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Neuropsychological Performance in Persons With Chronic Fatigue Syndrome: Results From a Population-Based Study

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Objective: To examine the neuropsychological function characterized in subjects with chronic fatigue syndrome (CFS) at the same time controlling for relevant confounding factors. CFS is associated with symptoms of neuropsychological dysfunction. Objective measures of neuropsychological performance have yielded inconsistent results possibly due to sample selection bias, diagnostic heterogeneity, comorbid psychiatric disorders, and medication usage. **Method:** CFS subjects ($n = 58$) and well controls ($n = 104$) from a population-based sample were evaluated, using standardized symptom severity criteria. Subjects who had major psychiatric disorders or took medications known to influence cognition were excluded. Neuropsychological function was measured using the Cambridge Neuropsychological Test Automated Battery (CANTAB). **Results:** Compared with controls, CFS subjects exhibited significant decreases in motor speed as measured in the simple and five-choice movement segments of the CANTAB reaction time task. CFS subjects also exhibited alterations in working memory as manifested by a less efficient search strategy on the spatial working memory task, fewer % correct responses on the spatial recognition task, and prolonged latency to a correct response on the pattern recognition task. A significantly higher percentage of CFS subjects versus controls exhibited evidence of neuropsychological impairment (defined by performance 1 standard deviation below the CANTAB normative mean) in tasks of motor speed and spatial working memory. Impairment in CFS subjects versus control subjects ranged from 20% versus 4.8% in five-choice movement time ($p = .002$) to 27.8% versus 10.6% in search strategy on the spatial working memory task ($p = .006$). **Conclusions:** These results confirm and quantify alterations in motor speed and working memory in CFS subjects independent of comorbid psychiatric disease and medication usage. **Key words:** chronic fatigue syndrome, neuropsychological impairment, psychomotor speed, working memory, depression, fatigue.

CFS = chronic fatigue syndrome; **MFI** = Multidimensional Fatigue Inventory; **SCID** = Structured Clinical Interview for DSM-IV; **SDS** = Zung Self-Rating Depression Scale; **WRAT-3** = Wide Range Achievement Test 3; **CANTAB** = Cambridge Neuropsychological Test Automated Battery; **RTI** = reaction time; **RVIP** = rapid visual information processing; **SWM** = spatial working memory; **PRM** = pattern recognition memory; **SRM** = spatial recognition memory; **EDS** = extra-dimensional shift; **ANCOVA** = analysis of covariance; **MANCOVA** = multivariate analysis of covariance.

INTRODUCTION

Chronic fatigue syndrome (CFS) is a debilitating and complex disorder characterized by profound fatigue that is not improved by rest and is worsened by physical or mental activity. In addition to fatigue, up to 85% of patients with CFS report neuropsychological symptoms, such as slowed thinking, reduced attention, and impaired memory (1–3). Primary neuropsychological alterations as defined by neuropsychological testing in CFS subjects seem to involve alterations in psychomotor speed and information processing as well as impairments in working memory (4–14). However, objective measures of neuropsychological performance have not consistently yielded evidence of neuropsychological dysfunction in CFS patients, with some (4–14) but not all (15–18) studies showing evidence of neuropsychological changes.

Conflicting reports may reflect sample selection bias, diagnostic heterogeneity, comorbid psychiatric disorders, medication usage, and variability among the types of neuropsychological testing batteries. For example, most studies of neuropsychological function in CFS have included patients identified from tertiary care or referral clinics, which may represent more severely ill and self-selected patients who do not represent the population of people with CFS (13,19). Moreover, although many studies have used the 1994 International Case Definition to diagnose CFS (20), consensus international recommendations regarding the use of criteria to establish the severity of CFS symptoms as well as the degree of functional impairment, as determined by validated and standardized instruments, have yet to be routinely applied (21). Another methodological issue is the inclusion of subjects with comorbid psychiatric disorders including major depression. Major depression is well known to affect cognitive performance and therefore represents a potential confound in the interpretation of neuropsychological function in CFS. CFS subjects also use a large number of prescription and over-the-counter medications that might affect cognition (22); however, most studies have not controlled for or, in some cases, have not reported medication usage in the study sample (2,3,8,12,15,18).

In a previous study, using an automated battery of computerized tests (Cambridge Neuropsychological Test Automated Battery known as CANTAB), we found significant impairment in the tasks of spatial working memory and sustained attention (rapid visual information processing (RVIP)) in those persons with CFS who also endorsed significant mental fatigue (23). The current study aimed to expand on these results and further characterize the neuropsychological domains altered in CFS at the same time controlling for factors that may have influenced results from previous reports. To accomplish this objective, we: 1) enrolled people with CFS

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and well controls identified from a population-based sample of metropolitan, urban, and rural Georgia (USA); 2) used standardized, empirical criteria to define CFS severity (24); 3) used validated psychiatric assessment instruments to exclude comorbid psychiatric conditions; and 4) excluded subjects who used psychotropic medications known to affect cognitive functioning.

The current study also investigated the relative contribution of symptoms of depression and various dimensions of fatigue to neuropsychological performance in the study sample.

METHODS

Subjects

Participants in this study represent a subset of persons enrolled in a 2004 to 2005 Survey of Chronic Fatigue Syndrome and Chronic Unwellness in Georgia (25). The survey was designed to estimate the prevalence of CFS in metropolitan, urban, and rural populations. The survey initially used random-digit-dialing to contact 10,837 households and obtain information concerning the health status of 21,165 adult residents. After an initial household contact, the survey attempted to complete detailed phone interviews with all residents identified as unwell (2438 or 71% agreed and completed their interviews) and an equivalent number of residents were identified as well. Based on their replies to the detailed interview, 469 respondents met the criteria of the 1994 CFS case definition (20), were considered to have a CFS-like illness, and were invited to participate in a one-day clinical evaluation (292 or 62% completed the evaluation). A similar number of persons classified as unwell not CFS-like and a similar number of persons classified as well after the detailed telephone interview were also invited for clinical evaluation. One objective of the clinical evaluation was to identify medical or psychiatric conditions considered exclusionary for CFS (20,21), catalogue all medications the participants were taking, and rigorously classify participants as CFS. In all, 113 persons met all criteria for CFS and 124 were considered well. Fifty-five (49%) of those with CFS and 20 (16%) of the well were using medications known to affect neuropsychological function (i.e., α-adrenergic agents, antidepressants, amphetamines, anticonvulsants, benzodiazepines, muscle relaxants, narcotics, sedative hypnotics, and parenteral glucocorticoids) and were excluded from the present analysis, leaving 58 persons with CFS and 104 well controls.

CFS Diagnostic Criteria

Subjects were classified as CFS if they had no exclusionary medical or psychiatric conditions (as determined by medical history, physical examination, laboratory testing, and the Structured Clinical Interview for the Diagnostic and Statistical Manual-IV) and met three standardized severity criteria for measuring specific dimensions of the 1994 CFS case definition (25): 1) severe fatigue as defined by scores $\geq$ the population median on the Multidimensional Fatigue Inventory (MFI) (26) subscales of general fatigue ($\geq$13) or reduced activity ($\geq$10); 2) substantial functional impairment as determined by scores $\leq$25th percentile of published norms on the physical function ($\leq$70), or role physical ($\leq$50), or social function ($\leq$75), or role emotional ($\leq$66.7) subscales of the Short-Form Health Survey (27); and 3) presence of substantial accompanying symptoms as defined by $\geq$4 accompanying symptoms and scoring $\geq$25 on the CDC Symptom Inventory Case Definition Subscale. Subjects who met none of these three criteria and were determined to be without medical or psychiatric exclusions were classified as well controls.

The study adhered to human experimentation guidelines of the Helsinki Declaration and was approved by the Centers for Disease Control Institutional Review Board. All subjects provided their written informed consent before study participation.

Assessment of Fatigue and Depressive Symptoms

Fatigue was assessed using the MFI, which is a self-report scale comprised of five subscales including reduced motivation, reduced activity, general fatigue, physical fatigue, and mental fatigue. Severity of depressive symptoms was assessed using the Zung Self-Rating Depression Scale (SDS) (28), which includes 20 questions that probe different symptoms of depression.

Neuropsychological Testing

General intellectual ability was estimated using the reading subtest of the Wide Range Achievement Test 3 (WRAT-3) (29). Neuropsychological functioning was assessed using CANTAB (30). Seven CANTAB tests were used to measure specific neuropsychological domains. Execution of the tests (including the instructions) took ~60 minutes. The test order was counterbalanced across subjects.

Psychomotor Speed

The reaction time (RTI) test independently evaluates psychomotor speed. The test includes simple and five-choice reaction time tasks and provides distinction between reaction (or decision) time and movement latencies (i.e., motor speed). Reaction (or decision) time is the time it takes the subject to release the press pad (space bar) in response to the detection of a stimulus. Movement time is the time taken to touch the stimulus on the computer screen after the pad had been released.

Attention

The RVIP test measures sustained attention. Digits (range = 2–9) appear one at a time (100 digits/min), in random order, in the center of the computer screen. Subjects must press a pad when they detect any one of three sequences (2-4-6, 4-6-8, 3-5-7). Performance accuracy was estimated from the target sensitivity score A′ (range = 0.00–1.00; bad to good); performance speed was assessed by the mean latency for correct responses.

Working Memory

Three tests of working memory were employed:

1) The Spatial Working Memory (SWM) test is a self-ordered searching task sensitive to fronto-subcortical dysfunction (31). The SWM requires that subjects find blue tokens in a series of boxes and use the tokens to fill up an empty column, at the same time not returning to boxes where a blue token had been previously found. The number of boxes increased from 3 to 8. The number of between-search errors (errors made when the subject revisits a box in which a token has previously been found) and a strategy score derived from the number of search sequences in the 4, 6, and 8 boxes were used as performance indices. The strategy score retraced the "route" previously used by subjects in searching through the spatial array of boxes (32,33); the lower the strategy score, the more efficient the subject. This test has previously been reported to be impaired in CFS patients (23).
2) The Pattern Recognition Memory (PRM) test assesses visual recognition memory in a two-choice forced discrimination paradigm and is sensitive to dysfunction in the temporal lobe and hippocampus. Percent correct responses and response latency for correct responses were used as performance indices.
3) The Spatial Recognition Memory (SRM) test is a two-choice forced discrimination paradigm. As for PRM, percent correct responses and response latency for correct responses were used as performance indices.

Executive Function

Two tests were utilized to evaluate executive function:

1) The Stockings of Cambridge task was used to evaluate spatial planning/problem solving. The task makes substantial demands on executive function and is sensitive to frontal-lobe damage (34). The test is based on the "Tower of London" task and contains incremental levels of difficulty. For each problem, the computer screen showed two displays of colored balls, and the subject must move the balls in the lower display in a minimum number of moves until they match the target configuration. Analysis of the test controlled for motor speed. Subjects' executive abilities were estimated from the time taken to

TABLE 1. Sample Demographics and Clinical Characteristics

	Controls (n = 104)	CFS (n = 58)	p
Age (range)	43.8 (19–59)	41.4 (18–59)	.18
Sex	27 male, 77 female	15 male, 43 female	.98
Race	79 white, 24 black, 1 other	41 white, 14 black, 3 other	.24
WRAT-3 (SE)	101.4 ± 1.0	100.6 ± 1.5	.65
SDS index score (SE)	36.2 ± 0.6	57.0 ± 1.3	<.001
MFI (SE)			
Total MFI score	30.9 ± 0.7	66.7 ± 1.7	<.001
General fatigue	6.8 ± 0.2	16.6 ± 0.3	<.001
Physical fatigue	6.1 ± 0.2	13.4 ± 0.4	<.001
Reduced activity	5.7 ± 0.1	11.4 ± 0.5	<.001
Reduced motivation	5.7 ± 0.1	11.7 ± 0.4	<.001
Mental fatigue	6.4 ± 0.2	13.5 ± 0.5	<.001

CFS = chronic fatigue syndrome; WRAT-3 = Wide Range Achievement Test 3; SDS = Zung Self-Rating Depression Scale; MFI = Multidimensional Fatigue Inventory; SE = standard error of the mean.
The χ^2 tests were used to compare CFS versus controls in sex and race; two-tailed t tests were used to compare CFS versus controls in age, WRAT-3 scores, SDS index scores, and MFI scores.

plan each solution (initial thinking time), the subsequent thinking time, the number of problems solved in the minimum number of moves (# perfect solutions), and the average number of moves made for each solution (# moves).

2) The Intra/Extra Dimensional Set Shift (IED) task evaluates rule acquisition and reversal and assesses the subject's visual discrimination and attentional set shifting. In this test, the subject is required to maintain attention to a reinforced stimulus (intra-dimensional shift, IDS) and then must shift attention to the previously irrelevant stimulus (extra-dimensional shift, EDS). This test is sensitive to neuropsychological dysfunction in Parkinson disease, basal ganglia lesions, and frontal-lobe deficits (35,36). Subjects progress through the test by satisfying a set of criteria of learning at each stage (nine stages in total). The number of completed stages, the total number of errors (adjusted to the number of completed stages), the number of errors made up until the EDS (Pre-ED errors), and the number of errors made at the EDS (EDS errors) served as performance indices.

Statistical Analysis

The χ^2 tests were used to compare distributions of sex and race in CFS and control subjects and to compare percentages of subjects with neuropsychological impairment between groups. The t tests were used to compare age, general intelligence (reading level), scores of depression and fatigue, and functioning on specific CANTAB subtests in CFS versus control subjects after determination of impairment in the relevant cognitive domains. The extent to which depression (SDS index) and fatigue (MFI) scores were correlated with neuropsychological functioning was established using correlation analyses with age as a covariate.

To evaluate differences in overall neuropsychological performance and to limit the likelihood of Type 1 error, the seven CANTAB tests were initially grouped into four cognitive domains (psychomotor speed, sustained attention, working memory, and executive function). Performance differences on these domains were analyzed using one-way omnibus multivariate analysis of covariance (MANCOVA), controlling for age and depression (SDS index score). In instances where the omnibus F test was significant, univariate analyses (t tests) were performed to further investigate group differences in specific subtests within relevant domains. To determine the extent of neuropsychological impairment in CFS subjects versus controls in tests where statistically significant group differences were found, χ^2 tests were used to compare the percentage of CFS versus control subjects who performed 1 SD below the mean of a normative sample provided in the database of the CANTAB test battery. As suggested by Taylor and Heaton (37), a cut-off of 1 SD below the mean of a representative control sample is an effective strategy to balance sensitivity and specificity in identifying neuropsychological impairment in clinical populations. Finally, to determine if elemental speed of cognitive processing accounted for significant differences in neuropsychological test performance between CFS and control subjects, analysis of covariance (ANCOVA) testing was performed using the simple reaction time measure of the RTI task as a covariate. Two-tailed tests of significance were used in all instances, and the α level was set at $p < .05$.

RESULTS

Subjects

As shown in Table 1, there were no significant differences between CFS and control subjects in terms of age, sex, race, or general intellectual ability as assessed by the WRAT-3 reading test. As expected, fatigue scores across the various dimensions were significantly elevated in CFS subjects compared with controls. Similar increases in SDS index depression scores were found in CFS versus control subjects. Because both depression and age have been associated with neuropsychological test performance, statistical analyses were conducted controlling for SDS index scores as well as age (38,39).

Neuropsychological Assessments

To determine cognitive domains that were altered in CFS versus control subjects, a series of omnibus MANCOVAs were performed on test scores in each of the four cognitive domains assessed on the CANTAB controlling for age and depression scores. The domains of psychomotor speed and working memory were significantly different between CFS and control subjects ($F = 2.79$, $p = .02$ and $F = 2.23$, $p = .04$, respectively). No significant differences were found in the domains of sustained attention or executive function ($F = 1.62$, $p = .21$ and $F = 0.57$, $p = .85$) (Table 2 for results of individual tests). Follow-up univariate analyses of the subtests of psychomotor speed revealed that CFS subjects exhibited significantly slower performance on the movement (motor) segments of the simple as well as the choice reaction time task (Table 3). No differences between groups were found in the reaction (decision) time component of the reaction time task.

Of note, compared with controls, significantly more CFS subjects performed 1 SD below the mean of the normative sample provided in the CANTAB database in simple movement time as well as choice movement time in the reaction time task (simple movement time: CFS 14.5% versus control 3.8%, $\chi^2 = 5.9$, $p = .01$; choice movement time: CFS 20.0% versus control 4.8%, $\chi^2 = 9.17$, $p = .002$).

Follow-up univariate analyses also revealed that participants with CFS performed significantly worse than controls on all of the three working memory tasks. Subjects with CFS exhibited a less efficient search strategy in the SWM task (as expressed by a higher strategy score), fewer percent of correct responses in the SRM task, and longer response latencies in the PRM task (Table 4). Significantly more CFS subjects performed 1 SD below the CANTAB normative mean in the strategy score of the SWM task compared with control subjects (CFS 27.8% versus control 10.6%, $\chi^2 = 7.7$, $p = .006$). There were no significant differences between groups in the number or percent of subjects who exhibited impairment in percent of correct responses in SRM task or response latencies in PRM task.

To evaluate the contribution of cognitive processing speed to alterations in working memory, ANCOVAs were conducted controlling for elemental processing speed as determined by performance on the simple reaction time task. Of note, differences between CFS and control groups in strategy scores in the SWM task and % correct responses in the SRM task remained significant after controlling for simple reaction time (SWM: $F(1,158) = 8.3$, $p = .004$); SRM: $F(1,158) = 4.0$, $p = .04$). In contrast, group differences in response latencies in the PRM task were no longer significant, suggesting that processing speed (as reflected by simple reaction time) did contribute to performance alterations in pattern recognition (latency of response) but not memory for visuospatial information.

TABLE 2. CFS Subjects Versus Well Controls, Means and SE of Individual Measures of Tests of Sustained Attention and Executive Function

Cognitive Domain and Variable	Controls (n = 103 to 104[a])	CFS (n = 58)
Sustained attention		
Rapid visual information processing		
A′	0.915 ± 0.005	0.901 ± 0.007
Mean latency (ms)	467 ± 9.0	493 ± 12.0
Executive function		
Stockings of Cambridge		
Total No. perfect solutions	8.7 ± 0.2	8.5 ± 0.3
4-move problems		
Average no. moves	5.3 ± 0.1	5.3 ± 0.1
ITT (s)	9.7 ± 0.7	9.3 ± 0.8
STT (s)	1.8 ± 0.2	1.8 ± 0.2
5-Move problems		
Average no. moves	6.6 ± 0.2	7.0 ± 0.2
ITT (s)	13.2 ± 1.0	11.0 ± 1.2
STT (s)	1.3 ± 0.2	1.3 ± 0.2
Intra-/extradimensional set shift		
Stages completed	8.5 ± 0.1	8.1 ± 0.2
Total errors (adjusted)	25.8 ± 2.4	36.1 ± 5.1
EDS errors	9.8 ± 0.9	11.1 ± 1.4
Pre-ED errors	7.7 ± 0.6	8.1 ± 0.8

SE = standard error of the mean; CFS = chronic fatigue syndrome; ITT = initial thinking time; STT = subsequent thinking time; EDS = extra-dimensional shift; ED = extra-dimensional.

[a] One control subject did not perform the rapid visual information processing test; one control subject did not perform the Stockings of Cambridge test.

TABLE 3. Psychomotor Speed: Comparison of Individual Measures of the Reaction Time Test in CFS Subjects Versus Well Controls

Reaction Time Test	CFS (n = 58)	Well (n = 103)[a]	t (159)	p
Simple reaction time (ms)	357.3 ± 9.5	340.2 ± 5.4	1.67	.09
Simple movement time (ms)	487.3 ± 16.3	445.3 ± 9.8	2.33	.02
Five-choice reaction time (ms)	384.3 ± 8.9	369.4 ± 5.1	1.55	.12
Five-choice movement time (ms)	489.1 ± 15.9	434.4 ± 9.3	3.17	.002

Data are shown as mean ± standard error of the mean.

[a] One control subject did not perform the reaction time test.

TABLE 4. Working Memory: Comparison of Individual Measures of Working Memory Tests in CFS Subjects Versus Well Controls

	CFS (58)	Well (104)	t (160)	p
Spatial working memory				
Strategy score	34.5 ± 0.6	31.8 ± 0.5	3.18	.002
Between-search errors	28.9 ± 2.4	24.1 ± 1.7	1.59	.11
Spatial recognition memory				
% Correct	82.8 ± 1.1	86.0 ± 0.8	2.20	.02
Mean correct latency (s)	2.62 ± 0.1	2.41 ± 0.1	1.10	.23
Pattern recognition memory				
% Correct	90.4 ± 1.4	91.9 ± 0.8	0.94	.34
Mean correct latency (s)	2.10 ± 0.1	1.91 ± 0.1	2.29	.02

Data are shown as mean ± standard error of the mean.

Effect of Fatigue Dimensions and Depression Severity on Neuropsychological Performance

Because significant group differences were found in several subtests within the domains of psychomotor speed and working memory, correlation coefficients were calculated between subtests that differed between groups and the five subscales of the MFI, controlling for age. Within the group as a whole, small but significant correlations were noted between mental fatigue and the strategy score on the SWM task ($r = .24$, $p = .002$) (the greater the mental fatigue, the worse the strategy score) as well as the latency for correct responses in the PRM task ($r = .23$, $p = .003$) (the greater the mental fatigue, the longer the response latency). General fatigue was also correlated with a worse strategy score on the SWM task ($r = .20$, $p = .01$) and fewer percent correct responses in the SRM task ($r = -.19$, $p = .01$). In addition, physical fatigue scores were correlated with five-choice movement times (the greater the physical fatigue, the longer the movement latency) ($r = .22$, $p = .005$) and with the latency for correct responses in the PRM task ($r = .20$, $p = .009$). Finally, reduced motivation was correlated with a worse strategy score on the SWM task ($r = .18$, $p = .02$).

Depression as measured by SDS index score correlated significantly with a higher (worse) strategy score in the SWM task ($r = .21$, $p = .007$) and less percent of correct responses in the SRM task ($r = .19$, $p = .01$) within the group as a whole.

DISCUSSION

Compared with control participants, subjects with CFS exhibited significant decreases in motor speed, as demonstrated by slower response times on the movement component of both the simple and choice reaction time task. Furthermore, subjects with CFS exhibited alterations in working memory as manifested by a less efficient search strategy on the SWM task, fewer % correct responses on the SRM task and a prolonged latency to a correct response on the PRM task. Of note, decreases in motor speed and working memory reflected neuropsychological impairment (as defined by a score of 1 SD below the CANTAB normative mean) in a significantly greater percentage of CFS subjects versus controls. Given the exclusion of subjects with comorbid psychiatric disorders and/or taking medications known to affect cognition, these results from a population-based sample confirm and quantify alterations in motor speed and working memory in CFS patients that were independent of comorbid psychiatric disease and medication usage.

The findings reported herein are in accordance with prior research indicating that alterations in motor speed and working memory are primary features of the cognitive changes that occur in CFS subjects. For example, Marshall et al. (6,7) and Michiels et al. (14) noted significantly slower psychomotor speed in subjects with CFS relative to controls. Moreover, several studies have documented altered working memory performance in CFS patients using the paced auditory serial addition test (PASAT) (7–10). The consistency of these results, especially after controlling for relevant confounding variables including comorbid psychiatric disorders, medication usage, and sampling bias, emphasizes the fundamental aspects of these cognitive changes and may provide clues regarding relevant neural circuits that may be involved in the pathophysiology of CFS neuropsychological symptoms.

Although motor slowing in CFS patients may in principle be attributable to several factors (for instance, functional alterations of motor and premotor cortices as well as midbrain structures regulating the general level of arousal), there are reasons to consider the involvement of basal ganglia nuclei (40,41). The basal ganglia play a primary role in the initiation of movement, and a common characteristic of disorders of the basal ganglia (e.g., Parkinson's disease) is reduced motor speed (42). Interestingly, basal ganglia damage or abnormalities are often associated with significant fatigue, leading some investigators to propose that central fatigue emanates from pathology in basal ganglia structures (43). Alterations in basal ganglia circuits that interact with cortical brain regions may also contribute to neuropsychological findings in CFS subjects including alterations in working memory (32). A number of studies have shown deficits in SWM in patients with frontal cortex and/or basal ganglia lesions or disorders, and imaging studies have indicated activation of these brain regions during tasks of working memory (31,44–47). Nevertheless, although studies using functional neuroimaging have found changes in CFS subjects in cortical networks subserving working memory, these changes have not been correlated with the basal ganglia (48–51). Moreover, no relationship was found between activity in the basal ganglia and cognitive fatigue in CFS patients performing a working memory task (49).

In addition to the considerations of the brain mechanisms that may be involved in neuropsychological changes in CFS subjects, it is also important to address their clinical consequences including the potential impact on real world performance. For example, psychomotor slowing has been associated with problems in carrying out vocational and other activities of daily living in patients with multiple sclerosis (52,53). Moreover, significant correlations between speed of cognitive processing and occupational outcome have been found in individuals with traumatic brain injuries (54,55). Significantly more CFS subjects performed in the impaired range in tests of motor speed and SWM compared with well controls. As suggested by Taylor and Heaton (37), neuropsychological impairment on these tasks was defined as performance 1 SD below the mean of the normalized database provided by the CANTAB. Using a 1 SD cut-off has been shown to provide an optimal balance between sensitivity and specificity in diagnosing impairment in clinical populations (37). More strict cut-offs (e.g., 1.5 or 2 SD) were found to provide modest gains in specificity with a large trade-off in sensitivity. Level of cognitive impairment among CFS patients has been found to correlate with the degree of functional impairment (56) as well as more real world outcomes including unemployment and disability (57). Moreover, Janal et al. (58) found a subgroup of CFS subjects characterized by head-

aches, postexertional fatigue, sleep disturbances, and cognitive dysfunction (particularly involving processing speed) who exhibited increased levels of disability. Thus, future studies integrating neuropsychological assessments (e.g., involving motor speed and working memory) with real world performance measures are warranted to determine the functional impact of CFS on occupational capacities as well as activities of daily living (e.g., managing financial affairs, driving).

Although none of the subjects in this study was diagnosed as suffering from major depressive disorder, SDS index scores revealed that a high percentage of persons with CFS reported symptoms of depression. Wearden and Appleby (59) showed that only CFS patients suffering from depression exhibited reduced verbal memory performance that correlated with severity of depressive symptoms. Although verbal memory was not assessed in the current study, subjects identified with CFS from the general population who did not suffer from major depression exhibited specific alterations in working memory and in motor slowing controlling for level of depression. These results are consistent with other reports (7,11,16–18) and indicate that alterations in neuropsychological performance in CFS subjects are not a primary function of depression. Nevertheless, severity of depressive symptoms did correlate with measures of working memory in the group as a whole, suggesting that symptoms of depression may contribute to the relative expression of working memory alterations in CFS subjects.

Specific dimensions of fatigue also correlated with neuropsychological performance (motor speed, spatial and pattern recognition, and spatial working memory) in the study sample. Previous studies have failed to find significant correlations between levels of fatigue and neuropsychological alterations in CFS patients (2,13,16,18). Nevertheless, previous studies did not distinguish between the various dimensions of fatigue, and in the current study, correlations with neuropsychological performance were restricted to specific fatigue dimensions including physical fatigue, general fatigue, reduced motivation, and mental fatigue, as previously reported by our group (23).

There are several limitations to our findings that should be noted. First, a relatively wide-ranging and nonfocused battery of seven subtests of the CANTAB was chosen to assess neuropsychological functioning. Given the results of the current study, future emphasis should be placed on a more detailed analysis of tasks of psychomotor speed and working memory including verbal working memory, which along with tests of episodic memory, are not included in CANTAB. For example, whereas computerized reaction time tests can be used to assess both reaction time and movement time, inspection time tests can be employed to assess basic speed of cognitive processing devoid of a confound with motor movement speed (60,61). Relevant assessments of working memory include computerized n-back working memory tests (62), the PASAT (63), the Salthouse Listening Span test (64), and the Brown-Peterson technique (65). Finally, the Cogscreen test battery (66), like the CANTAB tests, provides a measure of working memory as well as measures of speed of cognitive processing in the context of more complex cognitive tasks than those employed in inspection time paradigms.

A second limitation is that, although the present study examined one of the largest samples of CFS subjects to date, a larger sample size might have allowed the detection of further differences between CFS and the control subjects, and may have provided more power for detecting subtle alterations with smaller effect sizes.

Third, because we excluded CFS participants meeting the criteria for current major depression and those using psychotropic medications known to affect neuropsychological function, it may be difficult to generalize the results to the general population of patients with CFS, who often have major depression and are on a host of medication which can influence cognitive function (22). Thus, the study population does not allow evaluation of the potential interaction of depression and/or psychotropic treatment on cognitive performance. Nevertheless, given previously reported effects of depression on cognitive function, it is likely that even greater differences would have been observed in depressed and medicated CFS participants, with alterations potentially extending into other cognitive domains, including executive function (67).

Finally, the data of study subjects who may have skewed group scores and therefore study results were not removed, for example, by symptom validity testing.

In summary, this study extends previous findings of neuropsychological alterations in motor speed and working memory in a population-based sample of CFS patients free from comorbid psychiatric disorders and medications known to affect cognitive performance. These results further implicate the role of neural networks integrating frontal cortex and basal ganglia circuits in the pathophysiology of cognitive dysfunction in CFS. Moreover, a significant percentage of CFS patients were found to exhibit neuropsychological impairment, and the consequences of these cognitive changes for real world performance warrant further investigation.

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