Journal of the International Neuropsychological Society (2001), **7**, 835–839.

Neurobehavioral deficits associated with chronic fatigue syndrome in veterans with Gulf War unexplained illnesses

LAURENCE M. BINDER,[1] DANIEL STORZBACH,[1,2] KEITH A. CAMPBELL,[1,2] DIANE S. ROHLMAN[1], W. KENT ANGER,[1] AND MEMBERS OF THE PORTLAND ENVIRONMENTAL HAZARDS RESEARCH CENTER

[1]Oregon Health Sciences University, Portland Oregon
[2]Portland Veterans Affairs Medical Center

(RECEIVED April 27, 2000; REVISED September 29, 2000; ACCEPTED October 10, 2000)

Abstract

Gulf War unexplained illnesses (GWUI) are a heterogeneous collection of symptoms of unknown origin known to be more common among veterans of the Gulf War than among nonveterans. In the present study we focused on one of these unexplained illnesses. We tested the hypothesis that in a sample of Persian Gulf War veterans chronic fatigue syndrome (CFS) was associated with cognitive deficits on computerized cognitive testing after controlling for the effects of premorbid cognitive differences. We obtained Armed Forces Qualification Test (AFQT) data acquired around the date of induction into the military on 94 veterans of the Gulf War, 32 with CFS and 62 healthy controls. Controls performed better than participants diagnosed with CFS on the AFQT. Cognitive deficits were associated with CFS on 3 of 8 variables after the effect of premorbid AFQT scores was removed with ANCOVA. (*JINS*, 2001, *7*, 835–839.)

Keywords: Chronic fatigue syndrome, Cognitive function, Gulf War unexplained illnesses

INTRODUCTION

The Persian Gulf War of 1991 deployed approximately 700,000 American military personnel to the Persian Gulf. Previous studies showed an increased incidence of symptomatology in the musculoskeletal, cognitive, and emotional areas compared with nondeployed personnel (Iowa Persian Gulf Study Group, 1997). The etiology of these symptoms remains unexplained, hence the label Gulf War unexplained illnesses (GWUI).

We commenced formal study of GWUI in 1994. We developed a computerized neurobehavioral test battery, the BARS, for this project that had advantages compared with previously designed computerized batteries: it utilized a nine-key data sled superimposed on a standard 101-key keyboard in order to simplify responding and to reduce the possible test-taking advantage of persons with computer experience; it electronically entered test results into a data base, and it was truly self-administered in that easy to comprehend behavioral shaping instructions were incorporated into the software. The BARS consisted of cognitive and psychomotor speed tasks. We also designed another computerized battery, the HSS, using existing measures of psychosocial and emotional functioning originally designed as paper-and-pencil tasks such as the MMPI–2 and the Beck Depression Inventory. The BARS and HSS were used sequentially in the same software–hardware system (Anger et al., 1996; Kovera et al., 1996).

Using the BARS/HSS batteries, we found psychological deficits in a population-based Pacific Northwest sample of veterans with GWUI. We found that ill veterans, compared with case controls, showed mental slowing (Anger et al., 2000; Storzbach et al., in press). Mental slowing occurred in only 12% of those with GWUI by one estimate (Storzbach et al., in press). In another study we found that differences on measures of psychosocial distress showed larger effect sizes than our measures of neurobehavioral ability (Storzbach et al., 2000). This finding suggested that either our psychosocial measures were more sensitive than our

Reprint requests to: Laurence M. Binder, Ph.D., 4900 S.W. Griffith Drive, Suite 244, Beaverton, Oregon 97005. E-mail: Larry_Binder@email.msn.com

neurobehavioral measures, or that the major psychological abnormality was distress and not neurocognitive deficit. As was true of the neurobehavioral finding of mental slowing, we found considerable heterogeneity in level of distress. Many with GWUI did not show psychometric evidence of elevated levels of psychosocial distress. We also found that subjective cognitive complaints were related to measures of psychosocial distress, but that subjective cognitive complaints were not related to objective cognitive findings (Binder et al., 1999). In an MMPI–2 study, we showed that there were significant elevations on several scales in veterans with GWUI although the mean elevations on Scales Hs and Hy were lower in GWUI than in a sample of nonveterans with well-documented conversion disorders (Binder et al., 2000). However, our unpublished MMPI-2 data showed profile heterogeneity among ill veterans.

The existing data described above indicated that GWUI was associated with heterogeneous neurobehavioral and psychological test findings and symptoms. Other investigators also provided evidence of heterogeneity of symptoms in GWUI (Iowa Persian Gulf Study Group, 1997; Persian Gulf Veterans Coordinating Board; Roy et al., 1998). Therefore, we decided to examine characteristics of subgroups of GWUI. Our unpublished medical and psychological data indicated that among the illnesses were chronic fatigue syndrome (CFS), fibromyalgia, posttraumatic stress, and depression. Veterans of the Persian Gulf War have complained of numerous psychological and somatic symptoms, including fatigue, since their return from their deployment in 1990–1991 (Persian Gulf Veterans Coordinating Board, 1995). Fatigue was reported by 27 to 30% of the enrollees in the Comprehensive Clinical Evaluation Program (Roy et al., 1998). Fatigue was one of the most common complaints in a telephone survey of Persian Gulf veterans (Iowa Persian Gulf Study Group, 1997). Other symptoms that are part of the revised criteria for CFS (Fukuda et al., 1994) including memory loss, sleep disorders, and joint pain also were common in Persian Gulf veterans (Persian Gulf Veterans Coordinating Board, 1995). Complaints of fatigue and weakness in this population had been linked to CFS by others (Amato et al., 1997). In the present study we elected to focus on Gulf War veterans with CFS.

Although the etiology of CFS in the general population is of unknown origin and may be psychiatric, it is clear that there are neuropsychological deficits associated with the illness (DiPino & Kane, 1996; Tiersky et al., 1997). Tiersky et al. concluded that complex information processing speed and efficiency were the primary areas of cognitive deficit. To our knowledge, no existing study of CFS included data on premorbid cognitive abilities or ruled out the possibility that the cognitive abnormalities of persons with CFS were developmental rather than a result of CFS. In previous neurobehavioral studies of CFS, investigators often have attempted to control for possible premorbid differences between CFS patients and control subjects by equating groups on demographic variables related to cognition such as age and education and current performance on measures thought to estimate premorbid cognitive abilities such as verbal intelligence or reading recognition. The purpose of the present study was to compare Gulf War veterans with and without CFS after controlling for actual premorbid cognitive ability rather than estimated premorbid ability. In order to accomplish this task we studied a subset of our GWUI sample who met criteria for CFS.

The present analyses were designed to examine the cognitive functioning of veterans with CFS and to compare it with control data obtained from asymptomatic veterans of the Gulf conflict of 1990–1991. Veterans were assessed with a computerized battery of cognitive tests (Kovera et al., 1996). We also obtained Armed Forces Qualification Test (AFQT; Welsh et al., 1990) data collected approximately at the time of military induction for a majority of our subjects, allowing us to partial out the effects of premorbid general cognitive ability differences. We hypothesized that cognitive deficits would exist among Gulf War veterans with CFS compared with Gulf War control participants after the effect of possible premorbid cognitive ability differences, as measured by the AFQT, was removed statistically.

METHODS

The Portland Environmental Hazards Research Center obtained from the Department of Defense (DOD) a list of names and addresses of all 8603 military veterans deployed to the Persian Gulf Between August 1, 1990 and July 31, 1991 from the states of Oregon and Washington. Questionnaires regarding symptoms and exposure to hazards were sent in 1995–1997 to 2022 randomly selected veterans. Females and persons deployed only for selected phases of the Persian Gulf War operations were oversampled. Females were oversampled to obtain a sufficient number of females to study the effects of the war on this subgroup. Persons deployed only for selected phases of the war were oversampled because they could not have been exposed to certain potentially toxic substances. For example, veterans who arrived in the Gulf after the war ended did not consume pyridostigmine bromide as a nerve gas prophylactic agent and they were exposed to oil well fires. We employed this sampling methodology to learn more about the effects of specific toxins in future studies. We received 1126 completed questionnaires for a 58% response rate. For various reasons such as present residence location, only 801 were eligible to participate in the clinical case–control study, of whom we evaluated a total of 443.

The 443 persons who responded to the questionnaire and who also volunteered for medical and psychological testing were classified by a multidisciplinary committee as cases or controls, or were excluded from the study. All controls were asymptomatic. Cases reported at least one of the following symptoms: fatigue, muscle or joint pain, psychological or cognitive complaints, gastrointestinal symptoms, or skin lesions. The case definition of GWUI required that symptoms (1) began during or after deployment to the Persian Gulf, (2) persisted for 1 month or longer, and (3) occurred during the 3 months prior to recruitment into the study. Participants were excluded if the history or clinical or laboratory findings indicated a known medical explanation for the symptom(s). The primary bases for exclusion were the occurrence of diabetes mellitus, malignancy, hepatitis B, hepatitis C, HIV infection, Lyme disease, autoimmune disease, neuromuscular disease, or other conditions associated with our major symptom categories, such as head injury with loss of consciousness, bipolar affective disorder, or schizophrenia for cognitive or psychological symptoms or current pain in an area of previous surgery for muscle or joint symptoms. In addition, Vietnam veterans were excluded from the study. Of the potential cases 19% were eliminated from the study because of the presence of an exclusionary illness or other reasons.

Volunteers participating in the clinical case–control study provided informed consent and were paid $50 to complete an evaluation, including physical examination with emphasis on neurological and musculoskeletal systems, health history gathering, collection of blood and urine samples, and neurobehavioral and psychological testing. Of the 178 participants who reported at least four symptoms of fatigue on the initial questionnaire, 130 were seen for clinical evaluations. Of these 130 participants, 27 either were found by medical examination not to have unexplained fatigue or onset of their symptoms antedated the Gulf War. Of the veterans with fatigue, 3 were doing shift work which resulted in fatigue, 2 had abnormal liver function, 1 had hypothyroidism, and 1 had diabetes; these veterans were excluded. One veteran had a dementia of unknown etiology and was excluded because of unreliable history data.

There were 45 cases who met the revised definition (Fukuda et al., 1994) of CFS. Of our 45 CFS cases, we obtained AFQT data on 32 (Welsh et al., 1990) from the time of induction into the military obtainable from the DOD. The AFQT is a group-administered series of subtests of verbal and nonverbal abilities yielding an aggregate percentile score that is used for placement purposes. Of our controls, 62 people had AFQT data available. These 32 veterans with CFS and 62 controls were the participants in the present study.

Psychological and cognitive testing was administered on Macintosh PowerBook computers by user-developed software (Anger et al., 1996; Campbell et al., 1999; Kovera et al., 1996). Responses were made on a nine-key DataSled response unit, an input apparatus that simplifies keyboard operation by placing the nine-key unit over a conventional PowerBook keyboard. The DataSled, pictured in Anger et al. (1996), reduced any possible advantage associated with previous computer keyboard experience. The test battery included measures of neurobehavioral (BARS) and psychosocial/emotional (HSS) functioning. The present study utilizes only the neurobehavioral data.

Our computerized battery of neurobehavioral tests consisted of measures of digit span forward and backward, reaction time, a symbol digit coding task, a supraspan digit learning task, a forced choice measure of recognition memory for 5-digit numbers (Oregon Dual Task Procedure) modeled after the Portland Digit Recognition Test (Binder, 1993), and a selective attention measure. We employed a computerized test battery in order to efficiently collect and automatically enter data into a database.

The 32 cases averaged 28.78 years of age ($SD = 4.09$) and 13.00 years of education ($SD = 1.11$). Control participants averaged 29.55 years of age ($SD = 5.13$) and 13.37 years of education ($SD = 1.47$). The two groups did not differ significantly on age [$F(1,92) = 0.538$, $p = .465$], or on education [$F(1,92) = 1.568$, $p = .214$]. AFQT percentile for cases averaged 55.06 ($SD = 15.58$) while controls averaged 66.10 ($SD = 19.45$). Cases performed significantly better on the AFQT than controls [$F(1,92) = 7.725$, $p = .007$]. The cases included 12 females (37.5%) and the controls included 6 females (9.7%; $\chi^2 = 10.55$, $p = .002$). We did not make adjustments for the larger proportion of females among cases because CFS is more common among females than among males; equating groups on gender might have biased the sample.

Only 71 of 94 participants responded to our computerized query about ethnic background. Of the 20 respondents among the cases, there were 17 Whites, 1 African American, 1 Asian/Pacific Islander, and 1 *other*. Among the 51 control respondents, there were 46 White, 1 African American, 3 Native Americans, and 1 Asian/Pacific Islander. Although we have no specific information on the ethnic background of the remaining 23 participants, casual observation leads us to suspect that the proportion of non-Whites was approximately as low as it was among those participants who responded to this question.

RESULTS AND DISCUSSION

AFQT scores and age and education had modest but significant correlational relationships with many of the dependent, neurobehavioral variables. Hence, we analyzed our data using ANCOVA with three covariates (AFQT, age, years of education). We employed eight neurobehavioral variables. Because we made multiple comparisons, we chose .01 as our significance level. Our hypotheses were unidirectional, making one-tailed tests appropriate. Data were analyzed first with ANOVA and then with ANCOVA. In order to determine the impact of the AFQT scores, age, and education on our results, we performed ANCOVA on the neurobehavioral scores. As expected, p values were smaller in all cases with ANCOVA than with the ANOVA. However, ANCOVA did not reduce previously significant findings to nonsignificance on any variable.

As shown in Table 1, differences between groups with ANCOVA were significant at the .01 level for reaction time, ODTP latency, and ODTP number correct. Differences between groups for the other five variables were in the expected direction, but they were nonsignificant. Although the proportion of females differed significantly between groups, there were no significant gender differences on any dependent variable or on the AFQT.

https://doi.org/10.1017/S1355617701777065 Published online by Cambridge University Press

Table 1. Unadjusted means and standard deviations and ANCOVA *F* and *p* values

	Cases		Controls			
Measure	*M*	*SD*	*M*	*SD*	*F*	*p*
Digit Span Forward	5.97	1.15	6.60	1.58	1.52	.110
Digit Span Backward	5.28	1.89	6.00	2.17	0.75	.195
Reaction Time	348.94	76.87	311.68	53.25	6.31	.007
Symbol Digit Latency	1736.16	338.21	1676.29	337.19	0.08	.391
Serial Digit Learning	16.13	6.03	18.43	4.94	1.27	.132
ODTP Median Latency	1958.17	505.42	1702.30	355.43	6.42	.007
ODTP Total Correct	46.28	2.64	47.56	.074	9.20	.002
SAT Proportion Correct	.86	.17	.92	.09	4.27	.021

Note. ODTP = Oregon Dual Task Procedure, SAT = Selective Attention Test. *p* = one-tailed *p*. Reaction Time, Symbol Digit Latency, and ODTP Median Latency are in milliseconds.

Our results, corrected for age, education, and premorbid cognitive ability as measured by the AFQT, demonstrated that participants who were diagnosed with CFS performed less well than healthy veterans of the Persian Gulf War on three of eight neurobehavioral variables. We found differences on some measures of attention and mental processing speed. Our measure of digit learning did not yield a significant difference, but there was a group difference in number correct on the ODTP. Our findings appear to be consistent with findings in nonveteran CFS samples as reviewed recently (DiPino & Kane, 1996; Tiersky et al., 1997).

Our original rationale for employing a forced choice test, the ODTP, was to assess the validity of the effort of subjects on the neurobehavioral measures (Binder, 1993). Although the ODTP yielded a statistically significant difference in number correct, this does not imply that the cases were more prone to exaggerate a memory problem than the controls. Our cases averaged 96.4% correct on the ODTP compared with 99.1% correct for controls, a trivial difference. None of the participants fell near the range associated with motivation to perform poorly of 61% correct or less on the noncomputerized version of the ODTP, the Portland Digit Recognition Test (Binder & Kelly, 1996). We are unsure what cognitive domains are measured by the ODTP although we have labeled it a dual task procedure.

Previous studies have found neuropsychological deficits in persons with GWUI (Storzbach et al., 2001; Goldstein et al., 1996; Hom et al., 1997). GWUI is characterized by symptom heterogeneity (Persian Gulf Veterans Coordinating Board, 1995). The present study demonstrated deficits in a subgroup of GWUI veterans suffering from CFS.

A strength of these analyses was that we tested participants who were not obtained clinically. Although at the present time we have no data comparing persons who volunteered to persons who declined to participate, all participants were community dwelling volunteers. Essentially, this was a nonclinical sample. It is not surprising that the neurobehavioral performance of participants who meet CFS criteria was inferior to healthy controls. The unanswered question is the etiology of CFS (Tiersky et al., 1997).

Our study may have had some limitations. Because we employed a computerized battery in order to efficiently collect and analyze data, the memory measures that we employed may not be as sensitive as memory measures administered by an examiner. Our conclusions regarding the effect of premorbid mental ability are limited to the domains measured by the AFQT, a test battery that does not include the same sort of tasks as our computerized test battery. We are assuming that our subjects were free of CFS at the time of military induction because they reported that symptoms began during or after the Gulf War. If some subjects were ill at the time they were inducted, we do not believe that our conclusions are altered in any significant way.

In summary, we found premorbid ability differences as measured by the AFQT between CFS cases and controls. However, the mild cognitive deficits in our CFS sample were not attributable to premorbid cognitive differences. To our knowledge, this is the first study of CFS cognition that has controlled for performance on a standardized test of mental abilities administered prior to onset of the illness. We have employed the term *Gulf War unexplained illnesses* to describe a heterogenous set of somatic and psychological complaints associated with service in the Gulf War. CFS is one of several illnesses suffered by some veterans of the war. GWUI researchers also are studying other conditions including fibromyalgia and posttraumatic stress.

ACKNOWLEDGMENTS

Funding for this project was received from the Department of Veterans Affairs. This paper is in the public domain.

REFERENCES

Amato, A.A., McVey, A., Cha, C., Matthews, E.C., Jackson, C.E., Kleinegunther, R., Worley, L., Cornman, E., & Kagan-Hallet, K. (1997). Evaluation of neuromuscular symptoms in veterans of the Persian Gulf War. *Neurology*, *48*, 4–12.

Anger, W.K., Rohlman, D.S., Sizemore, O.J., Kovera, C.A., Albertini, M., & Ger, J. (1996). Human behavioral assessment in neurotoxicology: Producing appropriate test performance with written and shaping instructions. *Neurotoxicology and Teratology*, *18*, 371–379.

Anger, W.K., Storzbach, D., Binder, L.M., Campbell, K.A., Rohlman, D.S., McCauley, L., Kovera, C.A., Davis, K.L., & members of the Portland Environmental Hazards Research Center. (1999). Neurobehavioral deficits in Persian Gulf veterans: Evidence from a population-based study. *Journal of the International Neuropsychological Society*, *5*, 203–212.

Binder, L.M. (1993). Assessment of malingering after mild head trauma with the Portland Digit Recognition Test. *Journal of Clinical and Experimental Neuropsychology*, *15*, 170–182.

Binder, L.M. & Kelly, M.P. (1996). Portland Digit Recognition Test performance by brain dysfunction patients without financial incentives. *Assessment*, *3*, 403–409.

Binder, L.M., Storzbach, D., Anger, W. K., Campbell, K.A., Rohlman, D.S., & members of the Portland Environmental Hazards Research Center. (1999). Subjective cognitive complaints, affective distress, and objective cognitive performance in Persian Gulf War veterans. *Archives of Clinical Neuropsychology*, *14*, 531–536.

Binder, L.M., Storzbach, D., Campbell, K.A., Rohlman, D.S., Anger, W.K., Salinsky, M.C., Campbell, B.M., Mueller, R., and members of the Portland Environmental Hazards Center. (2000). Comparison of MMPI–2 profiles of Gulf War veterans with epileptic and nonepileptic seizure patients. *Assessment*, *7*, 73–78.

Campbell, K.A., Binder, L.M., Rohlman, D.S. Anger, W.K., & Storzbach, D. (1999). Test–retest reliability of a computerized test battery. *Assessment*, *6*, 21–32.

DiPino, R.K. & Kane, R.L. (1996). Neurocognitive functioning in Chronic Fatigue Syndrome. *Neuropsychology Review*, *6*, 47–60.

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

Goldstein, G., Beers, S.R., Morrow, L.A., Shemanski, W.J., & Steinhauer, S.R. (1996). A preliminary neuropsychological study of Persian Gulf Veterans. *Journal of the International Neuropsychological Society*, *2*, 368–371.

Hom, J., Haley, R.W., & Kurt, T.L. (1997). Neuropsychological correlates of Gulf War Syndrome. *Archives of Clinical Neuropsychology*, *12*, 531–544.

Iowa Persian Gulf Study Group. (1997). Self-reported illness and health status among Gulf War veterans. *Journal of the American Medical Association*, *277*, 238–245.

Kovera, C.A., Anger, W.K., Campbell, K.A., Binder, L.M., Storzbach, D., Davis, K.L., & Rohlman, D. (1996). Computer-administration of questionnaires: A health screening system (HSS) developed for veterans. *Neurotoxicology and Teratology*, *18*, 511–518.

Persian Gulf Veterans Coordinating Board. (1995). Unexplained illnesses among Desert Storm veterans. *Archives of Internal Medicine*, *155*, 262–268.

Roy, M.J., Koslowe, P.A., Kroenke, K., & Magruder, C. (1998). Signs, symptoms, and ill-defined conditions in Persian Gulf War veterans: Findings from the comprehensive clinical evaluation program. *Psychosomatic Medicine*, *60*, 663–668.

Storzbach, D., Campbell, K., Anger, W.K., Binder, L.M., Rohlman, D., McCauley, L., & members of the Portland Environmental Hazards Research Center. (2000). Psychological differences between veterans with and without Persian Gulf War unexplained symptoms. *Psychosomatic Medicine*, *62*, 726–735.

Storzbach, D., Rohlman, D., Anger, W.K., Binder, L.M., Campbell, K., & members of the Portland Environmental Hazards Research Center. (2001). Neurobehavioral deficits in Persian Gulf Veterans: Additional evidence from a population-based study. *Environmental Research*, *85*, 1–13.

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.

Welsh, J.R., Kucinkas, S.K., & Curran, L.T. (1990). *Armed Services Vocational Battery (ASVAB): Integrative review of validity studies*. Brooks Air Force Base, TX: Air Force Human Resources Laboratory.