights were displayed on the response box and when a light appeared in one of the keys the subject had to press the appropriate key and then a central home key. The next light was then displayed, and so on. This task measured the speed and accuracy of self-paced serial responding; it lasted for 3 min.

Detection of repeated numbers

Subjects were shown three-digit numbers on the screen at the rate of 100 per min. Normally each stimulus differed from the previous one but occasionally the same number was repeated on successive trials. The subjects had to detect these repeats and press the keyboard as soon as they appeared; the task lasted for 3 min.

Logical reasoning task

Subjects were shown statements about the order of the letters A and B followed by the letters AB or BA (e.g. A follows B BA). The subjects had to read the statement and decide whether it was a true description of the order of the letters. If it was the subject pressed the T key on the keyboard, if it was not they pressed the F key. The sentences ranged in syntactic complexity from simple active to passive negative (e.g. A is not followed by B). Subjects completed as many as possible in 3 min.

RESULTS

Description of participants

The groups did not differ in terms of age, gender, social class or pre-morbid intelligence (CFS: 47 females, 20 males; mean age females = 43·5 years, range 17–73; mean age males = 39·7 years, range 17–63 years; 33·3% single, 59·1% married, 6·1% divorced; pre-morbid intelligence NART mean correct score = 37·53, S.D. = 7·2. Controls: 83 females, 43 males; mean age females = 40·4 years, range 21–79 years; mean age males = 39·1 years, range = 21–66 years; 32·5% single, 50·8% married, 15·5% divorced; pre-morbid intelligence NART mean correct score = 37·52, S.D. = 7·9).

Profile of the patients

Reported aetiology

The HPRU chronic fatigue patients reported a range of precipitating factors with 95·5% of patients reporting a precipitating factor for their illness. These factors (not mutually exclusive) ranged from influenza (41%), a sore throat (32%), glandular fever (27%), stomach upset (14%) and stress (41%). These are the standard factors recalled by CFS patients, which confirms the similarity of the present sample with those described in other specialist clinics.

Table 1. *Symptom checklist (percentage reporting each symptom) and statistical difference between groups*

	Controls %	Chronic fatigue %	*P*
Physical weakness (50% more than before you were ill)	7·9	86·4	**
Excessive fatigue (50% more than before you were ill)	10·3	97·0	**
Legs feeling heavy	4·8	81·8	**
Muscle pain in back, arms or legs	27·8	89·4	**
Pain in chest	2·4	39·4	**
Painful joints	17·5	63·6	**
Nausea	4·8	48·5	**
Indigestion	11·9	25·8	*
Bloated stomach	14·3	40·9	**
Wind	12·7	45·5	**
Sore throat	7·9	47·0	**
Headache	11·9	66·7	**
Earache	1·6	24·2	**
Sore eyes	18·3	56·1	**
Sensitive to noise	5·6	65·2	**
Sensitive to light	11·1	63·6	**
Feeling hot/cold	9·5	77·3	**
Sweating	6·3	45·5	**
Shivering	0·7	45·5	**
Swollen glands	3·2	42·4	**
Racing heart	4·8	31·8	**
Insomnia	10·3	45·5	**
Depression	10·3	39·4	**
Anxiety/panic feelings	9·5	31·8	**
Loss of concentration	15·1	89·4	**
Loss of memory	8·7	80·3	*
Allergies	14·3	30·3	*

* $P < 0·05$; ** $P < 0·01$.

Illness duration

Patients reported an average illness length of 62·75 months with an average diagnosis length of 24 months.

Current severity

A self-assessment of the current state of their illness showed the following results: worse than at any stage of the illness, 6·1%; bad, 24·2%; bad with some recovery, 42·4%; recovering with occasional relapses, 27·3%; and almost completely recovered, 0%.

Symptom checklist at time of testing

A symptom check-list used in previous studies of chronic fatigue patients (Smith *et al.* 1993*a*) and measuring symptoms commonly reported by these patients (Komaroff, 1994) was administered. The percentage of patients and controls reporting various symptoms typically associated with CFS is shown in Table 1. The

Table 2. *Questionnaire measures of physical and mental health and cognitive problems*

	CFS Mean (S.D.)	Controls Mean (S.D.)
Profile of fatigue related symptoms[1]		
Fatigue	63·0 (12·4)	22·8 (11·2)
Somatic symptoms	49·7 (18·0)	23·4 (8·8)
Emotional distress	46·2 (18·6)	32·5 (15·7)
Cognitive difficulty	49·9 (12·1)	23·6 (10·6)
Cohen–Hoberman Index of physical symptoms[2]	24·4 (7·8)	6·4 (5·8)
Cognitive failures questionnaire[3]	60·8 (17·1)	38·3 (13·0)
State anxiety[4]	41·0 (9·8)	31·0 (8·2)
Beck Depression Inventory[5]	14·4 (6·8)	7·4 (6·5)
Mood last week[6]		
Negative mood	23·9 (10·9)	14·1 (9·6)
Positive mood	26·4 (8·9)	36·0 (9·6)
Perceived stress scale[7]	26·9 (8·4)	22·6 (8·6)

[1] Ray *et al.* (1992); [2] Cohen & Hoberman (1983); [3] Broadbent *et al.* (1982); [4] Spielberger *et al.* (1971); [5] Beck *et al.* (1961); [6] Zevon & Tellegen (1982); [7] Cohen & Williamson (1988).

patients differed from the controls for all symptoms and the results correspond well with those obtained in other studies (Smith *et al.* 1993*a*).

Sleep

Generally, the CFS patients reported an increase in sleep disorders with 80% rating the quality of their sleep as worse than before their illness onset. Statistical analyses, using *t* tests, showed that the patients rated the quality of their sleep as worse than the controls ($P < 0{\cdot}01$) and reported more problems getting to sleep ($P < 0{\cdot}05$) and awakening early ($P < 0{\cdot}01$). In terms of duration of sleep, there was no difference in the mean duration of the two groups but CFS patients were more likely to be very short or long sleepers than the controls.

Questionnaire scores for patients and controls

These scores are shown in Table 2. The patients reported more problems of physical health, mental health and more cognitive impairments than the controls. All of these differences were highly significant (based on *t* tests) and apparent in all the specific measures.

Performance

Analyses of variance were carried out on the performance data distinguishing the between subject factor of patients/controls and the within subject factor of session or time on task. Levene's

Table 3. *Changes with time on task*

	Minute 1 Mean (S.D.)	Minute 2 Mean (S.D.)	Minute 3 Mean (S.D.)
Simple reaction time task (ms)			
CFS	391 (190)	397 (198)	434 (216)
Controls	250 (69)	257 (90)	258 (78)
Five choice serial response task (number done)			
CFS	91 (27)	95 (29)	93 (29)
Controls	121 (21)	130 (21)	130 (22)
Repeated digits detection task			
Reaction times (ms)			
CFS	555 (114)	534 (109)	655 (167)
Controls	527 (102)	545 (114)	578 (135)
Hits (% correct)			
CFS	56·5 (22·5)	49·6 (27·3)	36·2 (23·2)
Controls	66·4 (21·0)	61·8 (22·0)	43·8 (23·6)

tests were conducted to test for normality and if this was not the case an appropriate transformation was obtained using Box–Cox diagnostic plots.

Tests at the start and end of the session

Variable fore-period reaction time task

A two-way repeated measured analysis of variance (logarithmic data) was performed comparing variable reaction time tasks performed at the beginning and the end of the test session. The analysis showed significant effects of group ($F = 76{\cdot}2$, df = 1,183, $P < 0{\cdot}01$) showing patients to be slower than controls. There was also a significant effect of test repeat ($F = 136{\cdot}65$, df = 1,183, $P < 0{\cdot}01$) showing both groups to be slower at test 2. The interaction between groups and test was not quite significant ($P > 0{\cdot}05$), although the patients showed greater slowing over time (mean reaction in ms with S.D. in parenthesis: CFS – first test, 422 (209); second test, 495 (230); difference between test 2 and test 1 = 73 and Controls – first test, 284 (51); second test, 325 (63); difference between test 2 and test 1 = 44).

Logical reasoning task

A two-way analysis of variance of the completed tasks looking at patients and controls for the first and second test showed a significant difference between groups ($F = 4{\cdot}3$, df = 1,184, $P < 0{\cdot}05$) and a significant difference between test sessions ($F = 163{\cdot}69$, df = 1,184, $P < 0{\cdot}01$). The interaction between group and test session just failed to achieve significance ($F = 3{\cdot}44$, df = 1,184, $P > 0{\cdot}05$). The results showed that controls completed more trials than patients and that performance for both groups improved in the second test, although the improvement was greater for the controls (mean number completed with, S.D. in parenthesis: CFS – first test, 32·4 (11·3); second test, 39·1 (12·8); difference between test 2 and test 1 = 6·7, and Controls – first test, 36·4 (12·6); second test, 44·6 (14·0); difference between test 2 and test 1 = 8·3).

There were no significant effects in the analysis of the accuracy data (mean percentage correct with S.D. in parenthesis: CFS – first test, 74·6 (20·2); second test, 76·5 (19·0); difference between test 2 and test 1 = 1·9% and Controls – first test, 78·1 (19·4); second test, 78·4 (18·4); difference between test 2 and test 1 = 0·4%).

Time on task effects

Simple reaction time task

The reaction times for each minute of this task are shown in Table 3. The data were logarithmically transformed and an analysis of variance showed significant differences between groups ($F = 52·37$, df = 1,186, $P < 0·01$) but no significant effect of time on task ($F = 2·93$, df = 2,372, $P > 0·05$). There was a significant interaction between group and time ($F = 3·03$, df = 2,372, $P < 0·05$). These results show that the CFS group were slower and that they showed greater fatigue in the last minute of the test.

Five choice serial response task

These data are shown in Table 3. An analysis of variance showed a significant effect of group ($F = 91·77$, df = 1,189, $P < 0·01$), a significant effect of time on task ($F = 68·65$, df = 2,378, $P < 0·01$) and a significant interaction of the two ($F = 15·26$, df = 2,378, $P < 0·01$). These results showed that patients consistently completed fewer trials than the controls, that rate varied over time for both patients and controls and that the difference in performance between patients and controls increased over time (minute 1, 30; minute 2, 35; minute 3, 37).

Repeated digits task

The reaction times to targets are shown in Table 3. The data were logarithmically transformed and the analysis of variance again showed a significant group × time on task interaction ($F = 5·7$, df = 2,344, $P < 0·01$) which reflected the much greater slowing of the CFS patients in the last minute.

The accuracy data (see Table 3) showed a highly significant difference between the CFS group and the controls ($F = 11·05$, df = 1,183, $P < 0·01$) and a highly significant effect of time on task ($F = 74·6$; df = 2,366, $P < 0·01$) but no interaction. The patients detected fewer targets than the controls, both groups showed a decline in performance with time on task, but the difference between patients and controls remained constant over time. This shows that accuracy was maintained by the patients but at the expense of slowing of response times in the last minute.

DISCUSSION

The main aim of the present study was to determine whether CFS patients were more sensitive to acute fatigue than a matched healthy control group. This was examined by comparing performance at the start and end of a lengthy test session and by considering changes over the course of tasks requiring sustained attention and/or sustained responding. All of the results supported the view that CFS patients are more susceptible to acute fatigue than controls, and the time on task analyses revealed significant interactions between CFS/controls and minutes doing the task. The profile of impairments is very similar to that obtained in sleep deprivation, where effects increase with time on task and are often observed in tasks involving sustained attention. Many of the effects could reflect an increase in motor fatigue, leading to slower response times. The ability to detect targets in a cognitive vigilance task did not show an increased difference between patients and controls over time whereas most of the speed measures did. This suggests that an explanation in terms of increased motor fatigue or reduced effort is plausible.

It is important to point out that differences between CFS patients and controls were present at the very start of the test session. In other words the groups differed initially but these differences became larger with increasing time on task. The initial impairments seen in the CFS group may reflect fatigue induced in ways other than prolonged work (e.g. sleep disturbance). Indeed, it is now desirable to determine whether CFS patients are generally more sensitive to all factors which reduce arousal. For example, one might predict that they would be especially impaired when their circadian arousal is low.

Similarly, CFS patients with high extraversion score might be especially sensitive due to their generally low level of cortical activation.

One must also now consider whether the increased sensitivity to acute fatigue can be reduced. This could take two alternative forms. First, if it is the case that the acute fatigue effects reflects an underlying sleep disorder then pharmacological treatment may remove the effects reported here. A second approach would be to try to increase alertness to determine whether this stops the rapid build-up of fatigue. The problem with the second approach is that many of the methods used to change low arousal states could have specific as well as non-specific alerting effects on CFS patients. For example, noise can reverse effects seen in low arousal situations (Smith & Nutt, 1996) but many CFS patients report very high sensitivity to noise. Similarly, caffeine is remarkably effective in reducing fatigue (Smith *et al*. 1993*b*) but many CFS patients report negative effects from caffeine consumption. At the moment it is unclear whether any unwanted side effects will occur if drugs changing the turnover of central noradrenaline are given to CFS patients. if they do tolerate these compounds then there may be some reduction in their fatigue. Furthermore, if the drugs also contain compounds which change the serotonin system then further benefits (e.g. reduction of sleep problems) may be found. The methods used in the present study provide a means of testing these views.

Overall, there would appear to be some value in considering certain features of CFS to be extreme forms of the problems associated with acute fatigue. It has already been mentioned that there are other aspects of the syndrome which can be better interpreted in other ways (e.g. physical de-conditioning). The major issue for interpretations based on a fatigue continuum is why the fatigue persists in these patients. A simple view of how this might occur can be found in the literature on fatigue and performance. Craig & Cooper (1992) suggests that the nature and extent of the fatigue associated with performance may depend on characteristics of the person doing the tasks. Observed effects may depend on personality or coping style as much as on the task demands themselves. Similarly, the ability to recover from a fatiguing situation may be much more important for long term health than the acute response to it. Bartlett (1953) pointed out that fatigue is not likely to be a problem until normal rest and sleep do not lead to full recovery before the next set of demands. Indeed, the mechanism by which fatigue is retarded may well comprise an emotional component of the previous demand. Therapy must aim to break this cycle and the best way to do it may clearly vary from person to person. Furthermore, the methods of reducing acute fatigue that were outlined earlier will probably have little effect on the pathogenesis of the disease unless the general demands placed on the person are changed as well.

In summary, the present study has demonstrated that objective tests of sustained attention and responding show differences between CFS patients and healthy controls. The size of these differences increases as the volunteers become more fatigued. This could either reflect motor fatigue or a reduction in effort with time on task. These results are consistent with results from previous studies of acute fatigue and suggest that understanding of some aspects of CFS may be enhanced by considering it as the end point of a fatigue continuum. Susceptibility to acute fatigue may be a good method of assessing a patient's current state. Similarly, recovering from fatigue may be a very good indicator of the patients' condition and the efficacy of treatments.

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