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A Twin Study of Cognitive Function in Chronic Fatigue Syndrome: The Effects of Sudden Illness Onset

Keith H. Claypoole
University of Hawaii, Honolulu

Carolyn Noonan, Roderick K. Mahurin, Jack Goldberg, Tom Erickson, and Dedra Buchwald
University of Washington School of Medicine

Variable reports of neuropsychological deficits in individuals with chronic fatigue syndrome (CFS) may, in part, be attributable to methodological limitations. In this study, these limitations were addressed by controlling for genetic and environmental influences and by assessing the effects of comorbid depression and mode of illness onset. Specifically, the researchers conducted a co-twin control study of 22 pairs of monozygotic twins, in which 1 twin met strict criteria for CFS and the co-twin was healthy. Twins underwent a structured psychiatric interview and comprehensive neuropsychological assessment evaluating 6 cognitive domains. Results indicated that twin groups had similar intellectual and visual memory functioning, but fatigued twins exhibited decreases in motor functions ($p = .05$), speed of information processing ($p = .02$), verbal memory ($p = .02$), and executive functioning ($p < .01$). Major depression did not affect neuropsychological functioning among fatigued twins, although twins with sudden illness onset demonstrated slowed information processing compared with those with gradual onset ($p < .01$). Sudden onset CFS was associated with reduced speed of information processing. If confirmed, these findings suggest the need to distinguish illness onset in future CFS studies and may have implications for treatment, cognitive rehabilitation, and disability determination.

Keywords: chronic fatigue syndrome (CFS), cognitive impairment, twin studies, illness onset, information processing

Chronic fatigue syndrome (CFS) is a perplexing illness characterized by persistent or relapsing fatigue of 6 months' duration or longer, accompanied by at least four of eight symptoms (Fukuda et al., 1994; Hickie et al., 1995). Impaired concentration or short-term memory, which is one of the qualifying symptoms, is a frequent and disabling complication of CFS (Assefi, Coy, Uslan, Smith, & Buchwald, 2003; Hill, Tiersky, Scavalla, Lavietes, & Natelson, 1999; Tiersky et al., 2001). Although up to 95% of patients with CFS report cognitive difficulties (Bombardier & Buchwald, 1996), a biological basis has not been elucidated (Hill et al., 1999), and studies of neuropsychological functioning have provided inconsistent findings (Busichio, Tiersky, Deluca, & Natelson, 2004; DeLuca, Johnson, & Natelson, 1994; Marcel, Komaroff, Fagioli, Kornish, & Albert, 1996; Marshall, Forstot, Callies, Peterson, & Schenck, 1997; Michiels & Cluydts, 2001; Moss-Morris, Petrie, Large, & Kydd, 1996; Tiersky, Johnson, Lange, Natelson, & DeLuca, 1997). Difficulties with memory dominate the complaints of patients with CFS (Bombardier & Buchwald, 1996), but objective evidence of memory impairment has been inconclusive (Marshall et al., 1997; Michiels & Cluydts, 2001; Tiersky et al., 1997). In the literature on CFS, impaired speed of information processing has been the most robust finding on neuropsychological testing (for review, see Michiels & Cluydts, 2001; Tiersky et al., 1997).

The inconsistent findings regarding CFS and cognition likely reflect several methodological limitations, including variability in defining cases and controls; reliance on comparison groups that did not account for heritable factors, such as intelligence; and failure to exclude participants with preexisting conditions associated with cognitive compromise. Studies adjusting for other factors that might influence neuropsychological function, such as comorbid psychiatric illness and especially depression, have been inconclusive (Tiersky et al., 1997; Vollmer-Conna et al., 1997; Wessely, Chalder, Hirsch, Wallace, & Wright, 1996). More specifically, because depression may interfere with information processing, attention, and memory functions (Lezak, 1995), the independent effects of CFS and depression on cognition have been difficult to distinguish (Lawrie, MacHale, Cavanagh, O'Carroll, & Goodwin, 2000; Vollmer-Conna et al., 1997). The importance of a sudden versus gradual onset of illness has also been debated. In one study, fatigued patients with both modes of illness onset demonstrated impaired speed of information processing, but those with a sudden onset experienced more memory impairment than sedentary controls (DeLuca, Johnson, Ellis, & Natelson, 1997). In another study, however, illness triggers and objective memory performance were unrelated (Grafman et al., 1993).

Our study used the co-twin control methodology, which is a matched-pair analysis that adjusts for many genetic and environ-

Keith H. Claypoole, Department of Psychology, University of Hawaii, Honolulu; Carolyn Noonan, Department of Medicine, University of Washington School of Medicine; Roderick K. Mahurin, Departments of Neurology and Radiology, University of Washington School of Medicine; Jack Goldberg, Department of Epidemiology, University of Washington School of Medicine; Tom Erickson, Regional Epilepsy Center, University of Washington School of Medicine; Dedra Buchwald, Department of Medicine, University of Washington School of Medicine.

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Correspondence concerning this article should be addressed to Dedra Buchwald, Harborview Medical Center, Box 359780, 325 Ninth Avenue, Seattle, WA 98104. E-mail: dedra@u.washington.edu

mental factors not generally considered in case-control studies (Brandt et al., 1993). This design offers a powerful alternative to traditional approaches that compare fatigued patients with healthy, depressed, or sedentary controls. Co-twin control studies are well suited to examinations of neuropsychological test results because the number of data points generated is large, the range of values observed in normal individuals is relatively wide, and many cognitive abilities are highly heritable (Bouchard, 1998; Brandt et al., 1993; Finkel & Pedersen, 2000; Kee, Cherry, Neale, McBride, & Segal, 1998; McGue & Bouchard, 1998; Myles-Worsley & Coon, 1997). We administered a comprehensive neuropsychological test battery to 22 monozygotic twin pairs discordant for CFS to address these questions: (a) Are specific cognitive impairments associated with CFS? and (b) Do major depression and mode of illness onset influence cognitive functioning in CFS? We hypothesized that twins with CFS would have slower speed of information processing than their healthy co-twin, with similar functioning across other cognitive domains. We did not expect that depression or mode of illness onset would affect cognitive functioning among twins with CFS.

Method and Materials

Registry Construction and Recruitment

Twins were participants in a national CFS Twin Registry who were identified through CFS support group newsletters (58%); CFS electronic bulletin boards (15%); CFS practitioners (11%); twin organizations and researchers (6%); and relatives, friends, and others (8%). Of the 600 intake questionnaires that were mailed to twins, 426 (71%) were returned, and complete intake data were available for both members of 193 twin pairs. We collected information on demographics, zygosity, lifestyle, habits, and medical and psychiatric disorders. For the fatigued twins, we asked about the duration and consequences of fatigue. Nonfatigued twins filled out a control version of the questionnaire that did not reference fatigue (Fukuda et al., 1994). A detailed description of the CFS Twin Registry is published elsewhere (Buchwald et al., 1999).

Participant Selection

From the CFS Twin Registry, 22 pairs of monozygotic twins discordant for CFS were selected for a 7-day, in-person evaluation based on information in the registry and additional telephone screenings. Twins were required to (a) be at least 18 years of age; (b) have been raised together; (c) be discordant for CFS (1 twin met criteria for CFS, the other was healthy); (d) be HIV negative; (e) travel together to the research site for a week, and (f) discontinue alcohol, caffeine, and all medications known to affect sleep or cognition for 2 weeks before and during the evaluation period. Twins provided written informed consent for participation in the CFS Twin Registry and again for in-person evaluations after the study had been completely described to them.

To determine whether a twin met CFS criteria, we used responses to the CFS symptom checklist, diagnoses generated by the Diagnostic Interview Schedule (Version III-A; Robins & Helzer, 1985), and information from medical record reviews. Inclusion and exclusion criteria (e.g., body mass index, psychiatric disorders with psychosis) were based on the Centers for Disease Control and Prevention CFS case definition and were uniformly applied to fatigued and healthy twins. Medical records covering the last 5 years were independently reviewed by two internists and a psychologist to identify exclusionary conditions. In addition, the records of potentially eligible twins with preexisting conditions that affect cognitive functioning were reviewed by a neuropsychologist. Twin pairs were excluded if either member reported a history of learning disability, participation in a special education program, chemical exposure requiring medical treatment, head injury in the past year, or any head injury accompanied by loss of consciousness over 5 min. In the week before the twins' in-person evaluations, the CFS screening checklist was readministered to verify that the medical and psychiatric status of the twin pairs remained unchanged.

Demographic and Clinical Characteristics

Demographic variables included age in years, sex, race, marital status, number of years of education, and employment. Fatigue duration was computed as the time interval between reported fatigue onset and the interview date. Possible responses for how fatigue began included (a) gradually—no clear onset; (b) suddenly—with a "flu," "cold," or "virus" characterized by two or more of the following (fever, headache, muscle aches, earache, sore throat, congestion, runny nose, cough, diarrhea, or fatigue); (c) suddenly—with no other symptoms; (d) after a surgical operation; (e) after a motor vehicle accident; (f) after another stressful event; and (g) could not remember. For the purpose of this analysis, Category a comprised the gradual onset group, and only Category b was considered typical of the sudden onset group.

Zygosity

The monozygotic status of each twin pair was initially determined with validated self-report methods (Torgersen, 1997), then confirmed by restriction fragment length polymorphisms. DNA samples were extracted, and the restriction fragments were separated, Southern blotted, and hybridized with tandem repeat probes. The probability of monozygosity was verified with a 99.9% certainty following six probes (Keith & Machin, 1997).

Psychiatric Diagnoses

To determine lifetime and current psychiatric diagnoses, trained examiners administered the Diagnostic Interview Schedule (Version III-A; Robins & Helzer, 1985) by telephone to Twin Registry participants. The modules that were administered included major depression and dysthymia, mania and bipolar mood disorders, generalized anxiety and panic disorders, agoraphobia, posttraumatic stress disorder, schizophrenia and other psychotic disorders, eating disorders, somatization, and substance abuse or dependence. Our analyses treated lifetime and current major depression diagnoses as either present or absent.

Neuropsychological Evaluation

Neuropsychological tests were administered in a standardized manner (Lezak (1995); Spreen & Strauss, 1998) by trained examiners blinded to CFS status. The lengthy test battery was designed to comprehensively assess six cognitive domains: (a) intellectual

functioning, (b) motor functioning, (c) speed of information processing, (d) verbal memory, (e) visual memory, and (f) executive functioning.

Intellectual functioning was evaluated by the seven-subtest short form of the Wechsler Adult Intelligence Scale—Revised (Ward, 1990; Wechsler, 1981), which minimizes time demands yet still provides highly reliable assessments (Iverson, Myers, Bengtson, & Adams, 1996). Verbal IQ subtests included Information, Digit Span, Arithmetic, and Similarities; the Performance IQ subtests included Picture Completion, Block Design, and Digit Symbol. Each twin's Full-scale IQ determined the intellectual functioning domain score. The motor functioning domain scores consisted of the mean for both the dominant and nondominant hand Halstead–Reitan Finger Tapping Test (Reitan & Wolfson, 1993), the mean time for the dominant and nondominant hand Grooved Pegboard Test (Matthews & Klove, 1964), and the mean reaction time from six random trials of the Simple Reaction Time Test from the neurobehavioral core test battery (World Health Organization, 1986). The speed of information processing domain included the mean number of words correct on Trials 1 and 2 of the Stroop Color and Word Test (Golden, 1978) and the total number correct from four trials of the Paced Auditory Serial Addition Task (Gronwall, 1977). The verbal memory domain was based on the total words learned from Trials 1–8 on the Rey Auditory Verbal Learning Test (Rey, 1964) and the Verbal Memory Index of the Wechsler Memory Scale—Revised (Wechsler, 1987), which includes Logical Memory Subtests I and II and Verbal Paired Associates I and II. The visual memory domain consisted of the mean score for recall Trials 2 and 3 of the Rey–Osterrieth Complex Figure Test (Osterrieh, 1944) and the total correct on the recognition format of the Benton Visual Retention Test (Benton, 1974; World Health Organization, 1986). The executive functioning domain included completion time on the Trail Making Test Part B (Reitan & Wolfson, 1993), number correct on Trial 3 (interference trial) of the Stroop Color and Word Test (Golden, 1978), total words generated for letters F, A, S on the Controlled Oral Word Attention Test (Benton, Hamsher, & Sivan, 1994), and number of perseverative errors on the Wisconsin Card Sorting Test (Heaton, 1981).

Statistical Analyses

Descriptive statistics for continuous variables were calculated as mean values (±standard deviations); percentages were computed for dichotomous variables. All neuropsychological test scores were verified, and test distributions were examined for outliers and missing data before analysis. In addition, test scores were rescaled, if necessary, so that higher scores indicated better cognitive functioning. We used three-level mixed effects linear regression models (Diggle, Heagerty, Liang, & Zeger, 2002; Lin et al., 2000) to compare fatigued and healthy twins in each of the six cognitive domains. Models included a random effect for twin pair and a fixed effect for CFS status. Multiple cognitive test indices within a domain were treated as repeated measures. This technique accommodates the nested structure of the data (i.e., multiple test indices within person within twin pair). Because neuropsychological test indices within a domain were not always measured on the same scale, we computed a standardized z score for each index before domain analyses. For ease of interpretation, descriptive statistics for neuropsychological test scores are presented in their original scales.

For each domain, we initially fit a model that allowed a heterogeneous CFS effect according to the neuropsychological test index. We then used a likelihood ratio test to compare this model with a model assuming a homogeneous CFS effect across test indices. If there was no evidence that the CFS effect differed by test index at the .05 level, we used a global 1-degree-of-freedom F test to assess the overall CFS effect on the domain. If a heterogeneous CFS effect was observed, we used a $(k - 1)$-degree-of-freedom F test to assess the overall CFS effect on the domain, where k equals the number of test indices in the domain. Only the executive functioning domain showed evidence of a heterogeneous CFS effect ($p < .01$).

For domains that showed a significant overall CFS effect, we conducted secondary analyses to examine whether the CFS effect differed by lifetime major depression, current major depression, or sudden versus gradual onset of illness. For analyses involving depression status, twins were categorized into three groups—healthy and without major depression, CFS without major depression, and CFS with major depression—to determine whether the nondepressed fatigued twins differed from the depressed fatigued twins and to assess how both groups compared with the healthy nondepressed twins. Similarly, analysis of CFS onset was accomplished by categorizing twins as healthy, sudden onset CFS, or gradual onset CFS. The modeling strategy for secondary analyses was similar to that described above, except that we included two fixed effects in each model. For the lifetime and current depression analyses, the fixed effects were indicators for CFS status with and without comorbid depression. In the CFS onset analyses, the fixed effect indicators were CFS status with sudden or gradual onset. All models were adjusted for sex, age, and education, and all used the healthy twins as the reference group.

All 22 twin pairs had complete data and were included in the primary analyses that examined the six neuropsychological domains. One pair, in which the healthy twin met criteria for lifetime major depression, was excluded from secondary analyses evaluating the effect of lifetime depression on cognitive function in CFS. All 22 pairs were used to examine the effect of current depression on cognitive function in CFS. In our comparison of participants with sudden onset CFS and those with gradual onset CFS, we excluded 3 pairs in which the CFS twin reported an onset that did not fall into one of these categories (2 with onset following a motor vehicle accident, 1 unable remember). Analyses were conducted in SAS Version 9.1. All tests were two-tailed, and the significance of domain comparisons was assessed at the .05 level.

Results

As shown in Table 1, the mean age for the 22 twin pairs was 41.43 years at the time of the examination, and 19 pairs (90.91%) were female. The fatigued twins averaged less education than the healthy twins (13.95 vs. 14.73 years; $p = .01$), and 59.09% of both fatigued and healthy twins were married. The fatigued twins had a higher frequency of unemployment and of lifetime and current depression. The average fatigue duration for the twins with CSF was 7.00 years. Of the fatigued twins, 10 (45.45%) reported a sudden onset with flulike symptoms, 9 (40.91%) reported a gradual onset, 2 (9.09%) reported onset after a motor vehicle accident, and 1 (4.55%) could not remember.

Table 1
Demographic and Clinical Characteristics of Monozygotic Twin Pairs Discordant for Chronic Fatigue Syndrome (CFS)

Characteristic	CFS twins $n = 22$	Healthy twins $n = 22$
Demographic		
Age, mean years (SD)	41.43 (9.87)	41.43 (9.87)
Female (%)	90.91	90.91
White (%)	100	100
Education, mean years (SD)	13.95 (2.36)	14.73 (2.43)
Married (%)	59.09	59.09
Unemployed (%)	59.09	9.09
Clinical		
Lifetime major depression (%)	59.09	4.55
Current major depression (%)	18.18	0
Fatigue duration, mean years (SD)	7.00 (4.36)	—
Fatigue onset (%)		
Sudden, with flulike symptoms	45.45	—
Gradual	40.91	—
Other[a]	13.64	—

[a] Two twins reported fatigue following a motor vehicle accident, and 1 twin could not remember.

As shown in Table 2, after adjusting for age, sex, and education, twins with CFS had lower cognitive functioning than their healthy co-twins for most individual neuropsychological tests and had significantly lower functioning in four of the six cognitive domains. Domain differences were evident for motor functioning ($p = .05$), speed of information processing ($p = .02$), verbal memory functioning ($p = .02$), and executive functioning ($p < .01$). Fatigued and healthy twins were similar in intellectual ($p = .11$) and visual memory functioning ($p = .84$).

Among fatigued twins, speed of information processing and motor, verbal memory, and executive functioning domains did not differ by either lifetime or current major depression status (data not shown; range $p = .09–0.80$). Likewise, the effect of CFS on cognitive functioning in the motor, verbal memory, or executive functioning domains did not differ according to sudden versus gradual onset (data not shown; range $p = .16–.59$). In contrast, information processing was slower among the twins with sudden onset CFS than among those with gradual onset CFS ($p < .01$). To illustrate this finding, Figure 1 presents the mean Paced Auditory Serial Addition Test scores for the twins with CSF by mode of onset, compared with the scores of their healthy co-twins. The performance of the gradual onset group was similar to that of the healthy co-twins, and the performance of the sudden onset group was significantly impaired in comparison with that of both other groups.

Discussion

We found that the neuropsychological performance of fatigued twins was worse than that of their healthy co-twins in four of the six cognitive domains evaluated. These domains were speed of information processing, verbal memory, and motor and executive functioning. Our results are congruent with those of studies that have reported an association between CFS and neuropsychological impairment across multiple domains (Busichio et al., 2004; for reviews, see Michiels & Cluydts, 2001; Tiersky et al., 1997). We did not see differences in visual memory or executive functioning; therefore, our findings help clarify the nature and extent of the cognitive dysfunction associated with CFS. We also observed that neither lifetime nor current major depression affected cognitive function in the twins with CFS. This observation is consistent with other studies of CFS that have found neuropsychological functioning to be independent of depression (Lawrie et al., 2000; Wessely et al., 1996). Nonetheless, as has been indicated for other neuropsychiatric conditions (Claypoole et al., 1998; Coleman et al., 1996), providers should be aware that the effective treatment of depression may lead to a decline in subjective complaints of cognitive dysfunction among patients with CFS.

Contrary to our own hypothesis, we also found that sudden onset CFS was associated with a significant decrement in speed of information processing. Results of two investigations that examined neuropsychological functioning in CFS as a function of onset type have been mixed. One early report did not find the nature of the precipitating illness to be associated with object memory performance (Grafman et al., 1993). A later investigation, however, noted that verbal memory was more impaired among patients with sudden onset CFS than among their counterparts with a gradual onset of illness (DeLuca et al., 1997). Our findings may parallel this later report, considering the proposed importance of information processing in mediating complex attention and memory functioning (DeLuca et al., 1994). Unexpectedly, we also found that the speed of information processing among the twins with gradual onset CFS was similar to that of the healthy co-twin group. These findings suggest that group differences may be attributable to the influence of sudden onset CFS and underscore the need to address mode of onset in studies of neuropsychological function.

Recently, several intriguing studies have provided insight into the pathophysiology of the cognitive complaints and dysfunction observed among individuals with CFS. For example, functional neuroimaging studies have demonstrated dorsolateral prefrontal

Table 2
Neuropsychological Functioning of Monozygotic Twins Discordant for Chronic Fatigue Syndrome (CFS)

Test	CFS twins		Healthy twins		
	M	*SD*	*M*	*SD*	p[a]
Intellectual functioning					.11
Wechsler Intelligence Scale—Revised					
Information	10.05	2.63	10.09	2.81	
Digit Span	9.68	3.20	10.27	2.91	
Arithmetic	9.14	3.09	10.27	3.27	
Similarities	10.68	2.46	10.45	2.81	
Picture Completion	8.45	2.76	9.14	2.90	
Block Design	10.14	2.98	10.27	3.94	
Digit Symbol	9.32	2.01	10.05	2.08	
Prorated Verbal IQ	101.55	13.86	103.41	13.49	
Prorated Performance IQ	100.59	14.83	103.50	15.50	
Prorated Full Scale IQ	100.95	14.11	103.59	13.37	
Motor functioning					.05
Finger Tapping					
Dominant Hand	48.00	7.45	50.14	4.73	
Nondominant Hand	46.55	5.78	46.91	6.65	
Grooved Pegboard					
Dominant Hand, *s*	67.23	10.13	68.32	11.61	
Nondominant Hand, *s*	74.77	14.37	71.18	10.94	
Simple Reaction Time Test					
Mean of six trials, *s*	0.35	0.12	0.31	0.07	
Speed of information processing					.02
Color Word Test Stroop					
Trial 1—words correct	94.00	17.44	97.14	11.37	
Trial 2—colors correct	70.05	11.02	71.00	10.00	
Paced Auditory Serial Addition Test					
Total Trials 1–4	109.36	26.59	118.27	24.31	
Verbal memory functioning					.02
Wechsler Memory Scale—Revised					
Logical Memory I	25.82	7.40	28.91	5.43	
Logical Memory II	21.95	8.22	23.27	5.57	
Verbal Paired Associates I	19.55	2.77	18.91	3.45	
Verbal Paired Associates II	6.91	1.31	7.55	0.86	
Verbal Memory Score Index	101.23	16.01	106.41	12.61	
Rey Auditory Verbal Learning Test					
Total Trials 1–5	52.64	9.51	57.32	6.53	
Trial 6	6.73	1.45	7.05	1.73	
Trial 7	10.41	3.03	11.68	2.71	
Trial 8	9.68	3.15	11.59	2.77	
Visual memory functioning					.84
Rey–Osterrieth Complex Figure Test					
Trial 1, copy	34.70	1.76	34.23	3.31	
Trial 2, 3 min delay	20.68	6.86	19.57	6.32	
Trial 3, 30 min delay	19.68	6.59	18.18	5.67	
Benton Visual Retention Test–recognition					
Total Correct	8.73	0.94	8.95	0.72	
Executive functioning					< .01
Color Word Test Stroop					
Trial 3—interference	39.68	7.89	41.73	7.94	
Trial Making Test					
A, *s*	24.50	7.36	25.95	6.81	
B, *s*	64.05	17.59	58.14	15.10	
Controlled Oral Word Attention Test					
Total words	41.36	10.81	36.55	8.97	
Wisconsin Card Sorting Test					
Categories completed	4.95	1.73	5.23	1.48	
Total errors	24.23	25.23	24.36	19.43	
Total perseverative errors	10.14	8.41	13.45	10.91	

[a] p values for domain models adjusted for sex, age, and education.

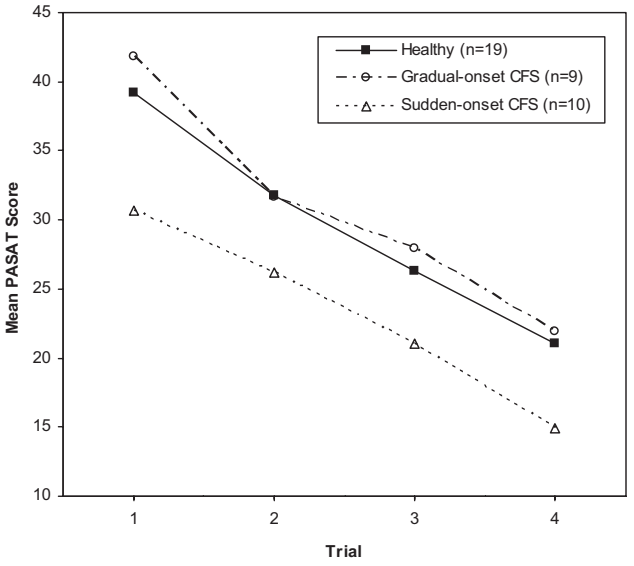

Figure 1. Mean Paced Auditory Serial Addition Test (PASAT) scores for twins with gradual and sudden onset of chronic fatigue syndrome (CFS) and their healthy co-twins.

cortex activation during performance of working memory tasks that rely on frontal lobe information processing (Fletcher & Henson, 2001). Likewise, magnetic resonance imaging studies of fatigued patients with dominant memory complaints have detected an increase in white matter lesions in the frontal region (Lange, Wang, DeLuca, & Natelson, 1998). Decreased perfusion in the anterior cingulate region and increased activation in the left anterior cingulate region among patients with CFS compared with healthy subjects has also been identified on single-photon emission computerized tomography during a challenge protocol involving speed of information processing (Schmaling, Lewis, Fiedelak, Mahurin, & Buchwald, 2003). Investigations such as these would be interesting to conduct among subgroups of patients with sudden onset and gradual onset CFS.

One noteworthy aspect of this study is our use of illness-discordant twins. Previous twin studies have demonstrated that many aspects of cognition and mental ability are heavily influenced by heredity (Brandt et al., 1993; Finkel & Pedersen, 2000; Kee et al., 1998; McGue & Bouchard, 1998; Myles-Worsley & Coon, 1997). Intelligence, which strongly influences many neuropsychological abilities, is largely under genetic control (Bouchard, 1998). Our co-twin approach adjusts for intelligence and other heritable neuropsychological abilities and early shared environmental factors that are typically not accounted for when controls are matched to cases only on demographic or clinical variables. Thus, the healthy monozygotic co-twin group is one of the best comparison groups possible, especially for a poorly understood condition, such as CFS.

This co-twin control study has several limitations. First, the method we used to identify the sample was not ideal. Solicitation by advertisement resulted in a volunteer sample of twin pairs with the potential for selection biases and skewed samples. However, the more desirable strategy of systematically identifying twins from a well-defined, population-based twin registry is not readily accomplished in the United States. Our concerns regarding potential biases were reduced after we noted that the intellectual functioning among both the fatigued and healthy co-twins corresponded closely to a normal population distribution (Wechsler, 1981) and that the two groups were, not unexpectedly, well matched. Second, we cannot state with certainty how representative our twins were, either of twins in general or of persons with CFS. Because our twin pairs were adult, primarily female, drawn from community practices, and composed of 1 twin who met strict criteria for CFS and 1 twin who did not, these results may not generalize to other settings. Nevertheless, the twins' demographic and clinical characteristics were similar to those described in the CFS literature. Third, our small sample size limited our ability to conclusively show the effects of depression and mode of illness onset across all neuropsychological domains. Finally, we were unable to address the biological basis of, or provide an adequate explanation for, the selective decrement in information processing observed among twins with sudden onset CFS.

In conclusion, CFS is associated with neuropsychological deficits across multiple cognitive domains, and in some domains—notably speed of information processing—individuals with a sudden onset of illness may be more impaired than those with a gradual onset. The reasons behind this are unclear, but they may reflect an infectious trigger and involvement of the central nervous system. In addition, our findings may have clinical implications for determining disability among individuals with CFS, a process that is complicated by the absence of accepted guidelines for physical and cognitive disability (Hickie et al., 1995). We suggest that neuropsychological evaluations could describe vocational capacity and the potential benefit of cognitive rehabilitation and workplace accommodation. Future studies should examine the functional and anatomical aspects of cognitive deficits associated with CFS and distinguish participants with sudden and gradual onset of illness.

References

Assefi, N. P., Coy, T. V., Uslan, D., Smith, W. R., & Buchwald, D. (2003). Financial, occupational, and personal consequences of disability in patients with chronic fatigue syndrome and fibromyalgia compared to other fatiguing conditions. *Journal of Rheumatology, 30,* 804–808.

Benton, A. L. (1974). *Revised Visual Retention Test—Clinical and experimental applications* (4th ed.). San Antonio, TX: Psychological Corporation.

Benton, A. L., Hamsher, K. deS., & Sivan, A. B. (1994). *Multilingual Aphasia Examination* (3rd ed.). San Antonio, TX: Psychological Corporation.

Bombardier, C. H., & Buchwald, D. (1996). Chronic fatigue, chronic fatigue syndrome, and fibromyalgia. Disability and health-care use. *Medical Care, 34,* 924–930.

Bouchard, T. J., Jr. (1998). Genetic and environmental influences on adult intelligence and special mental abilities. *Human Biology, 70,* 257–279.

Brandt, J., Welsh, K. A., Breitner, J. C., Folstein, M. F., Helms, M., & Christian, J. C. (1993). Hereditary influences on cognitive functioning in older men. A study of 4,000 twin pairs. *Archives of Neurology, 50,* 599–603.

Buchwald, D., Herrell, R., Ashton, S., Belcourt, M., Schmaling, K., & Goldberg, J. (1999). The Chronic Fatigue Twin Registry: Method of construction, composition, and zygosity assignment. *Twin Research, 2,* 203–211.

Busichio, K., Tiersky, L. A., Deluca, J., & Natelson, B. H. (2004). Neuropsychological deficits in patients with chronic fatigue syndrome. *Journal of the International Neuropsychology Society, 10,* 278–285.

Claypoole, K. H., Elliott, A. J., Uldall, K. K., Russo, J., Dugbartey, A. T., Bergam, K., & Roy-Byrne, P. P. (1998). Cognitive functions and complaints in HIV-1 individuals treated for depression. *Applied Neuropsychology, 5,* 74–84.

Coleman, E. A., Sackeim, H. A., Prudic, J., Devanand, D. P., McElhiney, M. C., & Moody, B. J. (1996). Subjective memory complaints prior to and following electroconvulsive therapy. *Biological Psychiatry, 39,* 346–356.

DeLuca, J., Johnson, S. K., Ellis, S. P., & Natelson, B. H. (1997). Sudden vs. gradual onset of chronic fatigue syndrome differentiates individuals on cognitive and psychiatric measures. *Journal of Psychiatric Research, 31,* 83–90.

DeLuca, J., Johnson, S. K., & Natelson, B. H. (1994). Neuropsychiatric status of patients with chronic fatigue syndrome: An overview. *Toxicology and Industrial Health, 10,* 513–522.

Diggle, P. J., Heagerty, P., Liang, K. Y., & Zeger, S. L. (2002). *Analysis of longitudinal data* (2nd ed.). New York: Oxford University Press.

Finkel, D., & Pedersen, N. L. (2000). Contribution of age, genes, and environment to the relationship between perceptual speed and cognitive ability. *Psychology and Aging, 15,* 56–64.

Fletcher, P. C., & Henderson, R. N. A. (2001). Frontal lobes and human memory: Insights from functional neuroimaging. *Brain, 124,* 849–881.

Fukuda, K., Straus, S. E., Hickie, I., Sharpe, M. C., Dobbins, J. G., & Komaroff, A. (1994). The chronic fatigue syndrome: A comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Annals of Internal Medicine, 121,* 953–959.

Golden, C. J. (1978). *The Stroop Color and Word Test—A manual for clinical and experimental uses.* Wood Dale, IL: Stoelting.

Grafman, J., Schwartz, V., Dale, J. K., Scheffers, M., Houser, C., & Straus, S. E. (1993). Analysis of neuropsychological functioning in patients with chronic fatigue syndrome. *Journal of Neurology, Neurosurgery & Psychiatry, 56,* 684–689.

Gronwall, D. M. A. (1977). Paced auditory serial-addition task: A measure of recovery from concussion. *Perceptual and Motor Skills, 44,* 367–373.

Heaton, R. K. (1981). *Wisconsin Card Sorting Test—Manual.* Odessa, FL: Psychological Assessment Resources.

Hickie, I., Lloyd, A., Hadzi-Pavlovic, D., Parker, G., Bird, K., & Wakefield, D. (1995). Can the chronic fatigue syndrome be defined by distinct clinical features? *Psychological Medicine, 25,* 925–935.

Hill, N. F., Tiersky, L. A., Scavalla, V. R., Lavietes, M., & Natelson, B. H. (1999). Natural history of severe chronic fatigue syndrome. *Archives of Physical Medicine and Rehabilitation, 80,* 1090–1094.

Iverson, G. L., Myers, B., Bengtson, L., & Adams, R. (1996). Concurrent validity of a WAIS–R seven subtest short form in patients with brain impairment. *Psychological Assessment, 8,* 319–323.

Kee, D. W., Cherry, B. J., Neale, P. L., McBride, D. M., & Segal, N. L. (1998). Multitask analysis of cerebral hemisphere specialization in monozygotic twins discordant for handedness. *Neuropsychology, 12,* 468–478.

Keith, L., & Machin, G. (1997). Zygosity testing. Current status and evolving issues. *Journal of Reproductive Medicine, 42,* 699–707.

Lange, G., Wang, S., DeLuca, J., & Natelson, B. H. (1998). Neuroimaging in chronic fatigue syndrome. *American Journal of Medicine, 105,* 50S–53S.

Lawrie, S. M., MacHale, S. M., Cavanagh, J. T., O'Carroll, R. E., & Goodwin, G. M. (2000). The difference in patterns of motor and cognitive function in chronic fatigue syndrome and severe depressive illness. *Psychological Medicine, 30,* 433–442.

Lezak, M. D. (1995). *Neuropsychological assessment* (3rd ed.). New York: Oxford University Press.

Lin, X., Ryan, L., Sammel, M., Zhang, D., Padungtod, C., & Xu, X. (2000). A scaled linear mixed model for multiple outcomes. *Biometrics, 56,* 593–601.

Marcel, B., Komaroff, A. L., Fagioli, L. R., Kornish, R. J., 2nd, & Albert, M. S. (1996). Cognitive deficits in patients with chronic fatigue syndrome. *Biological Psychiatry, 40,* 535–541.

Marshall, P. S., Forstot, M., Callies, A., Peterson, P. K., & Schenck, C. H. (1997). Cognitive slowing and working memory difficulties in chronic fatigue syndrome. *Psychosomatic Medicine, 59,* 58–66.

Matthews, C. G., & Klove, K. (1964). *Instruction manual for the adult neuropsychology test battery.* Madison: University of Wisconsin Medical School.

McGue, M., & Bouchard, T. J., Jr. (1998). Genetic and environmental influences on human behavioral differences. *Annual Review of Neuroscience, 21,* 1–24.

Michiels, V., & Cluydts, R. (2001). Neuropsychological functioning in chronic fatigue syndrome: A review. *ACTA Psychiatrica Scandinavica, 103,* 84–93.

Moss-Morris, R., Petrie, K. J., Large, R. G., & Kydd, R. R. (1996). Neuropsychological deficits in chronic fatigue syndrome: Artifact or reality? *Journal of Neurology, Neurosurgery & Psychiatry, 60,* 474–477.

Myles-Worsley, M., & Coon, H. (1997). Genetic and developmental factors in spontaneous selective attention: A study of normal twins. *Psychiatry Research, 71,* 163–174.

Osterrieth, P. A. (1944). Le test de copie d'une figure complex: Contribution à l'étude de la perception et de la mémoire. [Test of copying a complex figure: Contribution to the study of perception and memory]. *Archives de Psychologie, 30,* 206–356.

Reitan, R. M., & Wolfson, D. (1993). *The Halstead–Reitan Neuropsychological Test Battery* (2nd ed.). Tucson, AZ: Neuropsychology Press.

Rey, A. (1964). L'examen clinique en psychologie [Clinical examination in psychology]. Paris: Press Universitaire de France.

Robins, L. N., & Helzer, J. E. (1985). *Diagnostic Interview Schedule Version IIIA.* St. Louis, MO: Department of Psychiatry, Washington University School of Medicine.

Schmaling, K. B., Lewis, D. H., Fiedelak, J. I., Mahurin, R., & Buchwald, D. S. (2003). Single-photon emission computerized tomography and neurocognitive function in patients with chronic fatigue syndrome. *Psychosomatic Medicine, 65,* 129–136.

Spreen, O., & Strauss, E. (1998). *A compendium of neuropsychological tests: Administration, norms, and commentary* (2nd ed.). New York: Oxford University Press.

Tiersky, L. A., DeLuca, J., Hill, N., Dhar, S. K., Johnson, S. K., Lange, G., et al. (2001). Longitudinal assessment of neuropsychological functioning, psychiatric status, functional disability and employment status in chronic fatigue syndrome. *Applied Neuropsychology, 8,* 41–50.

Tiersky, L. A., Johnson, S. K., Lange, G., Natelson, B. H., & DeLuca, J. (1997). Neuropsychology of chronic fatigue syndrome: A critical review. *Journal of Clinical and Experimental Neuropsychology, 19,* 560–586.

Torgersen, S. (1997). The determination of twin zygosity by means of a mailed questionnaire. *ACTA Geneticae Medicae et Gemellologiae, 28,* 225–236.

Vollmer-Conna, U., Wakefield, D., Lloyd, A., Hickie, I., Lemon, J., Bird, K. D., Westbrook. R. F. (1997). Cognitive deficits in patients suffering from chronic fatigue syndrome, acute infective illness or depression. *British Journal of Psychiatry, 171,* 377–381.

Ward, L. C. (1990). Prediction of verbal, performance, and full scale IQs from seven subtests of the WAIS–R. *Journal of Clinical Psychology, 46,* 436–440.

Wechsler, D. (1981). *Wechsler Adult Intelligence Scale—Revised manual.* New York: Psychological Corporation.

Wechsler, D. (1987). *Wechsler Memory Scale—Revised manual.* New York: Psychological Corporation.

Wessely, S., Chalder, T., Hirsch, S., Wallace, P., & Wright, D. (1996). Psychological symptoms, somatic symptoms, and psychiatric disorder in chronic fatigue and chronic fatigue syndrome: A prospective study in the primary care setting. *American Journal of Psychiatry, 153,* 1050–1059.

World Health Organization, Office of Occupational Health. (1986). *Operational guide for the WHO Neurobehavioral Core Test Battery.* Geneva, Switzerland: Author.

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