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Effects of sarin and cyclosarin exposure during the 1991 Gulf War on neurobehavioral functioning in US army veterans☆

Susan P. Proctor [a,b,c,d,*,1], Kristin J. Heaton [a,b,d,1], Tim Heeren [a,e], Roberta F. White [a,b,f]

[a] Boston Environmental Hazards Center, VA Boston Healthcare System, Boston, MA, United States
[b] Boston University School of Public Health (Environmental Health), Boston, MA, United States
[c] National Center for PTSD, VA Boston Healthcare System, Boston, MA, United States
[d] Military Performance Division, US Army Research Institute of Environmental Medicine, Natick, MA, United States
[e] Boston University School of Public Health (Biostatistics), Boston, MA, United States
[f] Boston University School of Medicine (Neurology), Boston, MA, United States

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Abstract

Background: During the Gulf War (GW), in early March 1991, a munitions dump at Khamisiyah, Iraq, was destroyed. Later, in 1996, the dump was found to have contained the organophosphate chemical warfare agents, sarin and cyclosarin.
Methods: Data collected in a study conducted between 1994 and 1996, before the Khamisiyah incident was publicly disclosed, were used to examine neurobehavioral task performances of GW veterans ($n = 140$) categorized as having received high, moderate, or low-to-no exposure dose levels to sarin and cyclosarin at Khamisiyah, Iraq. Exposure levels were based on modeled estimates of the exposure plume and on troop location information at the time of the Khamisiyah event. Based on recent findings observed in follow-up studies of persons exposed to sarin during the 1995 terrorist attacks in Japan, we hypothesized that exposure to sarin and cyclosarin would be associated with poorer performances on objective neurobehavioral tasks in specific functional domains (particularly in visuospatial abilities and psychomotor functioning) in a dose-dependent manner.
Results: Sarin and cyclosarin exposure was significantly associated with less proficient neurobehavioral functioning on tasks involving fine psychomotor dexterity and visuospatial abilities 4–5 years after exposure.
Conclusions: Findings suggest a dose–response association between low-level exposure to sarin and cyclosarin and specific functional central nervous system effects 4–5 years after exposure.

Keywords: Sarin; Neurobehavioral functioning; Central nervous system effects; Exposure assessment; Gulf War veterans

1. Introduction

In early March 1991 US troops participating in the Gulf War (GW) detonated a munitions storage pit at Khamisiyah, Iraq, later found to contain stockpiled sarin (GB; *o*-isopropyl methylphosphonoflouridate) and cyclosarin (GF; cyclohexyl methylphosphonoflouridate). Both of these compounds are acetylcholinesterase inhibitors that are lethal and/or incapacitating upon acute, high level exposure. Symptoms of acute exposure to these compounds may include miosis (narrowing of the pupil of the eye), blurred vision, nausea, vomiting, weakness, and dizziness (Brown and Brix, 1998; Marrs et al., 1996). Published reports and theatre medical records of 1991 GW veterans in the vicinity of Khamisiyah have failed to provide evidence of clinical effects of sarin or cyclosarin

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* Corresponding author at: VA Boston Healthcare System (116B-4), 150 South Huntington Avenue, Boston, MA 02130-4893, United States. Tel.: +1 857 364 4826; fax: +1 857 364 6526.
E-mail addresses: sproctor@bu.edu, susan.proctor@us.army.mil (S.P. Proctor).
[1] The current primary affiliation for Drs. Proctor and Heaton is the US Army Research Institute for Environmental Medicine. The work described in the manuscript was performed while they both were at the VA Boston Heathcare System.

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toxicity at the time of exposure (Riddle et al., 2003). However, a small but growing body of research examining low-level sarin exposure in animals (Henderson et al., 2002; van Helden et al., 2003, 2004a, b) suggests long-term central nervous system effects and evidence of anticholinesterase inhibition occur at levels lower than those that produce miosis and other acute symptoms or that would trigger current field system alarms. Also, long-term delayed or residual effects have been observed in persons performing rescue and police work following the Japanese sarin attacks in 1994 and 1995 (e.g., Miyaki et al., 2005).

A terrorist attack in March of 1995 exposed more than 5500 people to sarin released within the Tokyo subway system (Suzuki et al., 1995). Although a follow-up investigation of 640 of those initially exposed revealed no obvious clinical effects 3 months after the incident (Okumura et al., 1996), differences were noted between the exposed clinical cases and control individuals 6–8 months later. These findings included differences in visual evoked potential measures (Murata et al., 1997), postural parameters (e.g., sway) in females (Yokoyama et al., 1996), and on a neurobehavioral test of psychomotor functioning after adjustment for post-traumatic stress disorder (PTSD) symptoms (Yokoyama et al., 1998). Subsequent investigations of Tokyo subway rescue workers and police officers 3 and 7 years after the event suggest possible long-term neurobehavioral effects (Miyaki et al., 2005; Nishiwaki et al., 2001). These later Japanese findings, although intriguing, are not conclusive: the studies involved small sample sizes requiring pooling across time points and the neurobehavioral task battery used was not consistent with the previous Japanese studies.

In 2000, the Institute of Medicine (IOM, 2000) convened a panel to review the possible long-term effects of sarin and cyclosarin exposure in GW veterans. The committee's conclusions, which were reevaluated and reiterated in 2004 (IOM, 2004), stated that subclinical effects are reasonable to hypothesize although there is inadequate/insufficient evidence to determine whether an association exists because few studies of long-term health effects in humans have been conducted.

In this report we test the hypothesis that low-level exposure from the 1991 Khamisiyah incident is associated with central nervous system effects 4–5 years after GW deployment, specifically with poorer performances on neuropsychological tasks assessing the domains of visuospatial abilities and psychomotor functioning. The analyses were conducted to focus on the specific question of toxicological significance concerning the effects of sarin and cyclosarin on neurobehavioral functioning in humans rather than address the role of the Khamisiyah incident and its association with GW veterans' illnesses in general.

This study provides a unique perspective on the study of neurobehavioral effects associated with the Khamisiyah detonation in two ways: (1) dose–effect relationships were examined using estimated sarin and cyclosarin exposure levels rather than self-report, and (2) objective outcome data were obtained *prior* to the 1996 public announcement that the munitions pit detonation at Khamisiyah involved stockpiled sarin and cyclosarin (Directorate for Deployment Health Support of the Special Assistant to the Under Secretary of Defense (Personnel and Readiness) for Gulf War Illness Medical Readiness, and Military Deployments, April 2002). Aside from studies looking at depleted uranium effects (McDiarmid et al., 2000), this investigation of 1991 GW postwar health issues is the first to examine relationships between objectively measured health outcomes (neurobehavioral test performances) and exposure estimates of a pertinent GW event in a dose-dependent manner.

2. Materials and methods

This report focuses on neuropsychological test performances of a subset of 1991 GW veterans from the Devens Cohort Study who underwent a comprehensive in-person evaluation between the fall of 1994 and summer of 1996 (3.5–5 years after GW deployment) (Proctor et al., 1998; White et al., 2001; Wolfe et al., 1999).

The Devens Cohort Study was first initiated in the spring of 1991 with a survey study of almost 3000 GW veterans, representing close to 100 different military units, who returned home from the GW through Ft. Devens, MA (Wolfe et al., 1993). A follow-up survey was conducted with Devens Cohort Study members in 1992–1993 to assess changes in the 18–24 months following GW deployment (Wolfe et al., 1998).

The 1994–1996 study was designed to evaluate a stratified, random subset of the larger cohort group through in-person evaluations to specifically examine GW environmental exposures and neurobehavioral function. The study protocol included a medical and occupational history questionnaire; a semi-structured environmental interview; a neuropsychological test battery; several scales assessing psychological symptomatology, including the Brief Symptom Interview (BSI; Derogatis, 1993) and the Mississippi Scale for PTSD (Keane et al., 1988); psychological diagnostic interviews, including the Clinician Administered Scale for PTSD (CAPS; Blake et al., 1990) and the Structured Clinical Interview for DSM-IIIR Axis I Disorders (SCID; Spitzer et al., 1990).

The VA Boston Healthcare System's Institutional Review Board approved the study protocol and informed consent was obtained from all participants.

Out of the 145 persons who participated in the in-person aspects of this study, complete data on health symptomatology, neuropsychological testing, and covariates of interest were available for 141 GW-deployed study participants. One GW-deployed participant was excluded from the analyses because he was not in the GW theatre at the time of the Khamisiyah detonation incident. The 140 GW-deployed participants represented 28 different military units.

Over 95% of the participants in this study phase were evaluated prior to the 1996 announcement by DoD that the destroyed munitions depot at Khamisiyah, Iraq, contained sarin and cyclosarin.

3. Exposure characterization

In June 1996, the Presidential Advisory Committee and the National Security Council requested that the Central Intelligence

Agency model any potential chemical warfare agent release events during the GW, including those associated with the detonation of specific bunkers and ammunitions pits at Khamisiyah, at al Muthanna, and Muhammidiyat (Presidential Advisory Committee on Gulf War Veterans' Illness, 1996). Using meteorological data and estimates of atmospheric transport and diffusion, initial models were developed to simulate and predict the direction and extent of these releases. Two levels of potential exposure were identified with the modeling scheme: first, an area where an exposed person would be expected to show "first noticeable effects" and second, an area of "low level hazard" that was defined as exposure at levels equal to or greater than the general population limit (GPL), defined as 0.01296 mg min/m^3 by the US Army and Centers for Disease Control and Prevention, 1988 (McNamara and Leitnaker, 1971). The plume areas for each of these two levels of exposure were then superimposed onto a map of the region. By integrating the plume area maps with unit-level geographical coordinates, individual units located in the area covered by the modeled plumes during a 4-day period in early March 1991 were identified.

No military units were identified as being in the area described as the "first noticeable effect" area, defined as exposure at levels equal to or greater than 1 mg min/m^3 (Directorate for Deployment Health Support of the Special Assistant to the Under Secretary of Defense (Personnel and Readiness) for Gulf War Illness Medical Readiness, and Military Deployments, April 2002; Hauschild, 1999). The identification of those units in the "low level exposure" area was first published on the Internet in 1997 (Directorate for Deployment Health Support of the Special Assistant to the Under Secretary of Defense (Personnel and Readiness) for Gulf War Illness, 1997) and members of those units were sent notification letters from the Office of the Special Assistant for Gulf War Illnesses at DoD. In 2000, the exposure plume data were re-analyzed and refined using additional meteorological modeling information, updated estimates of the total number of rockets destroyed, consideration of agent removal mechanisms, updated unit-level location and personnel data, exposure thresholds for sarin and cyclosarin, and combined toxicity aspects of sarin and cyclosarin (Assistant Secretary of Defense (Health Affairs) and Special Assistant to the Under Secretary of Defense (Personnel and Readiness) for Gulf War Illness Medical Readiness, and Military Deployments, 2002). Another DoD notification letter was then issued to individual military personnel determined to have been in the identified potential hazard area following the 2000 model revisions (Directorate for Deployment Health Support of the Special Assistant to the Under Secretary of Defense (Personnel and Readiness) for Gulf War Illness Medical Readiness, and Military Deployments, April 2002). The exposure modeling efforts are also described by Bullman et al. (2005) and Gackstetter et al. (2006) in their recent publications.

3.1. Group categorization by exposure dose-estimates

The 2000 Khamisiyah plume analyses, described above, produced four modeled hazard areas, one for each day in March 1991 between the 10th to the 13th when exposure to sarin and cyclosarin was considered possible following the detonations. Each of the four modeled hazard areas encompassed the area within the concentration contour of the GPL threshold level defined above. A military unit was considered exposed if it was determined to be located within any of the four modeled hazard areas. The estimated dosages assigned to each Devens Cohort Study unit classified as exposed by the 2000 Khamisiyah modeling were requested and received from the Directorate of Health Risk Management, US Army Center for Health Promotion and Preventive Medicine in 2003. Cumulative dosage estimates were provided in mg min/m^3 for each of the units considered to be in any of the four hazard areas.

The maximum estimated dose levels for the 11 units in this study with measurable exposure estimates greater than the GPL threshold ranged from 0.035 to 0.144 mg min/m^3. For the categorical data analyses (see below), those persons in units with exposure levels greater than 0.072 mg min/m^3 ($n = 23$) were defined as the *high* exposure group; those in units with exposure levels greater than the GPL but no more than 0.072 mg min/m^3 ($n = 47$) were defined as the *moderate* exposure group. The 0.072 mg min/m^3 level corresponds with the recommended maximum occupational or worker population limit (WPL) (Centers for Disease Control and Prevention, 1988; Mioduszeski et al., 1998) defined as the no effect level for workers without respiratory protection, when averaged over an extended 12-h workday.

The persons in the 17 GW-deployed troop units ($n = 70$) for which no exposure level was estimated, because they were not in locations within the modeled plume areas, were assigned exposure levels of zero and categorized as the low-to-no exposure group. The majority of persons in the low-to-no exposure group were located in the Saudi Arabia coastal cities (e.g., Dammam, Dharhan) during this time period (Proctor et al., 2005).

4. Outcome measures

4.1. Description of neuropsychological test battery and assessment of mood

Neuropsychological tests were used to assess five cognitive domains: simple attention, executive function, psychomotor functioning, visuospatial abilities, and short-term memory (Table 1). Mood states at the time of testing were assessed using the Profile of Mood States (POMS; McNair et al., 1971). The test battery was designed to included tasks with known sensitivity to neurotoxicants hypothesized to be present in the 1991 GW environment, well-established psychometric properties, and widespread application in clinical and research settings. General intelligence, a hold measure, was estimated using scores from the WAIS-R Information subtest (Wechsler, 1981). A detailed description of each of these tasks can be found in an earlier publication (White et al., 2001). To test the hypothesis being evaluated in this report, we predicted that sarin and

Table 1
Neuropsychological test battery

Functional domain	Neuropsychological task	Reference	Function measured	Outcome measures analyzed
Attention	Continuous performance test	Letz (1991)	Measure of sustained attention	Mean response time
	Trail-making test, A	Halstead (1947)	Evaluation of spatial attention and simple visuospatial tracking	Time to completion
	WAIS-R Digit spans (forward)	Wechsler (1981)	Evaluation of simple a ttention and tracking	Span score
Executive function	Trail-making test, B	Halstead (1947)	Evaluation of spatial attention	Time to completion
	Wisconsin card sorting test	Heaton et al. (1993)	Test of inferential reasoning and complex visuospatial tracking	Number of correct sorts
	WAIS-R Digit spans (backward)	Wechsler (1981)	See WAIS-R Digit span above	Span score
Psychomotor function	Finger Tapping	Halstead (1947)	Assessment of motor speed	Number of taps: dominant and non-dominant hands
	Purdue Pegboard	Purdue Research Foundation (1948)	Assessment of motor dexterity	Number of pegs placed: dominant hand, non-dominant hand and both hands
Visuospatial abilities	WAIS-R Block Designs	Wechsler (1981)	Evaluation of spatial abilities	Raw score
Short-term memory	California verbal learning test	Delis et al. (1987)	Assessment of verbal memory	Raw scores: short and long delayed memory
	WMS-R verbal paired associate learning	Wechsler (1987)	Evaluation of retention of verbal information	Raw scores, difficult items, delayed recall
	WMS visual reproductions	Wechsler (1945)	Evaluation of learning and retention of visual designs	Raw scores, immediate and delayed recall

cyclosarin exposure would be associated with performance on those tasks involving psychomotor and visuospatial abilities and not related to those of attention and executive function or visual and verbal memory after controlling for PTSD symptomatology and WAIS-R Information.

5. Analyses

Statistical analyses were conducted with SAS, version 8 (SAS Institute, 1999). Outlier values were reviewed for each of the primary covariate and outcome variables. Extreme values (more than 3 standard deviations (S.D.) from the group mean) were top- (or bottom-) coded and assigned the value corresponding with the 3 S.D. level. (Overall, less than 2% of cases required any truncation of values.) Transformations of the outcomes measures were also considered in an effort to yield approximate normality and homogeneity of variance. Several of the neuropsychological scores involving mean response times required log-transformation.

The exposure levels for the study participants ranged between no exposure to 0.144 mg min/m^3. Demographic and descriptive characteristics were compared across three groups: high exposure, moderate exposure, and low-to-no exposure group. For these comparisons, analyses of variance (ANOVAs) and Student's *t*-tests were run to compare continuous variables and the χ^2 or Fisher's exact tests were used for the categorical variables.

For all analyses, $p < 0.05$ was considered a significant effect unless otherwise described.

Because the dose-estimates were determined at the unit level (not at the individual level), analyses to examine the relationship between exposure and neuropsychological test performances were carried out by analyses of covariance methods, adjusting for unit groupings, within SAS (using GENMOD procedures to perform generalized estimating equations).

To test the hypotheses concerning neuropsychological test performances, first, an *exposure category model* was used in which high- and moderate-exposure groups as the independent variables were compared to the low-to-no exposure group, with adjustments for factors known to influence neurobehavioral performances (Lezak, 1995; Spreen and Strauss, 1998). These covariates included age, gender, officer status during the GW, WAIS-R Information test score, handedness (left and ambidextrous versus right-handed), head injury, and PTSD symptomatology (the latter using the summary score from the Mississippi PTSD scale (Keane et al., 1988)).

Second, to further evaluate the dose–response relationships between exposure and neurobehavioral functioning, *linear trend models* using the individual unit-level dose-estimates as the independent variable were used. Tabular results of the linear trend analyses are presented in which the parameter estimate indicates the test score increment associated with CWA exposure equal to 0.1 mg min/m^3.

To examine the relationships between sarin and cyclosrain exposure and mood state at the time of testing, similar models to those described above were used without adjustment for handedness.

The magnitude of the effect sizes (Cohen, 1988) for the significant results was determined using the adjusted difference in scores (from the analyses of covariance) divided by the unadjusted standard deviation. Because age is a significant

predictor of neurobehavioral performance scores, the observed exposure effect size is also described in terms of the effect size of age within this study on the given neuropsychological test scores. The effect size for age was determined using separate linear regression models regressing neuropsychological test score on age.

6. Results

As described above in Section 2, the high exposure group included 23 persons with cumulative exposure levels that ranged between greater than 0.072 and 0.144 mg min/m^3. The moderate exposure group included 47 persons with cumulative exposure levels between 0.01296 and 0.072 mg min/m^3. There were 70 persons in the low-to-no group (defined as exposure levels less than 0.01296 mg min/m^3 or the GPL).

There were few significant demographic or descriptive differences among persons in the three exposure categories. However, the level of combat exposure experienced was higher in both the moderate and high exposure groups compared to the low-to-no exposure group, and the rate of current major depressive disorder was higher in the low-to-no group compared to the moderate or high groups (Table 2). Although not statistically significant, the high exposure group compared both with the moderate or low-to-no exposure groups, included more ambidextrous or left-handed individuals and lower levels of PTSD symptomatology, psychological symptomatology, and psychiatric diagnoses.

Sarin and cyclosarin exposure was significantly associated with reduced proficiency of the neurobehavioral task performances in a dose-dependent manner in functional domains involving psychomotor and visuospatial abilities, namely on the Purdue Pegboard (timed, fine manual dexterity) and Block Design (visuospatial construction with a motor component) (Table 3). Significantly poorer performances on the Purdue Pegboard and Block Design tasks among the high exposure group and the moderate exposure group compared to the low-to-no exposure group were observed. The high exposure group and moderate exposure groups performed significantly better on the Finger Tapping task compared to the low-to-no exposure group.

Models run for linear trend confirmed significant dose–effect relationships in the functional domains involving psychomotor and visuospatial abilities (Table 4), indicating medium effect size differences for both Purdue Pegboard dominant hand ($d = 0.44$) and Block Designs ($d = 0.43$). The Purdue Pegboard scores for the dominant hand among veterans with estimated exposure levels of 0.1 mg min/m^3 were approximately 1 point lower than those in the low-to no-exposure referent group. This difference is equivalent to the performance effect of being approximately 20 years older on the motor task. For the Block Design task, a score 4 points lower is equivalent to being 15 years older.

Because both the high and moderate exposure groups performed significantly better than the low-to-no-exposure group on the Finger Tapping test, models for the Purdue Pegboard tasks were re-run to adjust for possible confounding due to gross motor abilities. Additionally controlling for the Finger Tapping performance (dominant hand) increased the explanatory power of exposure on all Purdue Pegboard outcome scores in both the exposure category and linear trend models. The effect size for the Purdue Pegboard performance with the dominant hand increased to 0.63. With adjustment for Finger Tapping performance with the dominant hand in the linear trend analyses, the parameter estimate for the Purdue Pegboard with the dominant hand was −1.3 (95% CI (−1.9,

Table 2
Characteristics of study groups

	High exposure group ($n = 23$) (exposure range: >0.072–0.144 mg min/m^3)	Moderate exposure group ($n = 47$) (exposure range: 0.01296–0.072 mg min/m^3)	Low-no exposure group ($n = 70$) (exposure range: <0.01296 mg min/m^3)	F, p-value
Age, mean (S.D.)	34.9 (9.5)	34.6 (10.0)	35.0 (8.8)	0.02, 0.98
Years of education	14.1 (2.5)	13.4 (1.6)	13.8 (2.1)	0.89, 0.42
WAIS-R information raw score[a]	18.5 (6.9)	18.0 (4.2)	19.4 (4.8)	1.16, 0.32
Combat exposure score	7.9 (5.3)	8.2 (4.2)	6.1 (3.4)	4.21, 0.02
Mississippi PTSD scale score	66.7 (16.8)	73.0 (18.4)	74.1 (25.3)	1.02, 0.36
BSI—general severity index	0.55 (0.55)	0.65 (0.61)	0.75 (0.82)	0.80, 0.45
	High exposure group ($n = 23$) (exposure range: >0.072–0.144 mg min/m^3)	Moderate exposure group ($n = 47$) (exposure range: 0.01296–0.072 mg min/m^3)	Low-no exposure group ($n = 70$) (exposure range: <0.01296 mg min/m^3)	χ^2, p-value
Female (%)	56.5	38.3	42.9	2.11, 0.35
Officer (in 1991) (%)	13.0	4.3	14.3	3.11, 0.21
Left-handed or ambidextrous (%)	26.1	6.4	15.7	5.13, 0.08
History of head injury with loss of consciousness (%)	8.7	12.8	10.0	0.34, 0.84
Current PTSD diagnosis (%)	0	6.4	5.8	1.48, 0.48
Current MDD diagnosis (%)	0	2.1	12.9	7.00, 0.03
CMI case (%)	65.2	61.7	75.4	2.63, 0.27

PTSD, post-traumatic stress disorder; MDD, major depression; CMI, chronic multisymptom illness (as defined by Fukuda et al., 1998).
[a] Higher score indicates better functioning.

Table 3
Exposure category relationships with neuropsychological performance outcomes, analyzed by analyses of covariance[a]

Outcomes organized by functional domain	Exposure group category[b]	Adjusted parameter estimate	95% CI	*p*-Value
Attention				
Continuous performance test, mean response time	High	0.54	−16.8, 17.8	0.95
	Moderate	−8.8	−19.8, 2.3	0.12
Trail-making test A, mean time to completion	High	−1.8	−3.7, 0.17	0.07
	Moderate	1.1	−0.84, 3.0	0.28
WAIS-R Digit spans (forward), span score[c]	High	0.32	−0.13, 0.78	0.16
	Moderate	0.11	−0.36, 0.58	0.64
Executive function				
Trail-making test B, mean time to completion	High	−2.9	−7.0, 1.1	0.15
	Moderate	3.0	0.44, 5.5	0.02
Wisconsin card sorting test,[b] of correct sorts[c]	High	−0.02	−0.66, 0.62	0.95
	Moderate	1.4	−0.21, 3.0	0.09
WAIS-R Digit spans (backward), span score[c]	High	0.40	−0.07, 0.86	0.10
	Moderate	−0.10	−0.59, 0.40	0.69
Psychomotor function				
Purdue Pegboard, dominant hand[c]	High	−0.93	−1.6, −0.28	0.005
	Moderate	−0.55	−0.92, −0.19	0.003
Purdue Pegboard, non-dominant hand[c]	High	−0.48	−0.92, −0.04	0.03
	Moderate	−0.24	−0.81, 0.32	0.40
Purdue Pegboard, both hands[c]	High	−0.50	−1.1, 0.06	0.08
	Moderate	−0.38	−0.96, 0.19	0.19
Finger Tapping, dominant hand[c]	High	2.4	0.96, 3.8	0.001
	Moderate	2.7	1.1, 4.2	0.0007
Finger Tapping, non-dominant hand[c]	High	2.2	0.83, 3.6	0.002
	Moderate	2.0	0.33, 3.6	0.02
Visuospatial abilities				
WAIS-R Block Designs, raw score[c]	High	−4.0	−5.8, −2.2	<0.0001
	Moderate	−1.9	−3.4, 0.47	0.01
Short-term memory				
California verbal learning test, short-term recall[c]	High	−0.06	−1.4, 1.2	0.92
	Moderate	−1.08	−2.3, 0.15	0.09
California verbal learning test, long-term recall[c]	High	−0.05	−1.3, 1.3	0.94
	Moderate	−0.84	−1.8, 0.16	0.10
Verbal paired associate learning, difficult items, delayed recall[c]	High	0.07	−0.32, 0.46	0.72
	Moderate	−0.006	−0.27, 0.26	0.96
WMS visual reproductions, immediate recall[c]	High	0.62	−0.65, 1.9	0.34
	Moderate	−0.50	−1.5, 0.45	0.30
WMS visual reproductions, delayed recall[c]	High	0.09	−0.98, 1.2	0.87
	Moderate	−0.38	−1.2, 0.42	0.35

[a] Models adjusted for unit group as well as age, gender, WAIS-R Information score, Mississippi PTSD scale scores, rank (officer vs. enlisted), handedness (left and ambidextrous vs. right), and history of head injury.
[b] Exposure group categories compared to low-to-no exposure group.
[c] Higher score indicates more proficient functioning.

−0.75), $p < 0.0001$), the adjusted parameter estimate for the Purdue Pegboard non-dominant hand was −0.57 (95% CI (−1.0, −0.09), $p = 0.02$); the adjusted parameter estimate for the Purdue Pegboard both hands was −0.66 (95% CI (−1.3, −0.07), $p = 0.03$). In all three models, Finger Tapping was significantly associated ($p < 0.005$) with better performance on the Purdue Pegboard tasks.

Higher exposure was not significantly related to mood state when examined by exposure category or linear trend analyses. In the linear trend models, the adjusted parameter estimates were −1.2 (95% CI (−3.8, 1.2), $p = 0.32$) for fatigue, 0.11 (95% CI (−2.0, 2.2), $p = 0.92$) for tension; −1.8 (95% CI (−4.2, 0.46), $p = 0.12$) for depression; −1.2 (95% CI (−3.9, 1.5), $p = 0.39$) for anger; −1.3 (95% CI (−3.2, 0.57), $p = 0.17$) for confusion.

7. Discussion

This is the first published study to examine the relationship between low-level sarin and cyclosarin exposure and objective neurobehavioral performances in 1991 GW veterans. Significant dose-response relationships between exposure and less proficient neuropsychological task performances for psychomotor dexterity and visuospatial abilities (Purdue Pegboard and Block Designs) were present 4–5 years following exposure. Similar results within these same functional domains have been observed in follow-up studies of sarin-exposed Tokyo residents (Miyaki et al., 2005; Nishiwaki et al., 2001; Yokoyama et al., 1998). Also, the results are consistent with persistent effects seen in persons with chronic low-level organophosphate pesticide exposure (Misra et al., 1994; Stokes et al., 1995),

Table 4
Linear dose–effect relationships with neuropsychological performance outcomes, analyzed to examine linear trends by analyses of covariance[a]

Outcomes organized by functional domain	Adjusted parameter estimate[b], for 0.1 mg min/m^3	95% CI	p-Value
Attention			
Continuous performance test, mean response time	0.54	−16.8, 17.8	0.95
Trail-making test A, mean time to completion	−1.8	−3.7, 0.17	0.07
WAIS-R Digit spans (forward), span score	0.32	−0.13, 0.78	0.16
Executive function			
Trail-making test B, mean time to completion	−2.9	−7.0, 1.1	0.15
Wisconsin card sorting test, # of correct sorts	0.65	−0.79, 2.1	0.38
WAIS-R Digit spans (backward), span score	0.40	−0.07, 0.86	0.10
Psychomotor function			
Purdue Pegboard, dominant hand	−0.93	−1.6, −0.28	0.005
Purdue Pegboard, non-dominant hand	−0.48	−0.92, −0.04	0.03
Purdue Pegboard, both hands	−0.50	−1.1, 0.06	0.08
Finger Tapping, dominant hand	2.4	0.96, 3.8	0.001
Finger Tapping, non-dominant hand	2.2	0.83, 3.6	0.002
Visuospatial abilities			
WAIS-R Block Designs, raw score	−4.0	−5.8, −2.2	<0.0001
Short-term memory			
California verbal learning test, short-term recall	−0.06	−1.4, 1.2	0.92
California verbal learning test, long-term recall	−0.05	−1.3, 1.3	0.94
Verbal paired associate learning, difficult items, delayed recall	0.07	−0.32, 0.46	0.72
WMS visual reproductions, immediate recall	0.62	−0.65, 1.9	0.34
WMS visual reproductions, delayed recall	0.09	−0.98, 1.2	0.87

[a] Models adjusted for unit group as well as age, gender, WAIS-R Information score, Mississippi PTSD scale scores, rank (officer vs. enlisted), handedness (left and ambidextrous vs. right), and history of head injury.
[b] Parameter estimate is adjusted for model covariates; the value signifies the change in the outcome task performance associated with exposure at the 0.1 mg min/m^3 level.

which operate also as anticholinerestase agents. Direct comparisons between our findings and those of the Japanese studies are hindered because the same neurobehavioral tasks were not administered. The Japanese did not administer the Purdue Pegboard or WAIS-R Block Design task. Also, the Finger Tapping and Digit span test used were computer-administered (Miyaki et al., 2005; Nishiwaki et al., 2001) and thus had different outcome measures than those in this study.

The findings suggest that lowered visuospatial and fine manual motor dexterity may reflect residual or possibly delayed effects of exposure to sarin and cyclosarin. However, whether these findings might represent residual or delayed effects cannot be confirmed within this study, as assessments of neurobehavioral functioning were not made prior to deployment or immediately after deployment. To make those conclusions, assessments of neurobehavioral task performances prior to deployment, then more proximal to the time of exposure (such as immediately upon return), and subsequently through follow-up examinations are necessary. In light of these findings, continued long-term follow-up of subcohorts of 1995 Tokyo and 1994 Matsumoto residents present during the sarin incidents and involved in the earlier studies with a standardized and consistently applied neurobehavioral task battery, would be informative.

A particular strength, and unique quality, of this study is that the assessment of outcomes included objective tests of neurobehavioral functioning conducted *prior* to the public announcement that the munitions detonated at Khamisiyah contained sarin and cyclosarin and the subsequent distribution of notification letters by DoD. The likelihood of reporting bias is limited in this study as the exposure categorizations were not based on an individual's self-report about whether they were in the area of Khamisiyah and the neurobehavioral outcomes were assessed via objective performance-based tasks. The modeled exposure estimates and thus the exposure-level categories may be subject to misclassification bias (US General Accounting Office, 2004), but this bias is likely to be random and thus would tend to reduce the size of any associations. Furthermore, rather than using notification status or binary exposure categories (Khamisiyah exposure versus not) as has been used in most studies investigating health effects of Khamisiyah (Bullman et al., 2005; Gray et al., 1999; McCauley et al., 2001, 2002; Smith et al., 2003), cumulative exposure estimates (e.g., Gackstetter et al., 2006) were used to permit the assessment of dose–response relationships.

Mood complaints were not found to be associated with sarin and cyclosarin exposure in this study. Changes in mood are most often the first noticeable effect with low-level neurotoxicant exposures (White et al., 1992), but they are also often reversible. It is possible that mood changes are proximal effects of low-level exposure that then dissipate over time.

One interesting secondary observation in this study was the finding of better Finger Tapping performance among persons with higher exposures. Both the Finger Tapping and the Purdue Pegboard tasks are related in that they measure general psychomotor functioning abilities. However, these tasks also test distinct functional capabilities. As noted, the Finger Tapping task involves simple gross motor speed, that is, how many times a person can tap the index finger within a certain time limit. The Purdue Pegboard task involves the fine motor

dexterity skills required for picking up pegs and placing them appropriately within specific holes within a time frame. In clinical observations of persons with neurotoxicant exposures (White et al., 1992) and in several disorders affecting the motor system, such as patients with early Parkinson's disease, dissociations between Finger Tapping and the Purdue Pegboard tasks can be seen in which there is normal performance on Finger Tapping but not on more complex tests such as Purdue Pegboard. Also, simple motor actions, such as Finger Tapping, are highly sensitive to training (Meister et al., 2005). As described above, those in the high and moderate groups experienced higher levels of combat exposure during their deployment, and review of their reported military occupational specialties revealed that a majority worked in jobs where manual dexterity and finger speed would be expected (forward medical unit staff, equipment repair personnel and military police). In this study, we speculate that the finding of better Finger Tapping in the high exposure group, compared to the low-to-no exposure group, reflects the occupational training and skill set abilities of Army personnel more likely to be in the higher exposure areas, rather than a direct association with sarin and cyclosarin exposure. This hypothesis warrants further investigation in additional studies with military personnel.

It is important to point out that the hypothesis being examined in this study focuses on exposure to sarin and cyclosarin in the area around Khamisiyah, Iraq in March 1991 and specific neurobehavioral effects 4–5 years after exposure. The focus was not on whether exposure to sarin and cyclosarin as a result of the Khamisiyah incident is associated with GW veterans' illnesses in general. In fact, in this cohort, the rate of chronic multisymptom illness (as defined by Fukuda et al., 1998) is significantly higher in the low-to-no exposed group than the two higher exposed groups. Etiological issues associated with the long-term neurological health of GW veterans may not ever be resolved completely (Vasterling and Bremner, 2006) due to the lack of prior baseline health information, limited objective information about exposures and experiences encountered during deployment, and the impact of intervening factors since deployment.

For future deployments, attention to assessment of pre-deployment functioning combined with conduct of in-theatre environmental exposure measurements and post-deployment biological and objective performance monitoring may enhance efforts to improve force health protection and further prevent potential long-term health consequences of military service.

DISCLAIMER

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

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