Neuropsychological Outcomes of Army Personnel Following Deployment to the Iraq War

Jennifer J. Vasterling, PhD
Susan P. Proctor, DSc
Paul Amoroso, MD, MPH
Robert Kane, PhD
Timothy Heeren, PhD
Roberta F. White, PhD

Context The effects of war-zone deployment on neuropsychological health remain poorly understood. Neuropsychological performance deficits serve as sensitive measures of neural dysfunction and are often associated with psychosocial and occupational problems. Previous studies have not conducted objective neuropsychological assessments both before and after a major war-zone deployment.

Objective To examine objective neuropsychological outcomes of Iraq War deployment in a large military cohort.

Design, Setting, and Participants The Neurocognition Deployment Health Study, a prospective, cohort-controlled study conducted at military installations. This report centers on 961 male and female active-duty Army soldiers drawn from the larger cohort. Deploying Army soldiers (n=654) were examined prior to deployment to Iraq (April-December 2003) and shortly after return (within a mean of 73 days [median, 75 days]; January-May 2005) from Iraq deployment. A comparison group of soldiers (n=307) similar in military characteristics but not deploying overseas during the study was assessed in sessions timed to be as close as possible to the assessment of deployers. Military unit sampling procedures facilitated representation of combat, combat support, and combat service support functions among both deployers and nondeployers.

Main Outcome Measures Individually administered, performance-based neuropsychological tasks. Estimates (β; the unstandardized parameter estimate) for the absolute differences in adjusted mean outcome scores between deployed and nondeployed groups were determined using generalized estimating equations.

Results Multiple linear regression analyses adjusted for battalion membership revealed that Iraq deployment, compared with nondeployment, was associated with neuropsychological compromise on tasks of sustained attention ($\beta=0.11$; $P<.001$), verbal learning ($\beta=-1.51$; $P=.003$), and visual-spatial memory ($\beta=-3.82$; $P<.001$). Iraq deployment was also associated with increased negative state affect on measures of confusion ($\beta=1.40$; $P<.001$) and tension ($\beta=1.24$; $P<.001$). In contrast, deployment was associated with improved simple reaction time ($\beta=4.30$; $P=.003$). Deployment effects remained statistically significant after taking into account deployment-related head injury and stress and depression symptoms.

Conclusions Deployment to Iraq is associated with increased risk of neuropsychological compromise. Findings point to the need to investigate further the impact of deployment on neural functioning. Public health implications include consideration of neuropsychological compromise in health prevention and postdeployment clinical and occupational management.

JAMA. 2006;296:519-529 www.jama.com

Since early 2003, significant numbers of military personnel have deployed in support of Operation Iraqi Freedom (OIF). Although contemporary battlefield measures[1] have improved war-zone survival, success in preventing fatalities has not eliminated adverse physical or mental[2,3] health consequences. One major war-related health risk is brain dysfunction.

Brain dysfunction is often indicated by neuropsychological (ie, cognitive and emotional) impairment. In past military conflicts, cognitive impairment figured prominently among veteran health complaints, ranking fourth among 1991 Gulf War veterans in government health registries.[4] Because of its potential negative impact on occupational and psychosocial functioning[5-7] in a predominantly young population, war-related neuropsychological impairment has significant public health implications.

Yet, the consequences of war-zone deployment on neuropsychological health remain poorly understood. Knowledge gaps stem largely from a lack of baseline (predeployment) health information, reliance in large studies on

For editorial comment see p 574.

Author Affiliations: Southeast Louisiana Veterans Health Care System and Tulane University School of Medicine, New Orleans (Dr Vasterling); VA Boston Healthcare System and Boston University School of Public Health, Boston, Mass (Drs Proctor, Heeren, and White); US Army Research Institute of Environmental Medicine, Natick, Mass (Dr Proctor); Madigan Army Medical Center, Fort Lewis, Wash (Dr Amoroso); and VA Maryland Health Care System and University of Maryland School of Medicine, Baltimore (Dr Kane).
Corresponding Author: Jennifer J. Vasterling, PhD, Research Service (COSF), Southeast Louisiana Veterans Health Care System, 1601 Perdido St, New Orleans, LA 70112 (jvaster@tulane.edu).

©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Dartmouth College User on 06/05/2014

subjective outcome indices, assessments conducted long (sometimes years) after war-zone exposure, and infrequent use of appropriate nondeployed comparison samples.

Our study objective was to examine neuropsychological outcomes following Iraq deployment. The study incorporated a prospective, cohort-controlled design measuring subjective and objective neuropsychological outcomes in US Army soldiers deploying to Iraq. Army soldiers with similar military characteristics from units not deploying overseas comprise the comparison group. Based on the anticipation that Iraq deployment would involve risks of neuropsychological compromise (eg, environmental exposures, prolonged physiological arousal associated with survival responses, head injury), we hypothesized that deployment would be associated with adverse neuropsychological outcomes.

METHODS

Study Population and Design

Human subjects approval was obtained from human subjects research review boards of the Army, Tulane University Health Sciences Center, and the Department of Veterans Affairs. All participants provided written informed consent prior to participation.

The target population was male and female active duty US Army soldiers serving between April 2003 and June 2005. Participants were categorized by their deployment status during the study period: those deployed to Iraq and those not deployed overseas. Military units at high likelihood of deployment during the study period were assessed prior to deployment to Iraq (time 1, between April and December 2003) and again following their return (time 2, between January and May 2005). Although military unit deployment status during the study period could be anticipated, each unit's and participant's deployment was subject to evolving military operational requirements and could not be verified until time 2. Units at low likelihood of Iraq deployment during the study were also assessed twice, at periods timed to be as close as possible to their deploying counterparts. At time 1, most deployers belonged to units that were anticipated to deploy to Iraq within 75 days and were functioning under conditions of increased operational demands. Because nondeployers were preparing for extended intensive desert training within the continental United States, they were also functioning at increased operational tempo.

Sampling

To capture heterogeneous deployment experiences and geographic separation within the war zone, unit selection was based on a modified categorization procedure.[8] Deploying and nondeploying units represented combat, combat support, and combat service support functions and were well matched in these attributes. Battalion-level units originated from Fort Hood, Texas, and Fort Lewis, Washington. Battalion leaders were asked to refer potential participants at random (eg, every third name on the unit roster) to facilitate a sample representative of the battalion.

Potential participants consented individually and were provided with a way to exit the study area unobserved if they declined to participate. Study volunteers were excluded if pending separation from service or reassignment to another installation at time 1 or if unable to complete the study protocol because of physical limitations (eg, a broken hand). In addition, time 1 participants no longer at their originating military installations were invited to complete the survey portion of the protocol via mail but are not included in the analyses because of the infeasibility of collecting primary performance-based neurobehavioral outcome measures without in-person administration.

Sample size determinations were calculated taking into consideration statistical power and possible attrition from time 1 to time 2. Estimated attrition (20%) was based on anticipation of atypical deployment durations and military discharges. Using attentional data from a previous deployment study, calculations determined that a sample of 600 deployed and 300 nondeployed soldiers (adjusted for attrition) would provide 80% power to detect average change between the 2 groups corresponding to a small to medium effect size of 0.29 at the .05 significance level after Bonferroni adjustment for 10 comparisons ($P \leq .005$).

Assessment Protocol

Comprehensive description of primary assessment data and secondary data obtained from automated military databases has been published elsewhere.[9] Measures relevant to hypotheses addressed in this report follow.

Demographic, Neuromedical, and Historical Information. Each assessment documented current demographic and military information (eg, age, rank), risk factors for neuropsychological disorders (eg, history of neurodevelopmental disorders, psychiatric disorders, brain injury), and situational factors (eg, recent sleep and alcohol use) potentially affecting neuropsychological performance. Self-reported race/ethnicity data were gathered to help gauge the representativeness of the sample. At time 2, deployed participants were interviewed about their locations while in Iraq.

Performance-Based Neuropsychological Tests. Although neuropsychological measures applied in clinical contexts are typically interpreted using deviations from normative values to form localized or syndromal diagnoses.[10,11] However, epidemiological studies use neuropsychological measures as continuous outcomes to identify relationships in populations between exposures and performance patterns indicative of brain dysfunction,[12,13] documenting subtle population shifts at scores frequently falling short of the range of clinical impairment.

Test battery selection emphasized continuous outcome measures and construct domains (sustained attention, working memory/executive functioning, fine motor speed, verbal and visual learning and memory, reaction time, and cognitive efficiency) sensitive to stress-related disorders and neurotoxicant exposures (TABLE 1).

 ©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Dartmouth College User on 06/05/2014

Computer-assisted tasks were derived from the Automated Neuropsychological Assessment Metric (ANAM)[19] and the Neurobehavioral Evaluation System, third edition (NES3)[20,21] and required button-press responses. For the ANAM, scores reflecting accuracy and response time ("throughput") were created to measure a reaction time variable and cognitive efficiency across other neuropsychological domains. Motor speed was measured by mean taps per 10-second interval on ANAM tapping. The NES3 Continuous Performance Task is a sustained (approximately 8-minute) attention task requiring detection of targets from a random sequence of distractor stimuli.

Non–computer administered tasks included the Trailmaking Test,[22] the Wechsler Memory Scale, third edition (WMS3)[16] Verbal Paired Associates (requiring learning and subsequent recall of unrelated word pairs), and the WMS[23] Visual Reproductions (requiring reproduction of 2-dimensional geometric designs from memory immediately after their presentation and after a delayed interval). For the Trailmaking Test, time to complete Part A (drawing lines between numerals in sequential order) was subtracted from time to complete Part B (drawing lines between sequential numbers and letters in alternation). The subtraction procedure parcels out basic attentional, speed, and visual tracking skills, resulting in a better measure of working memory and cognitive flexibility. For the WMS3 Verbal Paired Associates and WMS Visual Reproductions, the percentage of retention (Verbal Paired Associates: delayed recall/trial 4

Table 1. Description of Outcome Measures

Instrument	Domain Assessed	Variables	Possible Score Range	Normative/ Reference Group Mean (SD)[14-18]*
Subjective outcome indices				
MOS-CF	Self-reported impact of cognitive problems on daily functioning	Derived, 4-item composite score	Standardized to 0-100	82.4 (16.5)†
POMS	Self-reported state affect: anger, depression, confusion, fatigue, tension, vigor	Summary T scores	Standardized to 30-80	50 (10)
Attention, working memory, executive				
Trailmaking B–A	Working memory/executive functioning	Log-transformed time (s) to completion	NA	NA
NES3 CPT	Sustaining attention/vigilance over time; target detection	Log-transformed No. of omission errors, No. of commission errors	NA	NA
Learning and memory				
WMS3 Verbal Paired Associates I	Verbal-auditory learning	Total correct, trials 1-4	0-32	19-21‡
WMS3 Verbal Paired Associates II	Verbal-auditory memory over time	% retention (II/trial 4 × 100)	0-100	NA
WMS Visual Reproductions I	Visual-spatial short-term design recall	Accurate elements, cards A-C, immediate	0-14	10.48 (1.93)
WMS Visual Reproductions II	Visual-spatial memory over time	% retention (II/I × 100)	0-100	NA
Simple reaction time				
ANAM simple reaction time	Reaction time to simple, recurring stimulus	Throughput score§	NA	218.3 (33.7)
Cognitive efficiency				
ANAM code substitution, learning	Efficiency in matching digit-symbol pairs	Throughput score§	NA	46.4 (9.7)
ANAM code substitution, delay	Efficiency recognizing digit-symbol pairs from memory	Throughput score§	NA	42.4 (12)
ANAM matching to sample	Efficiency of design recognition memory	Throughput score§	NA	37.8 (12)
ANAM logical relations	Efficiency in reasoning	Throughput score§	NA	NA
ANAM mathematical processing	Efficiency performing simple mental computations	Throughput score§	NA	18.7 (6.3)
ANAM running memory	Efficiency of working memory	Throughput score§	NA	NA
Fine motor speed				
ANAM tapping (right, left)	Fine motor speed: dominant and nondominant hands	Mean No. of finger taps in 10 s across 2 trials	NA	NA

Abbreviations: ANAM, Automated Neuropsychological Assessment Metric; NA, not applicable; MOS-CF, Medical Outcomes Study Cognitive Functioning Scale; NES3 CPT, Neurobehavioral Evaluation System, third edition, Continuous Performance Task; POMS, Profile of Mood States; WMS, Wechsler Memory Scale; WMS3, Wechsler Memory Scale, third edition.
*Normative data are not available for log-transformed scores or for scores derived from subtraction and ratio computations.
†Normative data are based on the 6-item version.
‡Range that produces a scaled score of 10 for normative reference group.
§Throughput scores reflect efficiency (ie, speed in the context of accuracy).

©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Dartmouth College User on 06/05/2014

recall × 100; Visual Reproductions: delayed recall/immediate recall × 100;) reflects how well information was remembered over time.

All scores were free of subjective judgment except for WMS Visual Reproductions, in which designs drawn from memory were scored by a rater according to set criteria. Although the primary rater was aware of deployment status, 10% to 15% of a randomly selected sample of drawings from each assessment episode were also scored by a second rater blinded to deployment status. Intraclass correlations (0.78-0.95) indicated high interrater reliability.

Deployment Experiences, Emotional Distress, and Functional Neurocognitive Health Perception. Deployment experiences were quantified by a modified version of the Deployment Risk and Resilience Inventory (DRRI).[24] State affect, commonly affected by neurotoxicant exposure[10,25] was measured with the Profile of Mood States (POMS).[15] Persistent stress and depression symptom severity, assessed as potential covariates in outcome analyses, were quantified by the PTSD Checklist (PCL)[26,27] and the Center for Epidemiological Studies Depression Inventory, 9-item version (CES-D),[28,29] respectively. The 4-item version of the Medical Outcomes Study Cognitive Functioning Scale (MOS-CF)[14] assessed functional neurocognitive health perception. The DRRI, POMS, PCL, CES-D, and MOS-CF are all psychometric self-report inventories yielding continuous variables. Although cut-point scores can be applied to the PCL and CES-D as crude screening estimates, neither instrument yields clinical diagnoses.

Assessment of Response Validity. Validity of response profiles on questionnaires was assessed via inspection of scales with bidirectional items (eg, a score of 5 endorses pathological functioning on some items and intact functioning on others). If a respondent provided all extreme responses in the same direction on a scale with bidirectional items, that respondent's data were not analyzed. The Test of Memory and Malingering,[30] trial 1, was administered to assess cognitive engagement. Data from participants scoring below 38, a cutoff found to show reasonable sensitivity and specificity in detecting insufficient effort on neurobehavioral tasks,[31] were also excluded from analyses.

Procedures

Assessments were conducted at military installations by a civilian examiner team. All performance-based neuropsychological measures were individually administered according to scripted, standardized instructions. Participants completed the paper-and-pencil surveys in small groups. Examiners and participants were typically aware of each participant's anticipated deployment status at time 1 and actual deployment status at time 2.

Statistical Analyses

When data distributions departed significantly from normal, raw scores were normalized via logarithmic transformation. POMS summary scores were converted to sex-based T scores. Missing values for specific items on questionnaires (occurring in <3% of cases) were replaced by the mean value of the individual's completed items for that measure if the participant responded to at least 50% of the items. If fewer than 50% of the items on a measure were completed, summary scores were not computed. Outliers were truncated at 3 SDs from the mean.

Baseline characteristics and differences between time 2 respondents and nonrespondents were examined via *t* test or χ^2 test, as appropriate. To examine primary hypotheses, we used SAS software, version 8 (SAS Institute Inc, Cary, NC) to fit a generalized estimating equation linear regression model for each time 2 outcome variable. The study incorporated a cluster-sampling design, with participants sampled within battalion-level military units. The generalized estimating equation regression accounts for correlation in responses among participants from the same battalions to adjust for the multilevel structure of the sampling plan. Deployment status (deployed vs nondeployed) served as the independent variable of interest. To account for initial levels of outcomes, the time 1 value for the time 2 outcome measure of interest was entered as a covariate in each model. Age at time 1, sex, years of education, average hours of sleep per day in the week prior to time 2 assessment, and average number of standardized alcoholic drinks consumed per week during the month prior to time 2 assessment were also included as covariates because of their potential influence on cognitive performances. The model resulting from this covariate set is the core model.

Significance levels were adjusted via Bonferroni corrections to avoid type I error. Sixteen neurobehavioral outcome and 7 subjective outcome measures were considered, resulting in an adjusted significance level of $P = .003$ (.05/16) for neurobehavioral data and $P = .007$ (.05/7) for subjective data.

Because of the potential for stress-related symptoms and head injury to modify deployment-related outcomes, the core outcome analyses were repeated in 3 sets with PCL summary scores, CES-D summary scores, or head injury with loss of consciousness incurred between time 1 and time 2 included as a covariate.

RESULTS

Sample Characteristics

At time 1, approximately 94% (n = 1368) of the 1457 invited soldiers volunteered participation. At time 2, soldiers assessed at time 1 who remained assigned to units located at the same military installation were again invited to participate in the full study protocol. Of the 1368 soldiers assessed at time 1, approximately 75% (72% from deployed units and 80% from nondeployed units) participated in the on-site assessment at time 2. The predominant reason for nonparticipation at time 2 was separation from service (TABLE 2). Of the 1028 time 2 participants, 26 completed questionnaires but did not complete performance tasks because of scheduling conflicts and were excluded from the analyses. Twenty-six participants were excluded for invalid questionnaire re-

 ©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Dartmouth College User on 06/05/2014

sponses and 15 for questionable cognitive effort, resulting in a final sample of 961. All but 23 deployers examined predeployment and postdeployment served a 12-month OIF rotation.

In the final sample, 654 participants were categorized as deploying and 307 as nondeploying. Postdeployment assessments occurred a mean of 73.4 (SD, 19.8) days (median, 75 days; interquartile range, 58-84 days) from each participant's return from Iraq, except for 19 soldiers who returned early.

Participants in the final sample (TABLE 3) generally reflected the broader OIF-deployed Army population. Women were slightly underrepresented compared with the expected proportion of contemporaneously deployed Army women. Although enlisted personnel constitute the majority of deployers, commissioned officers were nonetheless underrepresented in the sample. At time 1, 11% had participated in a prior major overseas operational deployment (3% in 2001 or later). The most prevalent military occupational categories were infantry/gun crew (35%), communication/intelligence (19%), electrical/mechanical equipment repair (13%), and service supply (9%).

Comparison of Time 2 Respondents and Nonrespondents

Nondeployers (80%) were somewhat more likely than deployers (72%) to participate at time 2 ($P=.002$). Among both deployers and nondeployers, time 2 respondents and nonrespondents did not differ at time 1 in age, marital status, years of formal education, years served in the Army, self-reported race/ethnicity, or most baseline values of subjective and objective outcome measures. Among deployers, nonrespondents at time 2 were more likely at time 1 to be female (18% vs 8%; $P<.001$), to be officers (6% vs 2%; $P<.001$), to report more fatigue on the POMS ($P=.04$), and to perform less proficiently on simple reaction time ($P=.02$) but more proficiently on the WMS Visual Reproductions immediate recall ($P=.002$). Among nondeployers, nonrespondents at time 2 were more likely at time 1 to be female (24% vs 9%; $P<.001$) and to describe themselves as racial/ethnic minorities (48% vs 35%; $P=.02$). In sum, there were few differences between respondents and nonrespondents, especially on time 1 outcome measures.

Table 2. Reasons for Nonparticipation at Time 2 by Deployment Status

Reason for Time 2 Nonparticipation	Time 2 Nonrespondents, No. (%)		
	Deployed Units (n = 270)	Nondeployed Units (n = 79)	Total (n = 349)
Separation from military service	134 (49.6)	53 (67.1)	187 (53.6)
Reassignment to another military unit	44 (16.2)	12 (15.2)	56 (16.0)
On leave/at training/on special assignment	38 (14.1)	6 (7.6)	44 (12.6)
Declined	7 (2.6)	5 (6.3)	12 (3.4)
Still deployed	6 (2.2)	1 (1.3)*	7 (2.0)
Deactivated	5 (1.9)	0	5 (1.4)
Sick/injured	3 (1.1)	1 (1.3)	4 (1.1)
Deceased	3 (1.1)	1 (1.3)	4 (1.1)
Unknown	30 (11.1)	0	30 (8.6)

*Although the participant's unit did not deploy during the study as a group, the participant was deployed as an individual.

Table 3. Demographic and Contextual Sample Characteristics at Time 1*

Variable	Deployed (n = 654)	Nondeployed (n = 307)	Total (N = 961)
Age, mean (SD), y	25.0 (5.3)	24.9 (5.1)	25.0 (5.2)
Race/ethnicity†	285 (43.6)	105 (34.5)	390 (40.7)
White	369 (56.4)	199 (65.5)	568 (59.3)
African American	106 (16.2)	43 (14.1)	149 (15.6)
Hispanic American	96 (14.7)	27 (8.9)	123 (12.8)
Asian American	17 (2.6)	15 (4.9)	32 (3.3)
Other	66 (10.1)	20 (6.6)	86 (9.0)
Women	54 (8.3)	28 (9.1)	82 (8.5)
Education, mean (SD), y	12.5 (1.3)	12.5 (1.3)	12.5 (1.3)
Years in Army, mean (SD)	4.1 (4.2)	3.9 (3.8)	4.0 (4.1)
Rank (enlisted)	641 (98.0)	300 (97.7)	941 (97.9)
Junior enlisted (E1-E4)	479 (73.2)	231 (75.2)	710 (73.9)
Noncommissioned officers (E5-E9)	162 (24.8)	69 (22.5)	231 (24.0)
Officers (commissioned or warrant)	13 (2.0)	7 (2.3)	20 (2.1)
Previous operational deployment	72 (11.0)	33 (12.1)	105 (11.4)
Married	297 (45.4)	146 (47.6)	443 (46.1)
Sleep per night in past wk, mean (SD), h	5.9 (1.3)	5.9 (1.2)	5.9 (1.3)
Alcoholic drinks consumed per wk in past mo, mean (SD)	8.0 (11.9)	8.1 (12.4)	8.1 (12.1)
Current cigarette smokers	311 (47.6)	136 (44.3)	447 (46.5)
Reported taking medication (prescribed or over the counter) in past 48 h	184 (28.1)	99 (32.2)	283 (29.4)
Reported taking prescribed psychoactive or anticonvulsant medications in past 48 h	11 (1.7)	4 (1.3)	15 (1.6)
Reported developmental disorder	81 (12.4)	46 (15.3)	127 (13.3)
Reported psychiatric disorder	41 (6.3)	18 (5.9)	59 (6.2)
Reported past alcohol use disorder	27 (4.2)	10 (3.3)	37 (3.9)
Reported prior head injury with loss of consciousness >15 min	35 (5.4)	22 (7.3)	57 (6.0)
Reported other neuromedical disorder	19 (3.0)	8 (2.7)	27 (2.9)

*Data are expressed as No. (%) unless otherwise noted. The sample size varies slightly across observations because of missing data.
†$P<.01$.

©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Dartmouth College User on 06/05/2014

Baseline Comparison of Deployers and Nondeployers

Deployed and nondeployed participants did not differ at time 1 on demographic or contextual variables (eg, sleep, developmental disorders, alcohol consumption) (Table 3), with the exception that nondeployers more frequently identified themselves as racial/ethnic minorities ($P=.008$). The 2 groups did not differ at time 1 on neurobehavioral or emotional measures (TABLE 4) except that deployers performed more poorly on the WMS Visual Reproductions immediate recall ($P<.001$) than nondeployers.

Table 4. Scores on Primary Outcome Measures and Emotional Covariates at Time 1 and Time 2 Among Deployed and Nondeployed Participants*

	Mean (SD)			
	Time 1		Time 2	
Outcome Variable	Deployed	Nondeployed	Deployed	Nondeployed
Subjective outcome indices				
MOS-CF	78.07 (19.90)	77.68 (19.45)	73.53 (21.01)	75.42 (21.59)
POMS anger, T score†	48.76 (9.36)	48.76 (9.78)	48.20 (9.33)	48.60 (10.21)
POMS depression, T score†	41.63 (7.09)	41.37 (7.14)	41.19 (6.91)	41.26 (7.33)
POMS confusion, T score†	42.29 (7.23)	42.07 (6.85)	43.43 (7.18)	42.02 (7.37)
POMS fatigue, T score†	47.37 (7.94)	46.71 (7.24)	47.61 (7.90)	47.36 (8.15)
POMS tension, T score†	39.81 (7.46)	39.26 (7.08)	40.28 (7.50)	38.89 (7.36)
POMS vigor, T score	55.10 (10.11)	56.14 (10.05)	53.82 (9.20)	54.62 (9.58)
Attention, working memory, executive				
Trailmaking B–A, s†‡	0.81 (0.32)	0.82 (0.31)	0.81 (0.29)	0.83 (0.30)
NES3 CPT, commission errors†‡	0.54 (0.54)	0.57 (0.57)	0.52 (0.57)	0.49 (0.53)
NES3 CPT, omission errors†‡	0.29 (0.52)	0.24 (0.46)	0.27 (0.50)	0.16 (0.38)
Learning and memory				
Verbal				
WMS3 Verbal Paired Associates, learning trials, No. correct	18.44 (7.11)	17.73 (6.56)	20.04 (7.31)	21.30 (6.63)
WMS3 Verbal Paired Associates, % retention	90.11 (16.78)	88.67 (17.10)	91.13 (15.52)	92.01 (13.90)
Visual-spatial				
WMS Visual Reproductions, immediate recall	9.29 (2.18)	9.93 (2.24)	5.56 (1.76)	6.74 (1.87)
WMS Visual Reproductions, % retention	91.05 (12.26)	92.79 (10.51)	86.68 (19.69)	90.98 (14.03)
Simple reaction time				
ANAM simple reaction time throughput	181.34 (27.30)	184.60 (28.66)	182.92 (29.08)	179.94 (23.47)
Cognitive efficiency				
ANAM code substitution, learning throughput	52.11 (9.51)	52.73 (8.93)	54.58 (9.90)	55.70 (8.76)
ANAM code substitution, delay throughput	53.74 (13.19)	54.62 (12.68)	56.35 (12.30)	56.73 (11.62)
ANAM matching to sample throughput	32.14 (10.59)	32.45 (10.67)	32.66 (10.88)	33.45 (10.69)
ANAM logical relations throughput	23.75 (7.37)	24.45 (7.80)	25.25 (7.71)	25.56 (8.41)
ANAM mathematical processing throughput	21.08 (5.91)	20.80 (5.71)	21.39 (6.15)	21.50 (6.21)
ANAM running memory throughput	93.76 (18.22)	94.71 (18.67)	95.40 (18.86)	96.81 (16.71)
Fine motor speed				
ANAM tapping (dominant), mean No. of taps	59.23 (7.49)	58.51 (7.93)	59.70 (7.79)	59.49 (8.38)
ANAM tapping (nondominant), mean No. of taps	53.63 (6.94)	53.30 (7.75)	54.35 (7.53)	54.03 (7.76)
Emotional covariates				
PCL summary scores	29.12 (12.37)	29.62 (13.12)	32.30 (13.13)	29.20 (13.00)
CES-D summary scores	§	§	7.25 (5.26)	7.08 (5.64)

Abbreviations: ANAM, Automated Neuropsychological Assessment Metric; CES-D, Center for Epidemiological Studies Depression Inventory; MOS-CF, Medical Outcomes Study Cognitive Functioning Scale; NES3 CPT, Neurobehavioral Evaluation System, third edition, Continuous Performance Task; PCL, PTSD Checklist; POMS, Profile of Mood States; WMS, Wechsler Memory Scale; WMS3, Wechsler Memory Scale, third edition.

*The sample size varies slightly across observations because of missing data (n = 950-960, except for ANAM mathematical processing and running memory, n = 923-936).

†Lower scores reflect better functioning.

‡Log-transformed.

§The CES-D was not administered at time 1.

Test-Retest Interval

The interval between time 1 and time 2 for deployers was greater than for nondeployers (mean, 16.9 [SD, 3.1] months vs 8.3 [SD, 2.2] months; $P<.001$). This was attributable to scheduling time 2 testing for nondeployers early enough to avoid possible early deployment and an unanticipated delay in deployment for 1 of the deployed units. To assess the influence of duration of test-retest interval on outcomes while holding unit membership and deployment status constant, partial correlations controlling for core covariates (age, sex, education, alcohol use, sleep, and time 1 performance) were conducted within the 3 largest contributing brigade-level military units (2 deployed and 1 nondeployed with ≥288 personnel in each unit study sample) between test-retest interval duration and all primary outcomes. Of a possible 69 correlations, only 6 were significant at $P<.05$ and showed inconsistency across units, across variables, and in the direction of the association.

Description of Deployment

Deployed soldiers reported being located primarily within 3 regions of Iraq during their deployment, although some participants reported considerable movement throughout Iraq. Deployers reported significant combat activity, even when assigned to support roles. Frequently reported combat experiences included receiving hostile incoming small arms–type fire (98%), participating in a support convoy (95%), and going on combat patrols/missions (91%). Many deployers reported witnessing Americans/allies (55%) or enemy combatants (61%) being seriously wounded or killed. Numerous soldiers reported receiving hostile incoming fire (35%) or participating in a combat mission (49%) daily.

 ©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Dartmouth College User on 06/05/2014

Seeing people begging for food (98%), observing homes or villages destroyed (77%), and seeing Americans or allies after they had been severely wounded or disfigured in combat (63%) ranked among the most frequently reported of other potentially stressful war-zone events. Ninety-eight percent of deployed participants reported exposure to at least 1 potential environmental agent (eg, air pollution, pesticides, other routinely used chemicals), although less than 1% reported exposure to chemical or biological weapons. Fourteen percent of deployed participants reported being wounded or injured in combat; 7.6% of deployers (vs 3.9% of nondeployers) specifically reported experiencing head injury with related loss of consciousness between time 1 and time 2. Following their deployment, 11.6% of deployed participants screened positive for likely PTSD, as determined by the "strict" screening criteria outlined by Hoge et al[3]; 25.0% scored above a CES-D cutoff value,[29] suggesting a heightened probability of clinically significant depression symptoms.

Analysis of Primary Outcomes as a Function of Deployment

Generalized estimating equations revealed significant deployment effects on WMS3 Verbal Paired Associates I (initial) recall, WMS Visual Reproductions percentage retention, NES3 Continuous Performance Task omission errors, ANAM simple reaction time throughput scores, and POMS confusion and tension subscales (TABLE 5).

Deployers showed a greater decline from time 1 to time 2 on the WMS Visual Reproductions retention than did nondeployers (Table 4, Table 5, and TABLE 6). In addition, nondeployers showed anticipated practice effects from time 1 to time 2 on WMS3 Verbal Paired Associates I and NES3 Continuous Performance Task omissions, whereas deployers showed little or no improvement (Table 4, Table 5, and Table 6). The absence of practice effects on certain cognitive tasks reflects impairment. In contrast, ANAM simple reaction time performance changed little over time for deployers but declined from time 1 to time 2 for nondeployers.

Deployment was associated with longitudinal increases in confusion and tension (Table 4, Table 5, and Table 6). There were no significant deployment effects in subjective estimates of cognitive impairment on the MOS-CF.

Table 5. Results of Generalized Estimating Equation Adjusted for Battalion-Level Units With Core Covariate Set (Model 1) and Examining the Effects of Deployment Status on Neuropsychological Outcomes*

	Model 1: Core Covariates			
Outcome Variable	No.	β (95% CI)†	*P* Value	Direction of Effect of Deployment‡
Subjective outcome indices				
MOS-CF	939	−2.29 (−5.05 to 0.47)	.10	
POMS anger, T score§	939	−0.30 (−1.28 to 0.67)	.54	
POMS depression, T score§	939	−0.15 (−0.96 to 0.67)	.73	
POMS confusion, T score§	939	1.40 (0.71 to 2.09)	<.001	Toward greater distress
POMS fatigue, T score§	939	−0.10 (−1.15 to 0.94)	.85	
POMS tension, T score§	929	1.24 (0.58 to 1.89)	<.001	Toward greater distress
POMS vigor, T score	939	−0.34 (−1.21 to 0.52)	.44	
Attention, working memory, executive				
Trailmaking B–A, s§‖	934	−0.01 (−0.04 to 0.02)	.39	
NES3 CPT, commission errors§‖	932	0.06 (0.00 to 0.12)	.06	
NES3 CPT, omission errors§‖	932	0.11 (0.06 to 0.15)	<.001	Toward less proficient
Learning and memory				
Verbal				
WMS3 Verbal Paired Associates, learning trials, No. correct	942	−1.51 (−2.51 to −0.50)	.003	Toward less proficient
WMS3 Verbal Paired Associates, % retention	939	−1.14 (−3.03 to 0.75)	.24	
Visual-spatial				
WMS Visual Reproductions, immediate recall	941	−0.51 (−1.23 to 0.25)	.19	
WMS Visual Reproductions, % retention	940	−3.82 (−5.61 to −2.03)	<.001	Toward less proficient
Simple reaction time				
ANAM simple reaction time throughput	941	4.03 (1.37 to 6.69)	.003	Toward more proficient
Cognitive efficiency				
ANAM code substitution, learning throughput	941	−0.78 (−1.59 to 0.02)	.06	
ANAM code substitution, delay throughput	941	0.19 (−0.71 to 1.09)	.67	
ANAM matching to sample throughput	938	−0.63 (−1.51 to 0.24)	.16	
ANAM logical relations throughput	939	0.39 (−0.32 to 1.11)	.28	
ANAM mathematical processing throughput	890	−0.04 (−0.65 to 0.58)	.91	
ANAM running memory throughput	895	−0.61 (−2.44 to 1.22)	.52	
Fine motor speed				
ANAM tapping (dominant), mean No. of taps	938	−0.06 (−0.83 to 0.72)	.89	
ANAM tapping (nondominant), mean No. of taps	943	0.18 (−0.93 to 1.28)	.76	

Abbreviations: ANAM, Automated Neuropsychological Assessment Metric; CI, confidence interval; MOS-CF, Medical Outcomes Study Cognitive Functioning Scale; NES3 CPT, Neurobehavioral Evaluation System, third edition, Continuous Performance Test; POMS, Profile of Mood States; WMS, Wechsler Memory Scale; WMS3, Wechsler Memory Scale, third edition.

*Model 1 core covariates are time 1 values of time 2 outcomes and demographic/contextual variables (time 1 values of the outcome measure of sex, time 1 age and education, and time 2 sleep and alcohol use).

†β is the unstandardized parameter estimate for the deployment status variable and describes the absolute difference in adjusted mean outcome scores between the deployed and nondeployed groups.

‡The direction of effect is described only for statistically significant effects.

§Higher, more positive β coefficients reflect poorer outcomes for deployers compared with nondeployers; otherwise, higher, more positive β coefficients reflect better outcomes for deployers compared with nondeployers.

‖Log-transformed.

©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Dartmouth College User on 06/05/2014

Table 6. Deployed and Nondeployed Soldiers at Time 1 and Time 2 Exceeding "Deficit" Cutoffs for Significant Outcomes (in the Core Regression Model)*

	Percentage Exceeding Cutoff			
	Time 1		Time 2	
Outcome Variable	Deployed (n = 654)	Nondeployed (n = 307)	Deployed (n = 654)	Nondeployed (n = 307)
Subjective outcome indices				
POMS confusion	23.2	24.0	28.8	21.3
POMS tension	25.1	21.8	27.1	21.5
Attention, working memory, executive				
NES3 CPT, omission errors†	28.2	25.3	27.5	17.5
Learning and memory				
WMS3 Verbal Paired Associates, learning trials, No. correct	21.8	22.4	16.0	10.2
WMS Visual Reproductions, % retention	25.1	21.4	34.1	22.7
Simple reaction time				
ANAM simple reaction time throughput	26.6	21.4	25.1	24.0

Abbreviations: ANAM, Automated Neuropsychological Assessment Metric; NES3 CPT, Neurobehavioral Evaluation System, third edition, Continuous Performance Task; POMS, Profile of Mood States; WMS, Wechsler Memory Scale; WMS3, Wechsler Memory Scale, third edition.

*The sample size varies slightly across observations because of missing data (n = 950-960). Cutoffs are based on the most dysfunctional quartile within the overall sample at baseline. Because any given percentile cut point (eg, 25th percentile) does not necessarily correspond directly to the distribution of actual scores, the percentage exceeding deficit cutoffs may vary slightly from 25% at time 1.

†Log-transformed.

Influence of Stress Symptoms, Depression, and Head Injury on Primary Outcomes

The individual inclusion of time 2 PCL scores, CES-D scores, and head injury incurred between time 1 and time 2 as covariates to the core models revealed specific associations between the covariates and several outcome measures. However, taking into account variance attributable to these covariates revealed that deployment continued to exert a significant effect for all neurobehavioral outcomes found to be significant using the core model (TABLE 7). Post hoc analyses taking into account change in PCL scores from time 1 to time 2 as a covariate likewise indicated that deployment exerted a significant effect for neurobehavioral outcomes found to be significant using the core model, independent of any worsening of PTSD symptoms. Additional post hoc analyses that repeated the generalized estimating equations using the core model but excluded from the sample the 63 participants who reported incurring a head injury with loss of consciousness between time 1 and time 2 revealed the identical pattern of results to those generated using the entire sample.

COMMENT

This, to our knowledge, is the first controlled cohort study to incorporate prospective examination of objective neuropsychological outcomes associated with war-zone deployment. The design included primary data collection both prior to and shortly after deployment and a nondeployed comparison sample. Results suggest that OIF deployment is associated at least transiently with subtle alterations in neural functioning, as indicated by population shifts in the neuropsychological performance of deployed vs nondeployed soldiers. These shifts include reduced proficiency in sustained attention and memory, heightened negative state affect reflecting increased feelings of confusion and tension, and an advantage in reaction time. Conversely, there were no significant effects of deployment on fine motor speed, executive aspects of attention, cognitive efficiency, or state measures of irritability, depression, fatigue, and vigor. Previous reports have described significant negative mental health consequences associated with OIF deployment.[2,3] The findings of this study suggest that mental status changes related to Iraq War participation extend beyond psychiatric concerns to circumscribed adverse neuropsychological consequences, an outcome domain with high relevance to occupational and psychosocial functioning and highly sensitive to brain dysfunction.

The memory and attention problems commonly reported by Gulf War veterans highlighted neuropsychological dysfunction as an area of concern among deploying military personnel. However, results of studies examining the objective neuropsychological performances of Gulf War veterans yielded a mixed pattern of results that has been difficult to interpret because of the absence of baseline data and long intervals between war-zone return and neuropsychological assessment.[32] Our findings indicating deployment effects on sustained attention, learning, and memory suggest that negative neuropsychological outcomes following Iraq deployment cannot be attributed to preexisting dysfunction and that it is unlikely that intervening variables influenced performances significantly due to the relatively abbreviated interval between war-zone return and assessment. Consistent with a recent report of British military personnel deployed to Iraq,[33] we did not find a deployment effect for subjective indices of neuropsychological compromise as pronounced as that revealed by some Gulf War findings[34-36]; however, deployment to Iraq in this study was associated with increased self-report of confusion.

Our findings also suggest that deployment is associated with a neurobehavioral advantage in reacting quickly and efficiently to simple targets. This finding seemingly contradicts the decrements in memory and attentional outcomes revealed by this study. However, when considered within an evolutionary framework, the pattern of findings is consistent with neurobiological responses directed toward survival. That is, when confronted with life threat, physiological responses occur in preparation for life-preserving action. Among the array of neurobiological

 ©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Dartmouth College User on 06/05/2014

events encompassed by the "flight or fight" response, neurotransmitter systems associated with increased arousal (eg, noradrenergic system) become activated, while neuroendocrine responses become altered via the hypothalamic-pituitary-adrenal axis.[37-39]

Such neurobiological alterations can result in heightened behavioral reactivity (eg, quickened response times) but dampened attention, learning, and memory for non–threat-relevant stimuli and events.[37,40,41] Most of the participants in this study faced prolonged exposure to significant war-zone stressors while deployed, many of which would be categorized as imminently life-threatening. Such physiologically based responses could arguably have continued to affect cognitive functions into the period in which postdeployment assessments were conducted.

As predicted by previous research,[42-44] higher levels of PTSD and depression symptoms were associated with relative performance deficits on several neuropsychological measures. However,

Table 7. Results of Generalized Estimating Equation Adjusted for Battalion-Level Units Examining the Effects of Deployment Status on Neuropsychological Outcomes Using Enhanced Covariate Models*

Outcome Variable	Model 2: Core Covariates, Time 2 PCL		Model 3: Core Covariates, Time 2 CES-D		Model 4: Core Covariates, Time 2 Head Injury	
	β (95% CI)†	*P* Value	β (95% CI)†	*P* Value	β (95% CI)†	*P* Value
Subjective outcome indices						
MOS-CF	0.30 (–1.92 to 2.52)	.79	–1.74 (–3.94 to 0.47)	.12	–2.33 (–5.19 to 0.53)	.11
POMS anger, T score‡	–1.54 (–1.83 to –1.25)	<.001	–0.58 (–1.45 to 0.29)	.19	–0.32 (–1.28 to 0.64)	.52
POMS depression, T score‡	–0.98 (–1.44 to –0.51)	<.001	–0.30 (–0.96 to 0.35)	.36	–0.07 (–0.88 to 0.73)	.86
POMS confusion, T score‡	0.43 (–0.09 to 0.95)	.10	1.22 (0.40 to 2.04)	.003	1.36 (0.68 to 2.04)	<.001
POMS fatigue, T score‡	–0.78 (–1.77 to 0.21)	.12	–0.07 (–1.23 to 1.10)	.91	–0.11 (–1.12 to 0.90)	.83
POMS tension, T score‡	0.30 (0.06 to 0.54)	.01	1.19 (0.53 to 1.84)	<.001	1.21 (0.55 to 1.88)	<.001
POMS vigor, T score	0.01 (–0.76 to 0.79)	.98	–0.39 (–1.41 to 0.63)	.46	–0.36 (–1.22 to 0.50)	.41
Attention, working memory, executive						
Trailmaking B–A, s‡§	–0.01 (–0.04 to 0.02)	.41	–0.01 (–0.04 to 0.02)	.46	–0.01 (–0.04 to 0.02)	.36
NES3 CPT, commission errors‡§	0.06 (–0.01 to 0.12)	.11	0.06 (–0.01 to 0.12)	.09	0.06 (–0.01 to 0.12)	.08
NES3 CPT, omission errors‡§	0.10 (0.05 to 0.14)	<.001	0.10 (0.06 to 0.15)	<.001	0.10 (0.06 to 0.15)	<.001
Learning and memory						
Verbal						
WMS3 Verbal Paired Associates, learning trials, No. correct	–1.45 (–2.41 to –0.49)	.003	–1.57 (–2.49 to –0.64)	<.001	–1.57 (–2.54 to –0.60)	.002
WMS3 Verbal Paired Associates, % retention	–0.94 (–2.70 to 0.81)	.29	–1.09 (–2.95 to 0.77)	.25	–1.12 (–3.09 to 0.85)	.26
Visual-spatial						
WMS Visual Reproductions, immediate recall, No. correct	–0.54 (–1.25 to 0.17)	.14	–0.60 (–1.27 to 0.07)	.08	–0.54 (–1.25 to 0.17)	.13
WMS Visual Reproductions, % retention	–3.63 (–5.31 to –1.96)	<.001	–3.69 (–5.47 to –1.91)	<.001	–3.83 (–5.60 to –2.06)	<.001
Simple reaction time						
ANAM simple reaction time throughput	5.03 (2.57 to 7.49)	<.001	4.16 (1.69 to 6.64)	.001	4.03 (1.31 to 6.74)	.004
Cognitive efficiency						
ANAM code substitution, learning throughput	–0.56 (–1.33 to 0.20)	.15	–0.76 (–1.52 to 0.00)	.05	–0.81 (–1.62 to –0.01)	.05
ANAM code substitution, delay throughput	0.43 (–0.58 to 1.44)	.40	0.23 (–0.71 to 1.17)	.63	0.17 (–0.73 to 1.06)	.71
ANAM matching to sample throughput	–0.41 (–1.28 to 0.46)	.36	–0.61 (–1.42 to 0.19)	.14	–0.74 (–1.60 to 0.11)	.09
ANAM logical relations throughput	0.49 (–0.16 to 1.15)	.14	0.42 (–0.27 to 1.10)	.24	0.41 (–0.29 to 1.10)	.25
ANAM mathematical processing throughput	0.01 (–0.62 to 0.63)	.98	–0.01 (–0.63 to 0.62)	.98	–0.03 (–0.66 to 0.60)	.92
ANAM running memory throughput	–0.26 (–2.00 to 1.48)	.77	–0.63 (–2.34 to 1.09)	.47	–0.52 (–2.43 to 1.39)	.59
Fine motor speed						
ANAM tapping (dominant), mean No. of taps	0.10 (–0.70 to 0.91)	.80	–0.02 (–0.77 to 0.73)	.96	0.04 (–0.76 to 0.83)	.93
ANAM tapping (nondominant), mean No. of taps	0.33 (–0.73 to 1.38)	.54	0.18 (–0.89 to 1.25)	.74	0.14 (–0.97 to 1.24)	.81

Abbreviations: ANAM, Automated Neuropsychological Assessment Metric; CES-D, Center for Epidemiological Studies Depression Inventory; CI, confidence interval; MOS-CF, Medical Outcomes Study Cognitive Functioning Scale; NES3 CPT, Neurobehavioral Evaluation System, third edition, Continuous Performance Task; PCL, PTSD Checklist; POMS, Profile of Mood States; WMS, Wechsler Memory Scale; WMS3, Wechsler Memory Scale, third edition.

*Model 2 covariates are the core covariate set (time 1 value of the outcome measure of sex, time 1 age and education, and time 2 sleep and alcohol use) and time 2 posttraumatic stress disorder symptom severity; model 3 covariates are the core covariate set and time 2 depression severity; model 4 covariates are the core covariate set and occurrence of head injury with loss of consciousness between time 1 and time 2.

†β is the unstandardized parameter estimate for the deployment status variable and describes the absolute difference in adjusted mean outcome scores between the deployed and nondeployed groups.

‡Higher, more positive β coefficients reflect poorer outcomes for deployers compared with nondeployers; otherwise, higher, more positive β coefficients reflect better outcomes for deployers compared with nondeployers.

§Log-transformed.

©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Dartmouth College User on 06/05/2014

emotional symptoms did not fully account for associations between deployment status and neurobehavioral outcomes. Thus, although deployment-related neuropsychological decrements may be in part related to emotional status, neuropsychological dysfunction also occurred independent of emotional responses. Such dissociations between self-reported emotional symptoms and neuropsychological performances may reflect at least transient desynchrony between subjective and physiological components of the stress response.[45] Alternatively, it may be that participants underendorsed emotional symptoms.

These findings could not be explained by contextual or demographic variables such as formal educational attainment or recent sleep and alcohol consumption patterns. It is possible that other contextual variables, such as differing perceptions about the significance of the study and changes in motivation, contributed to a deployment effect. However, there were no differences between groups on a cognitive test of effort, and all participants performing below a threshold on the effort task were excluded from analyses. Furthermore, qualitative remarks made by participants suggested that deployment increased the participants' understanding of the study, unlikely leading to a deployment-related decrease in motivation.

It is also possible that other attributes of the deployment resulted in neuropsychological compromise. A subset of both deployed and nondeployed study participants reported mild concussive injury, but the presence of an intervening concussive head injury failed to exert significant impact on objective neuropsychological outcomes. This finding should be interpreted cautiously, given that the measure of head injury included in the analyses was quite general (potentially including a range of severities), that the small number of participants with head injury may have resulted in reduced statistical power to detect a head injury effect, and that we did not measure repetitive nonconcussive blast exposures.

In addition, many participants reported exposure to potential environmental hazards, although most were consistent with exposures typical of modern urban life (eg, air pollution, use of insect repellant), and deployment did not show an effect for some measures typically thought to be sensitive to some types of neurotoxicants (eg, fine motor speed, executive functioning). Nonetheless, follow-up efforts will necessarily include examination of potential mechanisms, such as more detailed head injury characteristics, extent and type of stress exposure, and objective environmental monitoring data, as they become available.

Regardless of the mechanism involved, these findings point to a possible negative health consequence of war-zone deployment: neuropsychological compromise. The levels of such compromise were relatively mild and circumscribed. That is, the neuropsychological disadvantages associated with deployment include a range of scores that overall do not reach absolute clinical thresholds of significant impairment akin to advanced neurological disease state; however, even small declines in the ability to sustain attentional focus and learn and remember new information may reflect subtle neural dysfunction, lead to problems in day-to-day life, and negatively affect performance in high-pressure contexts such as subsequent war-zone participation. Such subtle alterations may also represent a prodrome or surrogate for disease.[46] In this case, it could be speculated that the stress-consistent pattern of deficits, if sustained, represents a surrogate for biological stress responsivity and a prodrome for eventual development of stress-related somatic (eg, cardiovascular) and mental (eg, posttraumatic stress disorder) health disorders.

Epidemiological investigations of exposure-outcome relationships frequently document subtle brain dysfunction in which an affected group includes a few members with optimal outcomes but more members with poor outcomes, indicating a shift away from normal health. For example, scores of as little as 2.5 IQ-point equivalents have been found to differentiate children exposed to methlymercury and lead from those not exposed.[47,48] These "average" scores may not appear to be clinically significant but represent a population shift in which the risk for the population is significantly altered by the exposure variable.[46] Clinical implications of our findings include implementation of neuropsychological screening among military personnel returning from war-zone deployment and attention to the cognitive complaints of military personnel returning from deployment (even when medical workups do not support a clinical diagnosis).

Because we included only active-duty Army soldiers in this report, generalization of results to other military branches or to National Guard and Reserve personnel activated for deployment may be limited. In addition, our assessment of brain dysfunction was restricted to behavioral indices. Future efforts will benefit from inclusion of other measures of brain integrity, such as neuroimaging. Moreover, because this report includes only 1 postdeployment assessment, it is unclear whether changes in neuropsychological functioning endure or whether they are predictive of subsequent somatic or mental health problems. Nonetheless, this effort addresses many of the more significant limitations of prior deployment health outcome studies, including the lack of baseline data, small or regionally recruited convenience samples, reliance on subjective appraisals of neuropsychological health, and prolonged intervals between war-zone return and assessment. We have continued to follow this cohort longitudinally, broadened the assessment to include occupational outcomes, and included a sample of National Guard personnel, all necessary steps in determining the course of deployment-related neuropsychological decrements and understanding the longer-term public health impact of war-zone deployment.

Author Contributions: Drs Vasterling and Proctor had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

 ©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Dartmouth College User on 06/05/2014

Study concept and design: Vasterling, Proctor, Kane, White.
Acquisition of data: Vasterling, Proctor, Kane.
Analysis and interpretation of data: Vasterling, Proctor, Amoroso, Heeren, White.
Drafting of the manuscript: Vasterling, Proctor, White.
Critical revision of the manuscript for important intellectual content: Vasterling, Proctor, Amoroso, Kane, Heeren, White.
Statistical analysis: Vasterling, Proctor, Heeren.
Obtained funding: Vasterling, Proctor.
Administrative, technical, or material support: Vasterling, Proctor, Amoroso, Kane, White.
Study supervision: Vasterling, Proctor, White.

Financial Disclosures: None reported.

Funding/Support: This work was supported by US Army Medical Research and Materiel Command (DAMD 17-03-0020; HSRRB Log No. A-11815) and VA Clinical Science Research and Development awards. This work also was supported in part by resources provided by the South Central Mental Illness Research, Education, and Clinical Center and US Army Research Institute for Environmental Medicine, Natick, Mass. Some of the work was completed at the Department of Veterans Affairs Houston Center for Quality of Care and Utilization Studies and Tulane University Department of Psychology. The US Army Medical Research Acquisition Activity (Fort Detrick, Md) is the awarding and administering acquisition office for DAMD 17-03-0020.

Role of the Sponsor: The primary funding organizations had no role in the design or conduct of the study; in the collection, management, analysis, and interpretation of the data, or in preparation, review, or approval of the manuscript. However, the manuscript underwent scientific and administrative review within the US Army Research Institute for Environmental Medicine.

Disclaimer: The content of this article does not necessarily reflect the position or policy of the government, and no official endorsement should be inferred.

Acknowledgment: We are grateful to the soldiers who generously donated their time to participate in the study. We also appreciate the efforts of the key military personnel who facilitated conduct of the study for their units. In particular, we thank the leaders, medical staff, planners, and personnel officers from participating units and the associated Corp Surgeons' Offices. The study would not have been possible without the high level of support provided by the US Army Forces Command, Command Surgeon's Office, in identifying and facilitating access to participating military units. Finally, we thank Maxine Krengel, PhD, Boston University School of Medicine, for performing reliability ratings, the many examiners who volunteered their time, and time 1 and time 2 study coordinators, Gina Clausi, MSW, RN, and Deborah Arant-Daigle, BA.

REFERENCES

1. Okie S. Traumatic brain injury in the war zone. *N Engl J Med*. 2005;352:2043-2047.
2. Hoge CW, Auchterlonie JL, Milliken CS. Mental health problems, use of mental health services, and attrition from military service after returning from deployment to Iraq or Afghanistan. *JAMA*. 2006;295:1023-1032.
3. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *N Engl J Med*. 2004;351:13-22.
4. Department of Veterans Affairs, Veterans Health Administration, Office of the Assistant Secretary of Defense, Health Affairs (VA and DOD). *Combined Analysis of the VA and DoD Gulf War Clinical Evaluation Programs: a Study of the Clinical Findings From Systematic Medical Examinations of 100,339 US Gulf War Veterans.* Washington, DC; 2002.
5. Papero PH, Howe GW, Reiss D. Neuropsychological function and psychosocial deficit in adolescents with chronic neurological impairment. *J Dev Phys Disabil*. 1992;4:317-340.
6. Kalechstein AD, Newton TF, van Gorp WG. Neurocognitive functioning is associated with employment status: a quantitative review. *J Clin Exp Neuropsychol*. 2003;25:1186-1191.
7. Machamer J, Temkin N, Fraser R, Doctor JN, Dikmen S. Stability of employment after traumatic brain injury. *J Int Neuropsychol Soc*. 2005;11:807-816.
8. Blood CG, Aboumrad TL. A comparison of postdeployment hospitalization incidence between active duty Vietnam and Persian Gulf war veterans. *Mil Med*. 2001;166:648-655.
9. Vasterling JJ, Proctor SP, Amoroso P, et al. The Neurocognition Deployment Health Study: a prospective cohort study of Army soldiers. *Mil Med*. 2006;171:253-260.
10. White RF. Patterns of neuropsychological impairment associated with neurotoxicants. *Clin Occup Environ Med Neurotoxicol*. 2001;1:577-593.
11. White RF, Proctor SP. Solvents and neurotoxicology. *Lancet*. 1997;349:1239-1242.
12. White RF, Proctor SP. Research and clinical criteria for development of neurobehavioral test batteries. *J Occup Med*. 1992;34:140-148.
13. White RF, Cohen RF, Gerr F, et al. Criteria for progressive modification of neurobehavioral test batteries. *Neurotoxicol Teratol*. 1994;16:511-524.
14. Stewart AL, Ware JE, Sherbourne CD, Wells KB. Psychological distress/well-being and cognitive functioning measures. In: Stewart AL, Ware JE, eds. *Measuring Functioning and Well-being: The Medical Outcomes Study Approach.* Durham, NC: Duke University; 1992:102-142.
15. McNair DM, Lorr M, Droppelman LF. *Profile of Mood States.* San Diego, Calif: Educational and Industrial Testing Service; 1971.
16. Wechsler DA. *Wechsler Memory Scale.* 3rd ed. San Antonio, Tex: Psychological Corp; 1997.
17. Spreen O, Strauss E. *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary.* 2nd ed. New York, NY: Oxford; 1998.
18. Reeves DL, Bleiberg J, Roebuck-Spencer TM, et al. Reference values for performance on the Automated Neuropsychological Assessment Metrics (ANAM) in an active-duty military sample. *Mil Med*. In press.
19. Reeves D, Kane R, Elsmore T, Winter K, Bleiberg J. *ANAM 2001 User's Manual: Clinical and Research Modules.* San Diego, Calif: National Cognitive Recovery Foundation; 2002. Publication NCRF-SR-2002-1.
20. Letz R, Green RC, Woodard JL. Development of a computer-based battery designed to screen adults for neuropsychological impairment. *Neurotoxicol Teratol*. 1996;18:365-370.
21. Letz R. *NES3 User's Manual.* Atlanta, Ga: Neurobehavioral Systems Inc; 2000.
22. Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills*. 1958;8:271-276.
23. Wechsler DA. A standardized memory scale for clinical use. *J Psychol*. 1945;19:87-95.
24. King DW, King LA, Vogt DS. *Manual for the Deployment Risk and Resilience Inventory (DRRI): A Collection of Measures for Studying Deployment Related Experiences of Military Veterans.* Boston, Mass: National Center for PTSD; 2003.
25. Blokland A. Acetylcholine: a neurotransmitter for learning and memory? *Brain Res Brain Res Rev*. 1995;21:285-300.
26. Blanchard EB, Jones-Alexander J, Buckley TC, Forneris CA. Psychometric properties of the PTSD Checklist (PCL). *Behav Res Ther*. 1996;34:669-673.
27. Weathers FW, Huska JA, Keane TM. *The PTSD Checklist—Military Version (PCL-M).* Boston, Mass: National Center for PTSD; 1991.
28. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1:385-401.
29. Santor DA, Coyne JC. Shortening the CES-D to improve its ability to detect cases of depression. *Psychol Assess*. 1997;9:233-243.
30. Tombaugh TN. *Test of Memory Malingering.* Toronto, Ontario: Multi-Health Systems; 1996.
31. O'Bryant SE, Engel LR, Kleiner JS, Vasterling JJ, Black FW. TOMM Trial 1 as a screening measure for insufficient effort. *Clin Neuropsychol*. In press.
32. Vasterling JJ, Bremner JD. The impact of the 1991 Gulf War on the mind and brain. *Philos Trans R Soc Lond B Biol Sci*. 2006;361:593-604.
33. Hotopf M, Hull L, Fear NT, et al. The health of UK military personnel who deployed to the 2003 Iraq war: a cohort study. *Lancet*. 2006;367:1731-1741.
34. Iowa Persian Gulf Study Group. Self-reported illness and health status among Gulf War veterans: a population-based study. *JAMA*. 1997;277:238-245.
35. Unwin C, Blatchley N, Coker W, et al. Health of UK servicemen who served in Persian Gulf War. *Lancet*. 1999;353:169-178.
36. Proctor SP, White RF, Heeren T, et al. Neuropsychological functioning in Danish Gulf War veterans. *J Psychopathol Behav Assess*. 2003;25:85-93.
37. McEwen BS, Sapolsky RM. Stress and cognitive function. *Curr Opin Neurobiol*. 1995;5:205-216.
38. Habib KE, Gold PW, Chrousos GP. Neuroendocrinology of stress. *Endocrinol Metab Clin North Am*. 2001;30:695-728, vi-viii.
39. Morilak DA, Barrera G, Echevarria DJ, et al. Role of brain norepinephrine in the behavioral response to stress. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29:1214-1224.
40. Arnsten AFT. The biology of being frazzled. *Science*. 1998;280:1711-1712.
41. Sauro MD, Jorgensen RS, Pedlow CT. Stress, glucocorticoids, and memory: a meta-analytic review. *Stress*. 2003;6:235-245.
42. Burt DB, Zembar MJ, Niederehe G. Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychol Bull*. 1995;117:285-305.
43. Elliott R. The neuropsychological profile in unipolar depression. *Trends Cogn Sci*. 1998;2:447-454.
44. Vasterling JJ, Brailey K. Neuropsychological Findings in Adults With PTSD. In: Vasterling JJ, Brewin CR, eds. *Neuropsychology of PTSD: Biological, Cognitive, and Clinical Perspectives.* New York, NY: Guilford; 2005:178-207.
45. Mauss IB, Wilhelm FH, Groos JJ. Is there less to social anxiety than meets the eye? emotion experience, expression, and bodily responding. *Cogn Emotion*. 2004;18:631-662.
46. Bellinger DC. What is an adverse effect? a possible resolution of clinical and epidemiological perspectives on neurobehavioral toxicity. *Environ Res*. 2004;95:394-405.
47. Grandjean P, Weihe P, White RF, et al. Cognitive deficits in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicol Teratol*. 1998;21:1-12.
48. Canfield RL, Henderson CR Jr, Cory-Slecta DAA, Cox C, Jusko TA, Lanphear BP. Intellectual impairment in children with blood lead concentrations below 10 microg per deciliter. *N Engl J Med*. 2003;348:1517-1526.

©2006 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ by a Dartmouth College User on 06/05/2014