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Using an interleukin-6 challenge to evaluate neuropsychological performance in chronic fatigue syndrome

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ABSTRACT

Background. Individuals with acute infections experience a range of symptoms including fatigue, malaise, muscle aches, and difficulties with concentration and memory that are usually self-limited. This cluster of symptoms is otherwise, similar to those that characterize chronic fatigue syndrome (CFS). The goal of the present study was to evaluate the cognitive and psychological functioning of CFS patients and normal controls (NCs) when they both were experiencing acute influenza-like symptoms. To induce influenza-like symptoms, we administered interleukin-6 (IL-6), a cytokine that temporarily activates the acute phase immunological and endocrine responses.

Methods. Nineteen patients who met the 1994 International CFS Study Group Criteria and ten normal controls (NCs) completed routine clinical evaluations, neuropsychological tests of short-term memory, selective attention, and executive control, and self-ratings of somatic symptoms and psychological mood before, shortly following, and 1 day after IL-6 administration.

Results. CFS patients consistently reported more somatic symptoms, even when both groups perceived that they were ill. Both groups somatic symptoms increased during the IL-6 challenge, but the CFS patients symptoms increased more rapidly than controls. In general, the CFS patients performed similarly to NCs on the cognitive measures before, during, and after the IL-6. In contrast to predictions, IL-6 provocation did not impair the cognitive performance of either CFS patients or NCs.

Conclusions. The IL-6 provocation exacerbated the patients self-reported symptoms but did not reveal notable cognitive impairments between patients and controls during cytokine-induced acute influenza-like symptoms.

INTRODUCTION

Infectious diseases are frequently associated with behavioural disturbances, collectively referred to as sickness behaviour, that include increased sleep, decreased activity, decreased food and water intake, hyperalgesia, and decreased social interaction (Hart, 1988; Dantzer *et al.* 1992). Humans suffering from infectious diseases also report malaise and difficulties with concentration. Most of the systemic effects of infection result from cell-mediated immune responses to pathogens (Dinarello, 1984; O'Garra, 1989). Cytokine activity within the central nervous system (CNS) or secondary pathways triggered by peripherally produced cytokines are hypothesized to mediate the changes in cognition and mood associated with infectious diseases. The cytokine-mediated symptoms resemble many of

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the symptoms associated with chronic fatigue syndrome (CFS) (Hickie *et al.* 1990; Hickie & Lloyd, 1995).

In response to viral infection, for example, leucocytes synthesize and release pro-inflammatory cytokines (i.e. interleukin-1 (IL-1) and interleukin-6 (IL-6), tumour necrosis factor alpha (TNFα) and interferon alpha (IFNα)) that stimulate a cascade of other responses (Decker, 1990) including activation of the hypothalamic–pituitary adrenal (HPA) axis. Activation of the HPA axis leads to an increased release of glucocorticoids (cortisol in humans and corticosterone in rats) that provide negative feedback regulation to the immune responses, dampening further production of cytokines. By influencing the production and release of glucocorticoids, psychological stress also influences the immune response (McEwen *et al.* 1997).

Studies of experimental subjects and patients treated with cytokines indicate that subjects experience cognitive impairments similar to those associated with infectious diseases. For example, cancer patients treated with exogenous IFN-α or IL-2 have reported difficulties concentrating (Ravaud *et al.* 1991 as cited in Capuron *et al.* 1999) and memory disturbances (Denicoff *et al.* 1987; Smith *et al.* 1988*b*). Objective neuropsychological tests indicate that individuals with viral colds have visual-motor coordination deficits, while those with influenza have impairments on visual search tasks (Smith *et al.* 1988*a*). Recent research indicates that subjects with influenza-like illnesses have significantly lower scores on memory tests that involve complex cognitive processes including attention, acquisition, organization, and retention of new information, and that the impairment is independent of the magnitude of the fever (Capuron *et al.* 1999).

The pattern of cognitive impairment associated with acute infections and their concomitant cellular immune responses is similar to the profile of cognitive deficits in CFS. Although formal assessments of cognitive functioning in CFS largely have yielded conflicting results, one relatively consistent finding is that CFS patients demonstrate mildly impaired higher order information processing, a component of executive control (DeLuca *et al.* 1993, 1995; Marshall *et al.* 1997). Moreover, CFS patients demonstrate modestly delayed response times and slower information processing on tasks that require divided attention over a lengthy time period and when interference or memory load is increased (Moss-Morris *et al.* 1996).

Despite their overall mild objective cognitive impairments in attention, memory and information processing, CFS patients report significant functional impairments in these areas that fluctuate with the severity of their illness (Grafman, 1996). The basis of this discrepancy is not understood but has been posited to result from the lack of objective testing when CFS patients are feeling poorest. As a consequence, it is possible that investigators have underestimated the level of neuropsychological impairment in CFS.

To evaluate and characterize the cognitive impairments, somatic symptoms and psychological mood of CFS patients when their physical health is more compromised than usual, human recombinant IL-6, a synthetic form of IL-6 that induces a temporary influenza-like syndrome (Papanicolaou *et al.* 1998), was administered to NCs and CFS patients. Both groups completed a battery of neuropsychological tests before, shortly following and 1 day after IL-6 administration. The neuropsychological tests chosen were sensitive to the primary complaints of difficulties in concentration and memory that we had documented previously in CFS patients (Grafman *et al.* 1991). The tests measured selective attention, short-term memory, and executive functioning using response times and error rates as dependent measures. Additionally, self-reports of mood and somatic symptoms along with measures of body temperature were obtained at multiple time intervals.

We predicted that: (1) CFS patients would prove more impaired than normal controls on the neuropsychological tests of selective attention and short-term memory, particularly when they were the most distracted by irrelevant stimuli or when the memory load increased; (2) CFS patients world demonstrate slower response times compared to NCs on a measure of executive functioning; (3) at the peak of induced symptoms, both CFS patients and NCs would perform more poorly on cognitive tests, with CFS patients performance more adversely affected than that of the NCs; and (4) CFS patients would report more somatic and psychological symptoms compared to NCs, and both CFS

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patients and NCs would report more somatic and psychological symptoms during IL-6 administration compared to baseline.

METHOD

Subjects

Nineteen patients (13 females, six males) who met the 1994 International CFS Study Group Criteria participated in the study (Fukuda *et al*. 1994). The majority of patients were among a larger cohort at the National Institutes of Health (NIH) who volunteered to participate in the current study in response to an informational letter describing the study. Inclusion criteria included a diagnosis of CFS in patients between the ages of 18 and 50, the ability to complete cognitive testing, and the ability to adhere to study restrictions that prohibited medications during the course of the study. Patients were not eligible if they had used systemic glucocorticoids up to one year prior to the study. Women who participated were also required to have a negative pregnancy test and completed the study during the follicular phase.

To ascertain the diagnosis of CFS, each interested patient completed a standardized battery of assessments that included a patient history, a routine physical examination, laboratory tests, and a psychiatric evaluation (Fukuda *et al*. 1994; Schluederberg *et al*. 1992). The Computerized Diagnostic Interview Schedule (CDIS-R; Blouin *et al*. 1988), which is based on the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) criteria (American Psychiatric Association, 1987), was used to determine lifetime and current psychiatric diagnoses and exclude patients per diagnostic criteria. CFS patients who met criteria for major depression were excluded if their depression was of such severity as to require antidepressant medications during the course of the study. Of the patients who participated, two (10·5%) were on antidepressants before starting the study. For 2 to 6 weeks before enrolment (depending on the drug) and for the duration of the study, participants discontinued the use of antidepressants and most other prescription and over-the-counter drugs except acetaminophen.

Current DSM-III-R diagnoses

Based on the CDIS-R, six patients had no lifetime history of psychiatric disorders and 12 met criteria for somatoform pain disorder (SPD) due to symptoms that are also criteria for CFS. Five of the 12 patients who met criteria for somatoform pain disorder had additional psychiatric diagnoses. One patient also met criteria for lifetime somatization disorder and another patient had a history of alcohol abuse. A third patient had additional diagnoses of former nicotine and cocaine abuse. A fourth patient met criteria for social and simple phobia and former cannabis abuse, and a fifth patient met lifetime criteria for post-traumatic stress disorder, obsessive–compulsive disorder, and former nicotine abuse. One patient did not complete the CDIS-R.

Self-ratings to characterize the patient group

To characterize the CFS patients physical and emotional symptoms and level of functioning, patients completed the following self-rating questionnaires: the Wellness Score (Straus *et al*. 1988), a single-item global health scale ranging from zero, representing the worst they had ever felt, to 100, representing the best they had ever

Table 1. *Demographic variables for chronic fatigue syndrome patients* (*CFS*) *and normal controls* (*NC*)

	CFS	NC
Number of subjects, *N*	19	10
Age (years)	40·84 ± 6·27 (29–50)	39·8 ± 8·46 (28–54)
Number of females, *N*	13	7
Number of males, *N*	6	3
Education (years)	15·63 ± 2·69 (12–20)	16·0 ± 2·10 (13–20)
Duration of illness (years)	6·9 ± 2·8 (2–14)	—
Impaired employment (*N*)*	11	—

Unless otherwise stated, values are mean ± standard deviation (range).
* Number of subjects unable to work or working part-time.

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felt; the Symptom Checklist-90-R (Derogatis, 1977); the 36-item Short Form Health Survey (SF-36) (Ware & Sherbourne, 1992), which includes an assessment of physical functioning and general mental health; a 10-point Activity scale developed by the NIH investigators (McKenzie *et al.* 1998); the Duke Activity Status Index (Hlatky *et al.* 1989); and the Beck Depression Inventory (Beck *et al.* 1961). The results of the self-rating profiles were similar to those reported in previous studies of CFS (McKenzie *et al.* 1998; Rowe *et al.* 2001). The mean baseline CFS self-ratings with standard deviations were the following: Wellness Score 38 ± 16; Symptom Checklist-90-R General severity index $0{\cdot}7 \pm 0{\cdot}5$; SF-36 physical functioning $46{\cdot}3 \pm 24$; SF-36 general mental health $78{\cdot}4 \pm 16{\cdot}6$; 10-point Activity Scale $4{\cdot}3 \pm 0{\cdot}9$; Duke Activity Status Index $13{\cdot}2 \pm 13{\cdot}9$; and the Beck Depression Inventory $10{\cdot}4 \pm 5{\cdot}6$.

Normal controls

Ten (seven females, three males) normal controls (NCs) were recruited from an advertisement placed in the NIH volunteer office. Like the CFS patients, they completed a standardized battery of assessments that included a medical history, a routine physical examination and laboratory tests. They had no significant medical or psychiatric history, a normal physical examination and normal serum electrolytes, creatinine, liver enzymes, automated blood counts and resting electrocardiograms. None of the controls were on any medications during the study and 2 to 6 weeks prior to the study. They were matched to the patients for age and education level (see Table 1).

Study design

The study was planned as a repeated measures design. CFS patients and NCs completed neuropsychological tests and rated their mood at baseline, shortly following, and one day following IL-6 administration. Additionally, serial measures of physiological functioning (i.e. body temperature and pulse rate) and somatic symptoms were collected. The study was conducted on three separate days. The first day yielded the baseline data (Session 1). Between 8 and 9 a.m. on the second day (Session 2), a single subcutaneous injection of IL-6 was administered at a dose of 3 μg/kg of body weight. Subjects experienced IL-6 induced influenza-like symptoms for approximately 12 h (i.e. until about 9 p.m.) with peak effects occurring 6·5 h after administration (Papanicolaou *et al.* 1996), co-occurring with neuropsychological testing that began at approximately 2.30 p.m. each day. Subjects also completed a final battery of tests and self-ratings when all IL-6 induced symptoms had resolved (Session 3). All subjects provided written, informed consent to participate in the study whose various aspects were approved by the Institutional Review Boards of the National Institute of Neurological Disorders and Stroke, the National Institute of Child Health and Human Development, and the National Institute of Allergy and Infectious Diseases.

Neuropsychological tests

All of the neuropsychological tests were administered on a computer. Subjects were seated approximately 60 cm from a standard personal computer screen and responded using a keyboard.

Flanker Test of Selective Attention

The Flanker Test of Selective Attention measures a subject's ability to focus on a particular target while ignoring other interfering stimuli (Eriksen, 1995). A target letter (S or H), which subjects had to type as quickly as possible, was presented either without distractors (control condition) or flanked by letters at various distances (1, 3, or 8 pixels away). The flanking letters were either identical to the target letter (distractor compatible condition), targets on previous trials (distractor incompatible condition), or letters other than the target letters (distractor neutral condition).

The order of the four conditions and the location of the flanking distractors were randomly presented. A total of 192 trials were administered with 48 trials in each of the four conditions. The trials with compatible, neutral and incompatible flanking letters were equally distributed across each of the three distances. In the control condition, the target letter (S or H) was always presented in the centre of the screen. A different random order was used in each of the three testing sessions.

Task Switching Task

The Task Switching Task requires subjects to

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switch back and forth between two different tasks using the same stimuli. The test requires the maintenance of an anticipatory set, set-shifting, and inhibition of the irrelevant task – all components of executive functioning (Denckla, 1996). The stimuli were an array of dots presented in a white box in the centre of the computer monitor. The subject had to decide quickly and accurately whether the number of dots presented was over or under the value 5 (i.e. Over/Under) or an odd or even number (i.e. Odd/Even). The words 'Odd' or 'Even' or 'Over' and 'Under' appeared on the screen to remind the subject which task to complete.

The tasks were presented in blocks of 80 trials in the same order to all of the subjects during each of the three testing sessions (see Appendix for the order). Some blocks only presented a single task (Odd/Even, or Over/Under), other blocks systematically (Alternating) or randomly (Random) switched between tasks. There were 16 blocks, four of each type, for a total of 1280 trials. In the alternating and random blocks, subjects completed 40 trials of each task. Subjects were told which type of block (i.e. Odd/Even, Over/Under, Alternating, or Random) to expect before the start of each block. The order of the blocks remained the same across each of the three testing sessions.

Sternberg Memory Scanning Test

The Sternberg Memory Scanning Test (Sternberg, 1966) measures speed of searching through short-term memory. Subjects encode 1 to 6 digits presented in the centre of the computer monitor in a white box against a black background. The digits are presented for 500 ms and then a single target digit appears for 500 ms. Subjects have to decide if the target digit was part of the set they just encoded by pressing keys labelled 'Yes' or 'No'. Subjects are told to respond as quickly and accurately as possible. There are a total of 120 trials. A different random order is used for each subject in each of the three testing sessions.

Self-report questionnaires

Using a Likert Scale, subjects rated their mood from 1 to 11, with '1' indicating they did not experience the feeling and '11' indicating that the feeling was very severe. The feelings evaluated included sadness, depression, worthlessness, anxiety and happiness. Subjects also rated their somatic symptoms (i.e. aches, fatigue, nausea, fever and sweating, malaise, and headaches) on an 11-point scale with '1' representing no symptoms and '11' representing feeling the worst they have ever felt.

Physiological measures

Measures of heart rate and body temperature were obtained from both CFS patients and NCs at baseline (i.e. immediately before IL-6 administration) and at standardized intervals following the IL-6 injection.

Procedure

The self-ratings of mood symptoms were completed during the beginning of each of the three testing sessions followed by the neuropsychological tests, completed in a different order each testing session. The Task Switching data was administered but not collected due to computer error from two CFS patients and two NCs during the first session and from two different CFS patients during the second testing session. One CFS patient did not complete the Flanker Test of Selective Attention during the second testing session due to excessive fatigue and nausea following the IL-6 provocation.

Serial measures of somatic symptoms and physiological measurements were obtained at the following time intervals: immediately before IL-6 administration, several times (i.e. 0·5, 1, 2, 3, 4, 6 and 8 h) immediately following IL-6 administration, and at least 24 h after IL-6 administration, once the IL-6 effects had subsided. Ratings of somatic symptoms (i.e. aches, headaches, malaise) were not obtained from several patients (5–7 patients depending on the symptom) and two NCs 6 h after IL-6 because some subjects were still completing neuropsychological testing.[1] Two other NCs did not rate their somatic symptoms 8 h after IL-6 administration.

Eighteen of the 19 CFS patients completed the tests and ratings on consecutive days. One patient had one intervening day between session 1 and 2. Four of the normal controls completed the testing on consecutive days. Five normal

[1] Occasional logistical problems coordinating the collection of the physiological measures resulted in missing data. Careful inspection and analyses found no indication of a systematic bias with regard to which patients data was missing.

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controls had 3–5 days between session 1 and 2. One normal control had 3 days between the session 1 and 2 and 2 days between session 2 and 3. Given that the symptoms elicited by the IL-6 injection resolve within approximately 12 h (Papanicolaou *et al.* 1996), the delay between session 2 and 3 was acceptable.

Statistical analysis

The subjects' self-ratings were not normally distributed so we used non-parametric statistics to analyse their data. We completed within group comparisons to evaluate the effects of IL-6 over time in each group. The Friedman test was used to compare the self-ratings of mood obtained before, 6–8 h after and 24 h after IL-6 injection, eliminating one patient who did not have ratings for the second session. For somatic ratings, we compared ratings obtained at baseline, the median of those obtained 0·5 to 4 h following IL-6, the median of those obtained 6 to 8 h following IL-6 and ratings obtained at least 24 h after IL-6. Due to missing data at the 6 and 8 h time points, the median rating at the 6 to 8 h time point is a median of the two different ratings for most subjects and the rating from either the 6 or 8 h time point for other subjects. Separate paired comparisons for each group indicated that the ratings at the 6 h time point were not significantly different from those at the 8 h time point so this is an adequate estimate of somatic ratings during peak IL-6 effects. If the Friedman test indicated that there was significant difference in the self-ratings across the time intervals, we used non-parametric pairwise comparisons to determine which ratings differed (Siegel & Castellan, 1988). We used the Mann–Whitney *U* test to analyse between-group differences.

We used repeated measures mixed ANOVAs to compare cognitive performance across sessions (i.e. before, shortly following, and 24 h after IL-6) and between subject groups. If scores from one of the three sessions were missing, the scores from the other sessions were eliminated in the repeated measures mixed ANOVA. A similar analysis was performed on the physiological measurements collected at multiple intervals. Measurements 6 h after IL-6 injection were not obtained for several subjects because they were in the midst of psychological testing. Data from that time period was excluded. The repeated measures analysis also excluded three patients and three NCs who did not have pulse rate measurements and four patients and three NCs who did not have body temperature measurements at either the 8 or 24 h time interval. One-way ANOVAs were used to evaluate group differences at each single measurement point.

If there was an overall significant change across the three testing sessions or across the multiple physiological measurements, comparisons between the mean of each level (except the last) and the mean of the subsequent level were performed to find out which ratings differed. When the sphericity assumption was violated, we reported the degrees of freedom with the Greenhouse–Geisser correction (G). We calculated measures of effect size for the non-parametric mood and somatic ratings using Cohen's *r*. For the physiological data, we used the standard deviation of the control group in calculating Cohen's *d*. Eta squared (η^2) was used as an estimate of effect size for the results of the repeated measures mixed ANOVA. The significance level for all tests was set at 0·05.

RESULTS

Physiological functioning

Between group effects

Both CFS patients ($N = 15$) and NCs ($N = 7$) had similar physiological responses to the IL-6. A repeated measures mixed ANOVA indicated that there were no overall group differences in body temperature, $F(1, 20) = 3{\cdot}77$, $P = 0{\cdot}07$. One-way ANOVAs that included data for 18 CFS patients and 10 NCs indicated that the CFS patients body temperatures rose to statistically significantly higher levels 1·5, 2 and 3 h following IL-6 administration, Fs$(1, 27) = 4{\cdot}82$, 6·96 and 5·67 respectively, Ps $< 0{\cdot}05$ (see Table 2). The magnitude of temperature differences between the groups 1·5, 2 and 3 h after IL-6 was moderate to large, Cohen's $d = 0{\cdot}68$, 1·01, 0·75, respectively. There were no overall group differences in pulse rates (beats/min) between CFS patients ($N = 16$) and NCs ($N = 7$) at baseline or during the IL-6 challenge, $F(1, 21) = 1{\cdot}53$, $P = 0{\cdot}23$ (see Table 2).

Within group IL-6 effects

As expected, IL-6 activated the inflammatory response. A repeated measures mixed ANOVA

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Table 2. *Mean body temperatures (°C) and pulse rate (beats/min) at each time interval*

	Time interval shortly before or after IL-6 administration								
	Baseline	0·5 h	1 h	1·5 h	2 h	3 h	4 h	8 h	24 h
Body temperature (°C)									
CFS	36·49 ± 0·47	36·41 ± 0·52	36·91 ± 0·61	37·01 ± 0·49*	37·13 ± 0·63*	37·38 ± 0·60*	37·68 ± 0·64	37·63 ± 0·60	36·56 ± 0·60
NC	36·16 ± 0·86	36·25 ± 0·54	36·38 ± 0·71	36·49 ± 0·77*	36·47 ± 0·66*	36·71 ± 0·88*	37·13 ± 0·76	37·30 ± 0·58	36·28 ± 0·61
Pulse (beats/min)									
CFS	64·68 ± 10·9	64·94 ± 14·0	71·38 ± 10·7	75·75 ± 9·0	81·38 ± 11·5	85·75 ± 14·5	84·94 ± 16·0	94·38 ± 15·5	84·38 ± 14·4
NC	62·57 ± 9·8	63·71 ± 11·3	63·57 ± 10·1	66·29 ± 11·2	74·00 ± 9·6	78·57 ± 11·8	80·57 ± 15·8	91·43 ± 7·5	77·14 ± 9·9

Note: Means and standard deviation for CFS patients ($N = 18$) and NCs ($N = 10$) for body temperature. For pulse rate, CFS patients ($N = 16$) and NCs ($N = 7$).
* $P < 0·05$ between group effects for body temperature.

indicated that there were significant effects by time of measurement on body temperature and pulse, $F(1·54, 32·31) = 30·70$, $P < 0·01$ and $F(4·33, 90·95) = 36·11$, $P < 0·01$, respectively.

For body temperature, simple within-subject contrasts indicated that both CFS patients and NCs temperatures increased from 0·5 to 1 h and from 3 to 4 h following IL-6 administration, $F(1, 20) = 6·45$, $P = 0·02$, and $F(1, 20) = 15·04$, $P < 0·01$, respectively, As expected, both groups temperatures decreased from the 8 h time-point to the 24 h time-point, $F(1, 20) = 62·34$, $P < 0·01$ (see Table 2).

Both CFS patients and NCs pulse rates increased over time: from baseline to 30 min, 1 to 1·5 h, 1·5 to 2 h, 2 to 3 h, and from 4 to 8 h following IL-6 administration, Fs$(1, 21) = 4·29$, 5·87, 29·48, 8·94 and 11·95, respectively, Ps $<$ 0·05 (see Table 2). As expected, both groups pulses slowed from the 8 h to the 24 h time interval, $F(1, 21) = 27·56$, $P < 0·01$.

Self-ratings of physical discomfort

Between group differences

As expected, CFS patients reported significantly higher levels of somatic symptoms (i.e. fatigue, aches, headaches and malaise) as compared to NCs at baseline (see Table 3). They continued to experience higher levels of those somatic symptoms 30 min to 4 h following IL-6 injection, when most controls continued to report no somatic symptoms. When NCs began to experience symptoms (i.e. 6 to 8 h after administration), CFS patients continued to report significantly higher levels of fatigue, aches, headaches, malaise and nausea (see Table 3). There were fewer group differences 24 h after IL-6 administration, but CFS patients did continue to experience significantly higher levels of fatigue and malaise as compared to NCs (see Table 3). Cohen's r indicated a moderate effect size (approximately 0·5) for each of the group differences on the self-report ratings of somatic symptoms (see Table 3).

Within group IL-6 effects

As expected, the administration of IL-6 influenced the physical functioning of both CFS patients and NCs. In general, the CFS patients experienced more somatic symptoms shortly after the IL-6 injection rather than 6–8 h later as the NCs.

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Table 3. *Median self-ratings of physical symptoms across sessions*

	Baseline	0·5–4 h	6–8 h	24 h
Fatigue				
CFS	3·00 (1–7)	5·50 (1–8)	6·00 (1–10)	3·00 (1–8)
NC	1·00 (–)	1·00 (1–5)	2·00 (1–5·5)	1·00 (1–2)
Mann–Whitney *U*	25·00, $P < 0·01$*	18·00, $P < 0·01$*	26·00, $P < 0·01$*	33·50, $P < 0·01$*
Effect size (*r*)	0·65	0·67	0·59	0·57
Aches				
CFS	1·00 (1–6)	4·00 (1–8·5)	4·00 (1–9)	2·00 (1–6)
NC	1·00 (–)	1·00 (1–4)	1·50 (1–5)	1·00 (1–2)
Mann–Whitney *U*	50·00, $P < 0·01$*	33·00, $P < 0·01$*	48·00, $P = 0·03$*	58·00, $P = 0·06$*
Effect size (*r*)	0·47	0·54	0·41	NS
Feverishness				
CFS	1·00 (–)	1·00 (1–5)	2·00 (1–7)	1·00 (–)
NC	1·00 (–)	1·00 (1–1·5)	1·00 (1–4)	1·00 (–)
Mann–Whitney *U*	95·00, $P = 1·0$	60·50, $P = 0·05$	55·50, $P = 0·06$	95·00, $P = 1·0$
Effect size (*r*)	NS	NS	NS	NS
Headache				
CFS	2·00 (1–7)	3·50 (1–8)	5·00 (1–9)	1·00 (1–5)
NC	1·00 (–)	1·00 (1–3)	1·00 (1–4)	1·00 (–)
Mann–Whitney *U*	45·00, $P < 0·01$*	29·00, $P < 0·01$*	41·50, $P = 0·01$*	65·00, $P = 0·05$*
Effect size (*r*)	0·50	0·58	0·47	NS
Malaise				
CFS	2·00 (1–7)	4·00 (1–8)	4·50 (1–9·5)	1·00 (1–5)
NC	1·00 (–)	1·00 (1–3·5)	1·00 (1–4)	1·00 (–)
Mann–Whitney *U*	45·00, $P < 0·01$*	21·00, $P < 0·01$*	30·00, $P < 0·01$*	50·00, $P = 0·01$*
Effect size (*r*)	0·50	0·66	0·56	0·47
Nausea				
CFS	1·00 (1–3)	2·00 (1–6)	2·00 (1–5)	1·00 (1–4)
NC	1·00 (–)	1·00 (–)	1·00 (1–2·5)	1·00 (1–3)
Mann–Whitney *U*	80·00, $P = 0·19$	40·00, $P < 0·01$*	37·00, $P < 0·01$*	89·50, $P = 0·67$
Effect size (*r*)	NS	0·54	0·53	NS

Ratings (1–11): 1, no symptoms; 11, worst ever felt.
Minimum and maximum ratings are in parentheses; –, indicates that all the ratings were the same.
* Represents a significant group difference ($P < 0·05$); NS, not a significant group difference.
CFS, $N = 19$; NC, $N = 10$.

The CFS patients level of aches, fatigue, feverishness, headaches, malaise and nausea changed significantly across the four time intervals (before, shortly following, 6 to 8 h after and 24 h after IL-6), Friedman χ^2s(3) = 28·70, 43·71, 31·63, 30·77, 35·54, 18·41, respectively, Ps $< 0·05$. Pairwise comparisons, which compared differences in mean ranks to a critical value at $P < 0·05$ significance level, indicated that CFS patients experienced significantly higher levels of fatigue ($|-1·31|$, $P < 0·05$) and malaise ($|-1·36|$, $P < 0·05$) shortly following (0·5–4 h) the IL-6 injection as compared to baseline. From baseline to 6 to 8 h after IL-6, CFS patients experienced an increase in aches, fatigue, feverishness, headaches and malaise, $|-1·55|$, $|-2·05|$, $|-1·50|$, $|-1·13|$, $|-1·55|$, respectively, Ps $< 0·05$ (see Table 3).

As expected, the NCs ratings of aches, fatigue, feverishness, headaches and malaise changed across the sessions, Friedman χ^2s(3) = 9·29, 11·68, 11·00, 8·82, 8·60, respectively, Ps $< 0·05$. For the NCs, the only pairwise comparison to reach significance indicated that NCs experienced a significant increase in fatigue from before IL-6 to 6–8 h after IL-6, $|-1·25|$, $P < 0·05$. Visual inspection of the median self-ratings for each symptom indicate that NCs, in contrast to the CFS patients, did not experience more aches and fatigue shortly following IL-6. Neither did they experience any headaches or nausea following IL-6. Like CFS patients, they did experience an increase in aches, fatigue, feverishness and malaise 6–8 hours after IL-6 (see Table 3).

Self-ratings of mood

Between group differences

There were no between group differences on the mood questionnaires. In contrast to prior re-

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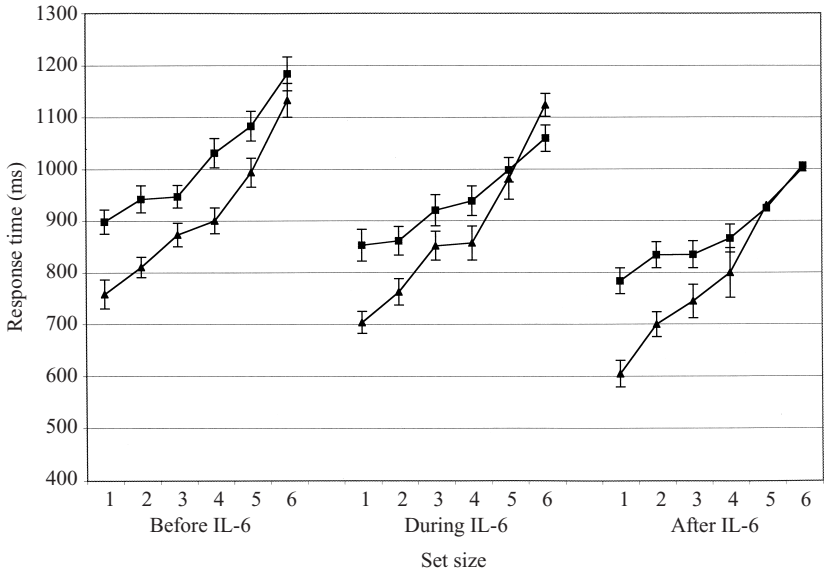


FIG. 1. Sternberg Memory Span: mean response times (RTs) for each set at baseline, immediately after and 24 h post IL-6. There was a significant group × set interaction ($P < 0{\cdot}01$). CFS (■) patients responded more slowly than NCs (▲) on the smaller sets as compared to the larger sets.

ports, CFS patients did not report feeling significantly more depressed or sad than NCs.

Within group IL-6 effects

IL-6 influenced both the CFS patients and NCs physical status, but had little effect on their psychological mood. The non-specific inflammatory response triggered by the IL-6 did not include changes in CFS patients or NCs ratings of depression, anxiety, or sense of worth, but the patients self-ratings or happiness did change, Friedman χ^2s(2) = 6·66, $P < 0{\cdot}05$. Pairwise comparisons did not reach significance; however, the medians indicate that CFS patients were happier after the IL-6 effects had abated as compared to during the influenza-like illness. They reported a mild level of happiness (median = 5·00, range = 1–8) 6 h after IL-6 administration and a moderate level of happiness (median = 6·00, range = 1–10) after the IL-6 effects had subsided. There was no change in the NCs happiness ratings, which were consistently moderate.

Neuropsychological test results

Memory

For the Sternberg Memory Test, there were two within subject factors analysed: session (three levels: before, 6 hours after, and 24 hours after IL-6) and set size (six levels: 1, 2, 3, 4, 5, and 6 digits in length) and one between subjects factor (CFS or NC). We performed separate analyses using accuracy (per cent correct) and response time (ms) as dependent measures.

Between group differences

For response time on the Sternberg Memory test, there were no overall group differences $F(1, 27) = 1{\cdot}13$, $P = 0{\cdot}30$, but there was an interaction between group and set, $F(2{\cdot}96, 79{\cdot}88) = 5{\cdot}24$, $P < 0{\cdot}01$. Statistical comparisons between response times from each set and the subsequent set (e.g. 1-digit *v.* 2-digits, 2-digit *v.* 3-digit, etc.) indicated significant group by set interactions, Fs(1, 27) = 5·08, 9·13, 7·36, respectively Ps $< 0{\cdot}05$. CFS patients responded more slowly than NCs to the smaller sets (1–3 digits) as compared to the larger sets (4–6 digits) (see Fig. 2). Eta squared (η^2) for the interaction was 0·16, indicating a small effect (see Fig. 1).

For accuracy, there were no group differences or group interactions. There were also no correlations between response time and accuracy that would suggest a speed *versus* accuracy trade-off.

Within group IL-6 effects

The performance of both CFS patients and NCs changed over the three sessions, $F(1{\cdot}74, 46{\cdot}84) =$

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14·57, $P < 0·01$. Within subject analyses indicated that there was a significant decrease in response time from the first session to the second session, $F(1, 27) = 14·96$, $P < 0·05$ and from the second session to the third session, $F(1, 27) = 13·84$, $P < 0·05$. Thus, rather than showing no change or a slight decline in performance when experiencing the peak IL-6 effects, the performance of all subjects actually improved with practice (see Fig. 1).

There was also a main effect for set size $F(2·96, 79·88) = 84·17$, $P < 0·01$. Within subject analyses that compared the mean response times for each level to that of the subsequent level (e.g. 1-digit *v.* 2-digits) indicated that both groups responded significantly faster on the smaller sets as compared to the next largest set, Fs$(1, 27) = 64·31$, 139·74, 140·06, 90·51, and 41·62, respectively, Ps $< 0·05$.

For accuracy, there was a main effect for set, $F(2·34, 63·05) = 4·88$, $P < 0·01$. Both groups made significantly more errors on the 6-digit targets as compared to the 5-digit targets, $F(5, 23) = 15·60$, $P < 0·01$ (see Fig. 2).

Executive control

On the Task Switching Task, each block consisting of 80 trials yielded a mean response time and mean number of errors (see Appendix for order of 16 blocks of four different types). To examine order effects, the mean response time from the same blocks (i.e. all four blocks of Odd/Even) within a session were compared using a repeated measures mixed ANOVA. Within subject comparisons indicated that there was a decrease in response time (improvement) with repetition, with the greatest improvement (decrease in response time) between the first and second time subjects completed the same block (i.e. between Odd /Even block 1 and Odd/Even block 2). There were no significant interactions between group and block. Given that CFS patients and NCs demonstrated similar rates of improvement, we collapsed the data from each of the 16 blocks into a mean response time and mean number of errors for each type of task (Odd/Even, Over/Under, Alternating, Random) (see Table 4). The within subject factors were session (three levels) and type of task (four levels: Odd/Even, Alternating, Random). Separate analyses were performed for response time and accuracy.

Between group differences

There were no differences in response times or accuracy rates between the CFS patients ($N = 15$) and the NCs ($N = 8$), $F(1, 21) = 0·25$, $P = 0·62$, and $F(1, 21) = 0·08$, $P = 0·79$, respectively. There were also no significant group interactions.

Within group IL-6 effects

For response time, there was an interaction between the type of task and session, $F(2·83, 59·47) = 11·12$, $P < 0·05$. There were also main effects for session, $F(2, 42) = 44·08$, $P < 0·05$, and type of task, $F(1·36, 28·54) = 159·07$, $P < 0·05$. Overall, as response times decreased with practice over the three sessions, the differences in response times between the different blocks decreased. This effect is the result of improvement on the most difficult blocks over the three sessions. The block during which subjects had to systematically switch back and forth between tasks (i.e. Alternating) was the most difficult; it induced the largest response time. The next most difficult task was the random condition followed by the single conditions (see Table 4 for response times).

The accuracy rate of both NCs and CFS patients depended on the block, $F(1·07, 22·43) = 5·43$, $P = 0·03$. The largest number of errors occurred in the odd or even task in each session. There was no change in accuracy rates across sessions (see Table 4 for number of errors).

Selective attention

For the Flanker Test of Selective Attention, the within subject factors consisted of the following: session (three levels), distance (flanking letters 1, 3, or 8 pixels from the target) and flanking letters (compatible, incompatible, or neutral to target). Separate analyses using response time and accuracy as dependent measures were performed.

Between group effects

There were no statistically significant differences in response times or accuracy between the CFS patients ($N = 18$) and the NCs ($N = 10$), $F(1, 26) = 0·05$, $P = 0·83$, and $F(1, 26) = 0·76$, $P = 0·39$, respectively (data not shown).

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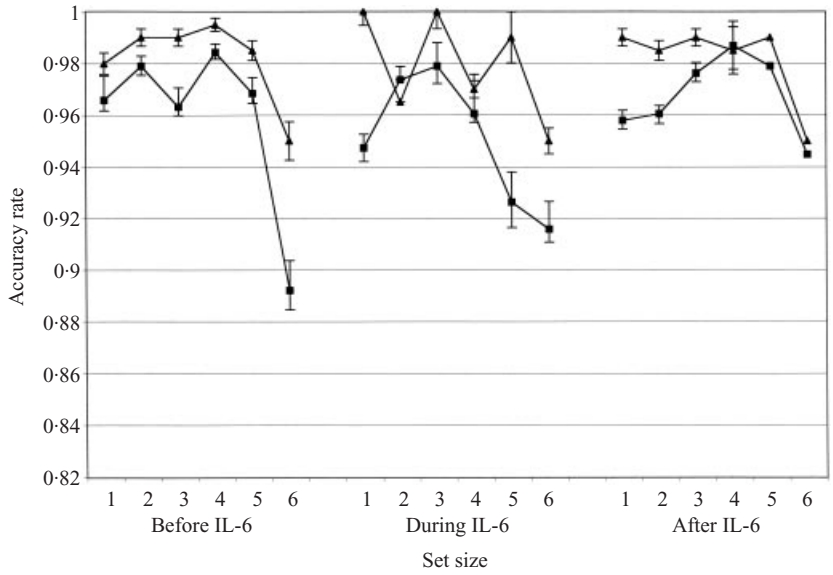


FIG. 2. Sternberg Memory Span: accuracy rate for each set before, shortly following, and 24 h after IL-6 (▲, Normal controls; ■, chronic fatigue syndrome).

Table 4. *Mean response time (RT) and number of errors on the Task Switching Task*

	Session 1	Session 2	Session 3
Odd Even			
CFS	954·98 (284·51); 3·25 (4·05)	807·21 (185·53); 3·13 (4·04)	725·42 (180·01); 2·85 (3·80)
NC	940·83 (240·66); 4·58 (7·29)	758·23 (189·21); 3·44 (6·92)	690·64 (178·70); 3·31 (6·89)
Over Under			
CFS	740·62 (171·77); 1·38 (1·07)	697·40 (188·59); 1·75 (1·53)	633·82 (148·16); 1·62 (1·16)
NC	731·99 (116·47); 0·88 (0·92)	651·75 (131·02); 0·69 (0·58)	611·38 (127·89); 1·00 (1·24)
Alternating			
CFS	1807·06 (518·79); 1·52 (1·38)	1479·29 (484·78); 1·74 (1·82)	1337·51 (291·76); 1·67 (1·61)
NC	1647·51 (359·54); 1·14 (1·97)	1379·87 (303·90); 1·09 (1·69)	1241·27 (262·49); 1·13 (1·70)
Random			
CFS	1569·36 (454·01); 1·58 (1·81)	1337·40 (362·55); 1·67 (1·65)	1230·27 (242·90); 1·55 (1·28)
NC	1513·78 (281·96); 1·32 (1·82)	1305·53 (278·45); 1·03 (1·92)	1209·34 (219·01); 1·13 (1·56)

CFS ($N = 15$); NC ($N = 8$).
Mean response time (in ms) followed by the mean number of errors are reported together in each cell. The standard deviation for each is in parentheses.

Within group IL-6 effects

As expected, there were statistically significant interactions between distance and flanking letters for both response time, $F(4, 104) = 8{\cdot}00$, $P < 0{\cdot}01$ and accuracy, $F(3{\cdot}02, 78{\cdot}42) = 4{\cdot}31$, $P = 0{\cdot}01$. Both CFS patients and NCs took longer to respond and made more errors in the condition that placed the highest demands on their selective attention (i.e. when the flanking letter was incompatible and close to the target).

For response time, there were significant effects for spacing ($F(1{\cdot}55, 40{\cdot}40) = 35{\cdot}09$, $P < 0{\cdot}01$), flanking stimuli, and session, Fs$(2, 52) = 63{\cdot}74$ and $12{\cdot}83$, respectively, Ps $< 0{\cdot}01$. Subjects responded faster when the distractors were further away from the target and when the distractors were compatible or neutral. As on other tasks, subjects performance improved (i.e. response times decreased) with practice over the three sessions.

For accuracy, there was an effect for flanking

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condition, $F(1{\cdot}27, 32{\cdot}97) = 6{\cdot}58$, $P < 0{\cdot}01$ and spacing, $F(2, 52) = 3{\cdot}73$, $P = 0{\cdot}03$. Subjects made fewer errors when the distractors were compatible or neutral as compared to when the distractors were incompatible to the target and when the flanking distractors were further away from the target.

DISCUSSION

The main purpose of this study was to determine whether a transient IL-6 induced exacerbation of symptoms unmasked greater cognitive impairments, somatic complaints and mood changes in CFS patients than in NCs.

IL-6 effects

The IL-6 increased both CFS patients and NCs body temperature and heart rate. This is consistent with previous human studies using recombinant human IL-6 (Tsigos *et al.* 1997) and animal studies, which find that the administration of IL-6 causes elevations in body temperature that are likely to be mediated by prostaglandins and corticotrophin releasing factor (Rothwell, 1994). Both groups also experienced a constellation of symptoms including fatigue, aches and malaise, symptoms characteristic of IL-6 induced inflammatory responses and of CFS itself.

IL-6 did not interfere with how either NCs or CFS patients performed on any of the cognitive tests. In fact, all subjects improved with practice over the three sessions. This is in contrast to previous research, which found that subjects who have experimentally induced influenza-like illnesses (Smith, 1988*a*) or are receiving pro-inflammatory immunotherapy experience mild cognitive disturbances (Denicoff *et al.* 1987; Smith *et al.* 1988*b*). Moreover, a recent study in healthy subjects (Reichenberg *et al.* 2001) found that a mild stimulation of the inflammatory response that had no effect on physical symptoms decreased normal subjects non-verbal and verbal memory performance. Future research should determine whether the presence and pattern of cognitive disturbances vary based on the specific cytokine (e.g. IFNα, IL-2, IL-6) or infection (e.g. influenza) to which the subject is exposed.

Cognitive functioning

For the most part, we failed to find significant differences in the cognitive functioning of CFS patients compared to NCs, matched for age and education. CFS patients were not impaired on tests of selective attention or executive control. Paradoxically, they had some difficulty on the short-term memory test when the processing load was the least. Reviews of numerous studies that examined the cognitive deficits in CFS suggest that, even when cognitive functions are intact, CFS patients process information slower than NCs as indicated by longer response times (Tiersky *et al.* 1997; Wearden & Appleby, 1996). They typically have deficits on more complex tasks that require divided attention and effortful processing over a lengthy period (Moss-Morris *et al.* 1996; Wearden & Appleby, 1996). The results in the present study indicate that CFS patients did not have longer response times than NCs, even on complex tasks that required divided attention, quickly switching attention, and inhibition of irrelevant distractors or tasks over time. In addition, the findings of the present study indicate that even when a physical stressor was induced, CFS patients did not exhibit impairments as compared to NCs.

One possible reason for the discrepancy between prior and the present study may be because previous studies (DeLuca *et al.* 1993, 1995; Marshall *et al.* 1997) that documented information processing deficits in CFS used the Paced Auditory Serial Addition Test (PASAT) (Brittain *et al.* 1991). The PASAT requires successive processing of auditory information whereas the task switching and the selective attention tasks we used require rapid visual processing. Though not evaluated in the current study, there is some evidence that suggests that the deficit in CFS patients information processing deficit is more pronounced in the auditory rather than the visual domain (Johnson *et al.* 1996).

Another explanation is the heterogeneity of CFS. Chronic fatigue syndrome may describe a collection of different disorders that have varying cognitive profiles, co-morbid diagnoses, endocrine abnormalities and immune dysfunction. In terms of cognitive functioning, some studies (e.g. Vercoulen *et al.* 1998) find that only a third of the patients studied demonstrate cognitive

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impairments, which are unrelated to depression, fatigue, or self-reported cognitive problems. It is also possible that the modest sample size in our sample reduced the statistical power to detect group differences, but given that the distribution of individual data points from several different cognitive measures were similar for individuals in both groups, we feel that our results are reliable.

Memory

The only statistically significant difference in performance that we found between the CFS patients and the NCs was on the Sternberg Memory Scanning Task. CFS patients had difficulty on the Sternberg Memory Scanning Task when they had to determine whether a probe digit was a member of a previously shown set of 1 or 2 digits but not when the to-be-remembered set size was increased to 5 or 6 digits. Both NCs and CFS patients had more difficulty, as expected, when the memory load was increased to 5 or 6 digits.

One explanation for the CFS patients difficulty on the Sternberg Memory Scanning Task is that they were distracted on easier items that did not demand all of their cognitive resources. Wolski & Maj (1998) found that patients with generalized anxiety disorders had slower response times on the Sternberg Memory Scanning Task, but that the effect diminished systematically with increasing task demands. Ellis (1990) found that depressed patients memory deficits were reduced or eliminated when they were forced to allocate more visual attention to a memory task. Both studies interpreted the observed memory deficit using a resource allocation explanation. When the task was not demanding, emotions or irrelevant thoughts occupied the depressed individual's cognitive capacity; however, under more demanding conditions a larger portion of the individual's resources were allocated to the memory task. On the other hand, CFS patients were not more impaired on the less demanding conditions of the Task Switching Task (e.g. performing just one task in a block) or on the conditions in the attention task that required less inhibition (when the distractors were far away and compatible with the target). There was also no correlation between performance (e.g. response time and accuracy rates) on the measure of memory and subjective self-reported mood ratings. Furthermore, CFS patients reported only mild levels of depression and no anxiety.

Somatic symptoms

Before the IL-6 induced illness, CFS patients reported a significantly higher level of somatic symptoms (i.e. fatigue, pain and malaise) as compared to the NCs. Following IL-6 injection, CFS patients immediately experienced an increase in somatic symptoms (e.g. aches and fatigue) whereas NCs did not experience any symptoms until 6 h after IL-6 administration. The CFS patients consistently felt their worst 4 h after IL-6 while NCs felt their worse 6 h after IL-6. The time course of the NCs symptoms following IL-6 is consistent with our observations from a separate study that focused on the effects of IL-6 on healthy normal volunteers (Papanicolaou *et al*. 1996). The time course of the CFS patients self-reported symptoms suggests that they may have an increased sensitivity to the IL-6 challenge. Objective measures also demonstrated that the CFS patients immune system was more sensitive to cytokine-induced provocation. The patients body temperatures were statistically higher than that of the NCs starting 1·5 h after IL-6 injection and continuing for 3 h after IL-6. We do not know why CFS patients experienced the effects of the physiological challenge before NCs. Interleukin-6 is characterized by marked pleitropy and the production, action, and regulation of the febrile response is complex and poorly understood (Mackowiak & Boulant, 1997). Patarca-Montero *et al*. (2001) suggested that HPA abnormalities might be secondary to the distress response of CFS patients in response to physical symptoms. Perhaps, the anticipation of physical symptoms that resemble the patients illness combined with cytokine provocation of the HPA resulted in the patients immediate onset of somatic symptoms. More comprehensive evaluations of immune and endocrine functioning are needed to evaluate the role of psychological stress on CFS symptoms. The early onset of symptoms following cytokine activation in the present study adds to the body of literature suggesting that stress modulation and beliefs may be important factors in the maintenance of

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CFS symptoms (Natelson, 2001) and possibly CFS aetiology (Scott & Dinan, 1999).

Twenty-four hours after the IL-6 induced illness, CFS patients reported fewer symptoms than they did at baseline; however, feelings of fatigue and malaise remained. These symptoms, which are central to CFS, also persist in individuals with acute infectious diseases even after other symptoms have improved (Bennett *et al*. 1998). This finding along with evidence that improvement in fatigue may be linked to improvement in cell-mediated immunity in individuals with acute infectious diseases (Lloyd *et al*. 1992; Bennett *et al*. 1998) provides some support for the hypothesis that CFS is associated with a dysregulation of the inflammatory cascade.

Mood symptoms

In contrast to predictions, there were no group differences in mood state ratings. Although CFS patients did not report emotional distress, they did report a severe level of fatigue. This is consistent with recent research demonstrating that depression, anxiety, psychological distress and fatigue are likely determined by separate genetic factors (Hickie & Lloyd, 1998). Furthermore, we had excluded the CFS patients with sufficient depression, anxiety and other psychiatric disorders that warranted medication management.

Conclusions

The present study has demonstrated that inducing an acute phase physiological illness in CFS patients that mimics how they feel in their worst period does not result in statistically significant concomitant declines in objectively evaluated cognitive abilities and mood state. It does influence patients somatic symptoms to a greater degree than in NCs, which may be providing important insights into the role of a hyperresponsive HPA in CFS.

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APPENDIX

Order of presentation of blocks in Task Switching Test

1 Odd Even (80 trials)
2 Odd Even (80 trials)
3 Over Under (80 trials)
4 Over Under (80 trials)
5 Odd Even (80 trials)
6 Over Under (80 trials)
7 Odd Even (80 trials)
8 Over Under (80 trials)
9 Alternating (40/40 trials)
10 Alternating (40/40 trials)
11 Random (40/40 trials)
12 Random (40/40 trials)
13 Alternating (40/40 trials)
14 Alternating (40/40 trials)
15 Random (40/40 trials)
16 Random (40/40 trials)

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