Memory Deficits Associated with Chronic Fatigue Immune Dysfunction Syndrome

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Performance on tests of memory in 39 patients who met Center for Disease Control (CDC) criteria for chronic fatigue immune dysfunction syndrome (CFIDS) was compared with 23 depressed patients (DSM-III-R) and 129 healthy controls. Although the CFIDS patients had normal neuropsychological profiles, they significantly overestimated their ability (metamemory), performed significantly worse on tests of recall as context increased (e.g., recognition), made more errors when rehearsal was prevented, and had delayed mental scanning as memory load increased. The overall pattern indicated that CFIDS patients had a significant memory deficit, far worse than implied by CDC criteria. The pattern for CFIDS patients was consistent with temporal-limbic dysfunction and significantly different than depressed patients and control subjects.

Key Words: Chronic fatigue syndrome, Epstein Barr Virus, memory, virus, temporal-limbic dysfunction

Introduction

The cause of Chronic Fatigue Immune Dysfunction Syndrome (CFIDS) is unknown but has been related to unusual profiles of antibodies to Epstein-Barr virus (EBV) (Tobi, et al 1982; Straus et al 1985), in vitro interleukin 2 (IL 2; Gold et al 1990), and human T-lymphotropic virus-II (HTLV-II) retrovirus (DeFreitas and Hilliard 1990). Several recent studies (Kruesi et al 1989; Gold et al 1990; Manu et al 1988; Lane et al 1991) concluded that psychiatric illness may contribute to the pathogenesis of CFIDS. Symptoms of depression and dysthymia were reported to coexist with CFIDS in one study (Kruesi et al 1989) and lifetime episodes of depression and/or current major depression were reported by Gold et al 1990). In ongoing studies involving a review of 100 (Manu et al 1988) and 200 (Lane et al 1991) patients, depression was reported to coexist often with CFIDS, but did not fully explain the symptoms.

Generalized neuropsychological complaints, including depression, are among the symptom criteria proposed as a working case definition of CFIDS by the Center for Disease control (CDC; Holmes et al 1988). However, three uncontrolled studies of CFIDS patients have yielded contrasting results. One report (Altay et al 1990) concluded that a sample of 21 CFIDS patients (Postinfectious neuromyasthenia) performed significantly better than normative values provided by test publishers. In an informal report (Bastien 1989), an apparently large sample of CFIDS patients were below the mean of test norms on nearly every test given in a 4-hr neuropsychological battery, including intelligence and general memory functioning. The third study (Ross et al 1987) reported subtle deficits related to attention, alertness, and flexibility of thought in a sample of 18 CFIDS patients.

The present study was designed to examine putative
cognitive deficits in CFIDS patients by addressing several critical issues raised in earlier studies. First, identification of CFIDS memory deficits was determined by contrast with a parallel group of healthy volunteers. Second, cognitive profiles of CFIDS and depressed patients were compared. Because depression has been proposed as etiologically significant for CFIDS, they may share cognitive features.

**Methods**

**Subjects**

**CFIDS Patients.** Thirty-nine patients had the diagnosis of CFIDS established by ruling out other disorders that might mimic CFIDS in some respects (e.g., cardiovascular, ear, nose, and throat (ENT), pulmonary, etc, see Goldstein 1992) and fulfilling the CDC case definition published by Holmes et al (1988). Duration of illness varied from 6 months to 8+ years. The patients had a physical examination that generally was normal except for the detection of tender points characteristic of fibromyalgia in 70%, and an occasional positive Romberg test. CFIDS patients rated subjective symptoms of cognitive dysfunction as significant on a 10-point symptom checklist. The features of these symptoms included attention deficit, dyscalculia, memory disturbance, spatial disorientation, and dysnomia. Immunological tests for EBV, alpha interferon, IL-2, CD4, and CD8 cells, and Raji cell assays did not reveal any detectable patterns and were not in the abnormal range for more than 21% of the patients. Multivariate modeling of immune markers did not identify a profile characteristic of this group. None of the patients reported pre-CFIDS history of, or treatment for, mental illness or depression. The patients were on a wide variety of medications (including vitamins, minerals, nootropics, pain medications, etc.) but none were taking major tranquillizers and fewer than five patients were taking antidepressants. The range of medications made it impossible to formally determine drug effects.

**Depressed Patients.** An independent sample of 23, age-matched, depressed patients were obtained from a University psychiatric inpatient service. All patients were diagnosed by Research Diagnostic Criteria and DSM-III-R with the Schedule of Affective Disorders (SAD) interview conducted by a psychiatrist. Criteria were satisfied for a Major Depressive Episode. All patients entered the hospital medication-free and were observed to be medication-free for at least 2 days before testing.

**Normal Volunteers.** Asymptomatic subjects \( (n = 129) \) were recruited from the University of California, Irvine and from the staff of Fairview Developmental Center. Subjects were selected for inclusion in the analysis to match the age range of the patient groups. None of the normal subjects had a positive history of mental illness, history of drug use, or any enduring physical complaint.

**Procedures**

A battery of neuropsychological tests were administered only to the CFIDS patients, including the Mini-Mental State Examination (MMSE; Folstein, et al 1975), WAIS-R (Wechsler 1981), Wechsler Memory Scale-Revised (WMS-R; Wechsler 1987), Wisconsin Card Sort Test (WCST; Berg 1948), Trail-Making Test (TMT; Reitan 1955), Boston Naming Test (BNT; Kaplan et al 1978), and the Visual-Function scale (C4) of the Luria Nebraska Neuropsychological Battery (LNNB; Golden et al 1980).

The memory tests (Irvine Memory Battery) were administered with an interactive computer system (Neuromed, Newport Beach, CA). Instructions, stimuli, and test modules were presented in standardized form on a computer monitor. The scoring was automated and error-free. All testing was conducted in comfortable, sound-attenuated offices.

**Recall.** The Recall subtests consisted of a metacognitive estimate, free recall, paired associates, recognition, and letter-priming subtests. The metacognitive score was the estimation of the number of words out of 10 patients expected to remember on the free-recall test. For free recall, 10 words were presented one at a time (1-sec duration) and the patients were asked to recall as many as they could. For paired-associates, 10 word pairs were presented and recall was cued by the stem word of a previously presented word pair. The recognition test also presented 10 word pairs but recall was a forced choice from four alternatives presented on the screen. Ten word pairs were also presented for letter-priming, but recall was cued by the stem word and the first letters of the word to be remembered. These tests assessed encoding, memory consolidation and retrieval. Increasing structure or context (paired associates, recognition, and priming) increased the probability of recalling the information (Craik 1984). A retrieval slope was calculated as the number of words recalled from the free recall, paired-associates, and recognition tests (Willhardt and Sandman 1988). A steep slope reflected a retrieval deficit and flat slope (and imperfect free recall) was evidence of a stimulus registration or memory consolidation deficit. The relationship between expected and actual free recall performance was calculated as the ratio: estimate/free recall.

**Proactive Inhibition.** The test of proactive inhibition (PI: Peterson and Peterson 1959) was modified for the computer and required the patient to briefly retain three items in memory. Three items (numbers, letter, or words) were presented simultaneously on the computer screen for 1200 msec followed immediately by a video game for 10 sec. The primary purpose of the game was to distract the patient and discourage active rehearsal of the three items. In addition, distraction through manipulation of the semantic similarity of the memory set was achieved. Triads of the three items were very similar (i.e., sets of numbers.
letters, or related words). The fourth trial of three items was different than the triad (release from proactive inhibition). Thus, if the first triad of three items was numbers, the fourth trial was letters. Prevention of rehearsal often results in confusion between previously learned information and recent information. Furthermore, if the recent information was similar to previous information, the probability of distortion was greater (PI error). Presentation of semantically dissimilar recent information released the patient from PI and memory of the new information was enhanced. This test allowed assessment of interference on memory and specifically: (1) the decay in memory when rehearsal was discouraged and (2) the organization of memory when similar information is presented.

**ITEM RECOGNITION.** This test was adapted from Sternberg (1969) to assess the effects on memory of mental load. Mental load was controlled by asking the patient to remember on each trial either 1, 2, or 4 items (memory set) presented on the computer screen for 800–1200 msec. After a 1200-msec delay, a number target, surrounded by letters, appeared on the computer screen. The patient pressed a hand-held key matched with the dominant hand if the target was in the memory set and a second key matched with the nondominant hand if it was not. Half the targets were in the memory set and half were not. As the number of items in the memory set increased, the time required to decide if the target was in the memory set and to press the key (reaction time, RT) increased. The slope of this function was the memory scanning time and reflected the efficiency of visual memory. The intercept of this function reflected the time required to encode the probe (attention) and to initiate a motor response. Efficient performance required that the patient disregard the irrelevant information (letters) and respond only to the number target.

**SEMANTIC MEMORY TEST.** This test (SMT) examined access to information accumulated over the course of a lifetime. Common categories (e.g., Fabrics) were presented one at a time for 1200 msec, followed by words that were (e.g., wool) or were not (e.g., desk) exemplars. Patients depressed one hand-held button (Reaction Time [RT]) as fast as possible if the exemplar was related to the category and a second key if it was not. Each semantic category was presented two times with different exemplars. For instance, “Fabric” was presented two times but was followed with different exemplars (e.g., wool and on a subsequent trial, silk). A second successive (primed) retrieval from the same semantic category was accomplished faster (i.e., faster RT) than the first retrieval. Strength of the priming effect was controlled by imposing a lag of 0, 1, or 2 items between the first and second category-exemplar pairs. Lags of 0 produced the strongest priming effect and generated the fastest RT. Lags of two items resulted in the slowest RT.

| Table 1. Screening and Demographic Variables in CFID Patients |
|--------------------------------------------------------------|
| Parameter | CFIDS |
|-----------|-------|
| Age       | 41    |
| Mini mental status | 28 ± 1.9 |
| Wisconsin card sort Correct | 66 ± 7 |
| Errors    | 18 ± 13 |
| Categories| 6 ± 0.7 |
| Trails A (SEC) | 34 ± 12 |
| Trails B (SEC) | 76 ± 35 |
| Boston naming | 55 ± 3 |
| Luria     |       |
| Critical level | 49 ± 18° |
| Gender    |       |
| Women     | 31    |
| Men       | 8     |
| Education | 15    |

*p < 0.05.

**Results**

The results of demographic data and screening for neuropsychological tests are presented in Table 1. Scores for the CFIDS patients compared favorably with the published norms for all of the tests. Full scale IQ (102) was lower than expected from the achieved level of education (3 years of college) among CFIDS patients.

Comparisons of CFIDS, depressed, and control subjects on the tests of recall are presented in Figure 1. There were no significant differences among the groups on the metacognitive estimate or free recall. However, on tests of increasing context, paired associates, and recognition, the CFIDS patients made significantly more errors (p < 0.01), than both controls and depressed patients. CFIDS patients had a significantly flatter retrieval slope than controls, reflecting a relative inability to benefit from cuing and context. Compared with the underestimation of performance of depressed patients, CFIDS patients significantly (p < 0.01) overestimated the efficiency of their memory. There were no differences between controls and depressed patients.

The CFIDS patients were dramatically impaired on the proactive inhibition test (Figure 2). Compared to controls and depressed patients, the CFIDS group made significantly (p < 0.001) more errors in memory when rehearsal was prevented. No differences were detected in the number of errors for semantically similar material (PI errors).

Mental scanning (memory) was significantly delayed in the CFIDS patients compared to the depressed patients (p < 0.001) in the NO condition and to the controls in both the YES and NO conditions (p < 0.05). There were no differences between CFIDS patients and controls in the intercept. The depressed patients were significantly slower than CFIDS (p < 0.01) and controls (p < 0.01) in the NO intercept (Figure 3). There were no differences for any measures in semantic memory.
**RECALL**

![Figure 1](image1.png)

Figure 1. Top panel presents number correct for metamemory estimate (META), free recall (FR), paired associates (PA), and recognition (REC). Bottom panel is recall slope illustrating rate of improvement with increasing context and ration of META and FR. (! = difference between controls and CFIDS; * = difference between CFIDS and depressed).

**ITEM RECOGNITION**

![Figure 2](image2.png)

Figure 2. Number of errors caused by distraction and proactive errors related to semantic similarity in test of interference.

**MULTIVARIATE MODELING.** Multivariate equations were constructed with Stepwise Discriminant Function Analysis (SDFA: Jennrich and Sampson 1990) that combined the variables to maximize the separation of the patient groups (i.e., classification function). Variables were selected in stepwise order to compute the linear classification function (Table 2). At each step, a new variable was selected that contributed most to the separation of the groups. The final combination was weighted, and the equation classified patients based on similarity of memory profile. A "jackknifed" classification requests Mahalanobis' $D^2$ for each patient without using that patient's data in the calculation of the mean or the pooled within-group covariance matrix. Three comparisons were tested, all three groups, depressed versus CFIDS, and normal controls versus CFIDS. Comparison of three groups yielded equations that significantly ($p < 0.0001$) distinguished the groups (Table 1, first column). A total of 68% (33% is chance) of the subjects were classified accurately based solely on

**INTERFERENCE**

![Figure 3](image3.png)

Figure 3. Top panel is the slope (mental scanning speed) for the yes (match) and no (mismatch) trials. Bottom panel is the intercept (input/output speed) for yes and no trials.

Table 2. Stepwise Discriminant Function Analysis of Learning and Memory Tests in Predicting Group Membership

| Variable                        | 3-Way | CFID versus depressed | CFID versus normal |
|---------------------------------|-------|-----------------------|--------------------|
| Interference errors             | 1     | 1                     | 1                  |
| Proactive inhibiton error       | 2     | 2                     | 2                  |
| IRT no slope                    | 3     | 3                     | 3                  |
| Paired associates               | 4     | 3                     | 4                  |
| IRT no intercept                | 5     | 2                     | 2                  |
| Metacognition                   |       | 4                     | 4                  |
| Semantic memory priming         |       | 5                     | 5                  |
| IRT yes intercept               |       | 5                     | 5                  |
| Jackknifed classification       | 68%   | 82%                   | 90%                |
| Chance                          | 33%   | 50%                   | 50%                |
| Probability                     | $p < 0.0001$ | $p < 0.0001$ | $p < 0.00001$     |

The values indicate the order that variables entered the equation for optimal separation of the groups. Significance levels for each combination of variables are listed at the bottom of the table.
memory performance. Only two depressed patients were misclassified as CFIDS patients (91% specificity). The tests responsible for detecting deficits in the CFIDS group in order of significance were interference errors, PI errors, and mental scanning efficiency.

Two-way contrasts of depressed and CFIDS patients (Table 2, second column) yielded 82% classification (50% is chance), which was highly significant (p < 0.0001). Interference errors in CFIDS patients, delayed input/output response speed in depressed patients, poor paired associate learning in CFIDS patients, and characteristic estimation of performance distinguished the groups.

Two-way comparison of control subjects and CFIDS patients (Table 2, third column) yielded 90% classification (50% is chance). The CFIDS profile was distinctive (p < 0.00001) and only 4% of the normal patients were misidentified as CFIDS patients (96% specificity). The same variables (interference, PI errors, input/output response speed, and paired associates) contributed to the separation.

Discussion

CFIDS patients with normal neuropsychological profiles exhibited a characteristic memory deficit. Unlike the healthy controls or depressed patients, the CFIDS patients failed to benefit from priming or increasing context in tests of recall, suggesting a memory consolidation or stimulus registration deficit (Willhardt and Sandman 1988). Additional, helpful cues apparently distracted CFIDS patients, and either limited stimulus registration or interfered with consolidation.

In addition, CFIDS patients lost the ability to retain three-item lists when a simple, irrelevant 10-sec task was interposed between the items and recall. The performance of the CFIDS patients was seven-fold worse than either the control or depressed group and 90% of the CFIDS patients made more errors than the mean value of healthy controls and depressed patients. CFIDS patients also exhibited significant delay in memory scanning with increasing memory load. Although the CFIDS patients were slightly slower than controls on input/output (intercept) measures, the effects were not significant.

Thus, CFIDS patients had highly significant deficits in memory consolidation, were vulnerable to interference, and slow or uncertain in decision making. Apparently, CFIDS patients made weak memory traces that were very easily perturbed. Significant slowing of mental but not motor scanning as information increased, established that the CFIDS patients were inefficient and uncertain. These results indicated the memory deficit in CFIDS was more severe than assumed by CDC criteria (Holmes et al 1988), more specific than observed in two previous reports (Altay et al 1990; Bastien 1989), but generally consistent with the report of Ross et al (1987).

The pattern of weak consolidation and vulnerability to interference has been reported in patients with diseases affecting the medial temporal cortex, hippocampus, and structures of the limbic system (Lezak 1978) including Huntington’s Disease (Butters et al 1978; Meudell et al 1978) and herpes simplex encephalitis (HSE; Hierons et al 1978). The similarity with HSE is interesting because human herpesvirus 6 (HHV 6) has been associated with CFIDS (Komaroff 1990). Furthermore, the recent reports of temporal-lobe hypoperfusion as measured with single photon emission computed tomography (SPECT) scans in CFIDS patients (Mena 1990) is consistent with the pattern of memory deficits in these patients.

The second significant result of this study was that depressed and CFIDS patients had distinctly different cognitive/memory profiles. For the most part, the depressed patients did not have a primary loss of memory (Weingartner et al 1981; Weingartner 1984), but a significant loss in confidence about, or underestimation of, their memory (Kahn et al 1975; Wells 1979) and slowing in the input/output function of an RT task (Weingartner 1984). As described above, this pattern is different than the CFIDS patients who had clear and consistent deficits in memory consolidation, perhaps related to incomplete stimulus registration or capacity limitations. It is an apparent (and interesting) paradox that a chief complaint of CFIDS patients is confusion and deteriorating memory, but when asked to estimate performance on a specific problem, they characteristically expect to perform far better than their current ability. Because the dimensions of cognitive deficit in CFIDS and depressed patients were different, it is reasonable to speculate that they are not related.

Although these data should be considered preliminary, a pattern emerged of brain-behavior relationships supporting neurological compromise in CFIDS. The CFIDS deficit was characterized by poor memory consolidation and vulnerability to interference. These results are consonant with lesions of the temporal lobe, hippocampus, and limbic system. The recent findings with SPECT scans (Mena 1990) indicating temporal lobe hypoperfusion in CFIDS patients and similarities with herpes simplex (HSF), are compatible with this interpretation. Although the cause of CFIDS is not known the findings may be consistent with exposure to neurotoxic viral agents (Goethe et al 1989) or environmental toxins (Kilburn et al 1989). However, confusing inconsistencies between systemic disease and neurological manifestations, observed in human immunodeficiency virus-1 (HIV-1) (Brew et al 1988) also characterize CFIDS. Certainly, the relationship has been difficult to establish among the primary symptoms of CFIDS, immunological markers, and neurological manifestations, implying more than a single cause.

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