

JP-8 Jet Fuel Exposure and Divided Attention Test Performance in 1991 Gulf War Veterans

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Introduction: Previous research indicates that a large cohort of veterans from the 1991 Gulf War report polysymptomatic conditions. These syndromes often involve neurocognitive complaints, fatigue, and musculoskeletal symptoms, thus overlapping with civilian illnesses from low levels of environmental chemicals, chronic fatigue syndrome, and fibromyalgia. **Methods:** To test for time-dependent changes over repeated intermittent exposures, we evaluated objective performance on a computerized visual divided attention test in chronically unhealthy Gulf War veterans (n = 22 ill with low-level chemical intolerance (CI); n = 24 ill without CI), healthy Gulf War veterans (n = 23), and healthy Gulf War era veterans (n = 20). Testing was done before and after each of three weekly, double blind, low-level JP-8 jet fuel or clean air sham exposure laboratory sessions, including acoustic startle stimuli. **Results:** Unhealthy veterans receiving jet fuel had faster mean peripheral reaction times over sessions compared with unhealthy veterans receiving sham clean air exposures. Unhealthy Gulf veterans with CI exhibited faster post- vs. pre-session mean central reaction times compared with unhealthy Gulf veterans without CI. Findings were controlled for psychological distress variables. **Discussion:** These data on unhealthy Gulf veterans show an acceleration of divided attention task performance over the course of repeated low-level JP-8 exposures. The present faster reaction times are consistent with rat neurobehavioral studies on environmental toxicant cross-sensitization and nonlinear dose-response patterns with stimulant drugs, as well as some previous civilian studies using other exposure agents. Together with previous research findings, the data suggest involvement of central nervous system dopaminergic pathways in affected Gulf veterans.

Keywords: Persian Gulf syndrome, environmental illness, jet fuel, divided attention, sensitization, dopamine.

PRIOR RESEARCH ON health problems of 1991 Persian Gulf War (PGW) veterans has shown that many suffer from polysymptomatic conditions that overlap with controversial civilian syndromes such as multiple chemical sensitivity or chemical intolerance (CI), fibromyalgia, and chronic fatigue syndrome (11,18–20,30,35,51,55,60,62). Neurocognitive complaints are common in these syndromes, including attention, executive function, and memory disturbances in ill PGW veterans (17,24,39,46). Consistent with memory abnormalities, a recent neuroimaging study with proton magnetic resonance spectroscopy showed hippocampal dysfunction in younger PGW veterans with chronic fatigue and acquired chemical sensitivity (49). War-related chemical exposures that may have contributed to polysymptomatic illnesses in Gulf veterans in-

cluded jet fuel, kerosene, pesticides, insect repellents, corrosion-resistant paints, burning oil wells, pyridostigmine, and neurotoxic chemical weapons such as sarin (during Allied destruction of storage bunkers) (1,15,37,40).

Part of the variance in the veterans' cognitive problems may be explained by psychological distress (5,42,63). However, Gulf veterans and chronic fatigue syndrome patients exhibit cognitive dysfunctions above and beyond those attributable to purely emotional factors (24,28,46). Civilians with chronic fatigue syndrome who do not have psychiatric comorbidity show greater cognitive disturbance than do those who carry psychiatric diagnoses (28). Overall, growing evidence indicates that stress and psychiatric disorders explain only a limited portion of the variance in these chronic multisymptom illnesses, including Gulf War syndrome (1,10,12–14,34,44,57).

Fatigue itself can play a role in neuropsychological disturbances. Ross et al. (60), for example, demonstrated deficits in divided attention in chronic fatigue syndrome patients correlated with severity of fatigue, even when other cognitive measures were objectively normal. Divided attention, a key ability for safe automobile driving (or airplane piloting), is also impaired by sleep loss, alcohol ingestion, and various types of brain injury (47,59). The early post-war follow-up study

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findings of increased death rates in Gulf veterans from motor vehicle accidents (43) could have derived, in part, from deficits in divided attention resulting from multiple factors.

Individual differences in tolerance to low levels of environmental chemicals (CI) alter neurocognitive performance and motivational behaviors, including divided attention task performance. For example, middle-aged persons with CI who have made lifestyle changes in response to their chemical sensitivities exhibit shortening of central reaction times on a complex visual divided attention task over repeated chemical exposure sessions (galaxolide, propylene glycol) separated by 1 wk (9). On the other hand, older individuals with CI show slower resting performance in central and peripheral reaction times compared with normal older controls on the same divided attention task (16).

Apart from age-related human differences, animal studies on JP-8, a widely used military jet fuel, reveal nonlinear neurobehavioral dose-response patterns. Compared with controls, repeated intermittent JP-8 exposures at lower doses have been shown to improve (6), whereas higher doses have been shown to impair, learning ability for complex tasks in rats (58). Furthermore, repeated intermittent exposure to toxicants such as JP-8 jet fuel, formaldehyde, or toluene can initiate progressive amplification or sensitization, and, eventually, bi-directional oscillation of dopamine-dependent behavioral activation responses over time in animals (25,45). The chemical effects cross-sensitize with those of stimulant drugs such as amphetamine or cocaine (61,66–68,74,75). Dopaminergic pathways in the interconnected mesolimbic system and prefrontal cortex play an important role in modulation or expression of sensitization processes (31,73) and attentional abilities (27,36).

A one-session exposure test study in PGW veterans with CI found no cognitive impairments during occupational levels of JP-8 exposure (33). However, the latter study had no sham exposure controls, did not use repeated exposure sessions, and did not test the extremely low-level exposures reported as problematic by persons with CI. Prior research indicates that repeated exposure sessions to low-level chemicals that test for laboratory-based time-dependent sensitization (amplification) may be necessary to elicit altered chemical responsivity in persons with CI (7,12). Moreover, elicited neurobehavioral changes in CI are potentially nonlinear and/or bi-directional, with either improvements or impairments of a given outcome as a function of host exposure history, current state, and/or toxicant dose (26,56). The purpose of this study was to extend prior research to compare unhealthy U.S. Gulf veterans with and without CI vs. healthy Gulf War and healthy Gulf era veterans (i.e., veterans in military service during the same time period or era, but who were not deployed to the Persian Gulf) on visual divided attention task performance before and after three repeated, very low-level jet fuel (jet propulsion 8, JP-8) and sham clean air exposure sessions.

METHODS

Subjects

Military veterans, both men and non-pregnant women, living in southern Arizona, screened to be non-smokers, non-alcoholics, non-psychotic, non-epileptic, and non-asthmatic, were recruited with newspaper advertisements, announcements, and flyers sent to Veterans Affairs (VA) Gulf War Registry participants at the Southern Arizona VA Health Care System, local active duty posts in the southern Arizona area, and local veterans' organizations. Subjects were screened for criteria into four different groups: 1) unhealthy Gulf veterans with CI ($n = 22$); 2) unhealthy Gulf veterans without CI ($n = 24$); 3) healthy Gulf veterans ($n = 23$); and 4) healthy Gulf era veterans who had served in the military at the time of the Gulf War but had never been deployed to the geographic region of the Persian Gulf ($n = 20$).

Based on pilot data, the criteria for "illness" and "health" derived from the 12-item subscale of the previously validated Quick Environmental Exposure and Sensitivity Inventory [each item rated 0–10 with 10 = disabling, rated for the time period immediately prior to joining the military (preservice), within 1 yr after the Gulf War (postservice), and at the current time (current)] (50). For unhealthy veterans (groups 1 and 2), preservice scores were < 12 , difference scores between post- and preservice were > 13 , and difference scores between current and preservice were > 19 . For healthy veterans (groups 3 and 4), preservice scores were < 5 , difference scores between post- and preservice were < 12 , and difference scores between current and preservice were < 15 .

CI scores derived from a 17-item version of the validated Bell CI Index (71) (5-point Likert ratings; possible range 17–85), listing common environmental chemicals identified as salient for Gulf veterans from Miller et al.'s previous research (51). Veterans classified with CI (group 1) had difference scores between current time and preservice of > 12 . Those without CI (groups 2, 3, 4) had current and preservice scores both < 35 and difference scores between current time and preservice of ≤ 4 . Participants had to be stable on any medications for 1 mo before and during the study.

The project was reviewed and approved in advance by the Southern Arizona Veterans Affairs Health Care System Research and Development Committee and the University of Arizona Human Subjects Committee. All participants gave written informed consent before participating in this study.

Apparatus

During the exposure periods, the veterans wore a nasal cannula connected to an air-flow pump (SKC model 222, SKC Gulf Coast West, Inc., Fullerton, CA) with Teflon tubing. The pump delivered the contents of each 3-L session Teflon test bag (SKC, Fullerton, CA), which was filled with 2 L of medical quality compressed air (Nelcor-Puritan Bennett, Pleasanton, CA), and delivered at a rate of $2.4 \text{ ml} \cdot \text{s}^{-1}$. Prior to use, test bags containing jet fuel were prefilled with $2 \mu\text{l}$ of JP-8

fuel, sealed, and heated in an incubator (Model 12-140, J&H Berge-Quincy Lab Inc., S. Plainfield, NJ) for at least 4 h at 50°C to volatilize the contents. The computed JP-8 concentration was 0.00057 parts per million. The contents of the clean air sham and JP-8 test bags were periodically sampled and confirmed using gas chromatography every 3 mo. The JP-8 jet fuel for this study was drawn from the same source as that used in a previous animal study showing behavioral hyperreactivity (6). JP-8 was chosen because of its widespread use as a multi-purpose, complex kerosene fuel. Human exposure to JP-8 typically occurs through inhalation or dermal routes.

Procedures

All veterans completed the North American Adult Reading Test (as an estimate of premorbid intelligence) (72), Profile of Mood States Scale (54) (Educational and Testing Service, San Diego, CA), and the Daily Stress Inventory (21,22). Within each of the four groups, veterans were randomized to receive 7-min continuous double-blind exposures of either low-level JP-8 jet fuel or clean air sham for the 3 successive weekly sessions, all scheduled for the same time of day for each participant (context-dependent sensitization protocol). Clean air rather than a presumptively benign "masking" odor was chosen for the sham condition because of the focus on possible sensitization in the present design. Data on civilians with CI have demonstrated that use of a comparison chemical odor presumed to be "inactive" or benign, e.g., peppermint, can nonetheless initiate a sensitizing process in susceptible individuals (32).

Participants did not cross over between exposure conditions at any time during the study. Each participant underwent either all three JP-8 or all three sham clean air exposures to avoid within-subject carry-over effects and resultant confounds. Therefore, no subject ever had an opportunity to compare how the JP-8 or sham clean air exposures smelled. Furthermore, the divided attention testing was done before and after, but never during, the laboratory exposures in each session. During each chemical exposure session, participants underwent 15 trials of randomly presented acoustic startle stimuli (psychophysiological results, Bell et al., 2005, in preparation). Acoustic startle stimuli were presented binaurally through a Startle Telephonics Headset using the Coulbourn LabLinc V-85-05 System Human Startle System (Allentown, PA), with randomized computer generation of 1000-Hz tone stimuli at 1 V amplitude.

Veterans performed the visual divided attention test before and after each chemical exposure/acoustic startle session. The divided attention test is a computer-administered proprietary visual vigilance test developed at the University of Chicago that is sensitive to the effects of sleep loss and various sedative-hypnotic medications (29) as well as stimulants (52). The divided attention task challenges subjects to monitor a computer screen for any of three different visual stimuli and to respond differentially to the random appearance of each event. This type of task has proven useful for assessing fatigue in sleep loss research (41,59) and

chronic fatigue syndrome studies (60), for detecting cognitive difficulties of civilians with illness from low levels of environmental chemicals (9,16), and for demonstrating enhanced human performance on stimulant drugs (52). The task involves three simultaneous requirements: 1) tracking a moving stimulus in the center of a monitor screen while pressing one of two different buttons on detection of the random appearance of new stimuli in the 2) center or 3) periphery of the screen. Each divided attention test sequence involves 13 min of testing divided into 4 trials, all together involving a total of 52 central and 52 peripheral visual stimuli.

RESULTS

Baseline Group Differences

Statistical analyses: One-way analyses of variance with post hoc Tukey tests and Chi-square tests were conducted prior to the main analyses in order to identify any demographic and baseline trait differences between the groups and subgroups.

Results: The overall sample was 86% male; groups did not differ in gender distribution. Hispanic ethnicity was significantly different between the groups [χ^2 (3) = 12.146, $p < 0.007$]. There were more Hispanics in the group of unhealthy veterans with CI (50%) than in either of the healthy groups (healthy Gulf: 13%; Gulf-era: 10%); the unhealthy Gulf War veterans without CI were 29% Hispanic. Controlling for Hispanic ethnicity, age was significantly different between the groups ($p < 0.05$). The Gulf-era veterans were older than each of the Gulf War groups [F (3,86) = 5.3, $p < 0.05$, post hoc $p < 0.05$; Gulf-era: 45.1 SD 7.7 vs. unhealthy Gulf with CI: 39.2 SD 6.6, unhealthy Gulf without CI: 37.6 SD 8.1 yr].

Unhealthy Gulf War veterans with CI had lower estimated IQs (as estimated by the North American Adult Reading Test for a full scale Wechsler IQ score) than did healthy Gulf-era veterans [F (3,83) = 4.8, $p < 0.05$; post hoc $p < 0.05$]. The unhealthy Gulf War veterans without CI had a marginally significant lower estimated IQ than the Gulf-era veterans ($p < 0.06$). The unhealthy Gulf War veterans with CI had significantly more negative mood total scores on the Profile of Mood States Scale than did the two healthy groups [F (3,84) = 4.0, $p < 0.05$; post hoc $p < 0.05$]. Groups did not differ in baseline scores on the Daily Stress Inventory or on distribution of exposure to medications (the most common drugs were non-prescription analgesics, vitamin supplements, and gastrointestinal agents).

Analyses were also conducted to determine if there were differences between groups in their ability to guess correctly whether or not they received JP-8 or sham exposures during the sessions. A Chi-square analysis, collapsed across the first three sessions, showed that veterans in the sham condition were more likely to guess correctly [χ^2 (1) = 7.068, $p < 0.008$]. Controlling for both age and group membership, a general linear model repeated measures analysis was also performed across the three sessions. There was a significant main effect for exposure type [F (1,79) = 14.89; $p < 0.001$]; persons in the sham condition were still more likely to guess correctly (70.2% vs. 44.7%). It is important to

emphasize, however, as described in the Methods section, that no subject was ever exposed to both the JP-8 and the sham clean air. Any given subject received either all JP-8 exposures or all sham clean air exposures and thus had no opportunity to compare the exposure types.

Change on Divided Attention Test Variables Over Session/Trials

Statistical analyses: For sessions 1–3, hierarchical random coefficient regression models were estimated using the SAS PROC general linear model. This approach permits assessment of the slope, or the linear effect of time, on the outcome variable over sessions or trials. Hierarchical random coefficient regression is an analytic method of multilevel growth curve analysis conceptualizing individual change in a two-level hierarchical regression model. The first level represents an individual's growth trajectory, or rate of change, expressed as a set of parameters (intercept, slope, and error). At the second level, the individual parameters (slopes) become the dependent variables with more stable characteristics (e.g., covariates, group membership) as predictors allowing one to determine which factors or experimental manipulations significantly influence the rate of change.

Hierarchical random coefficient regression analysis has several advantages over traditional repeated measures analysis of variance. The primary advantage is the ability to handle missing data. Traditional repeated measures analysis requires complete data for each person. In hierarchical random coefficient regressions, participants with incomplete data are included in the analysis; however, cases with complete data are given greater weight (23). Another problem is that repeated measures analysis of variance can produce inaccurate estimates of the error terms and parameters (see 53 for a complete discussion).

The results of hierarchical random coefficient regression analysis are presented in the figures as estimated slopes calculated from parameters generated from regression equations, not means; therefore, error bars are not applicable. Session (1–3) and trial (one pre-exposure, two post-exposure within a session) were subjected to natural logarithmic transformations to address the anticipated curvilinear sensitization pattern. In this type of analysis, contrasts can be added as predictors to the model to determine the effect of group on the linear time slope, i.e., does the rate of change across sessions or trial vary based on group membership as defined in the contrast.

In the present analysis three orthogonal contrasts were created to test for the hypothesized differences between groups: 1) a combination of both unhealthy groups (with and without CI) vs. a combination of both healthy groups (healthy Gulf and Gulf-era); 2) unhealthy with CI vs. unhealthy without CI; and 3) healthy Gulf vs. healthy Gulf-era. The model estimates main effects (session collapsed across group, trial, and exposure; trial collapsed across group, session, and exposure), two-way interactions (contrast \times trial collapsed across exposure and session, contrast \times session

collapsed across trial and exposure, exposure \times session collapsed across trial and group, exposure \times trial collapsed across trial and group, and interactions between the covariates and exposure, trial and session), and three-way interactions (contrast \times exposure \times session collapsed across trial, contrast \times exposure \times trial collapsed across session).

In addition to estimating main and interaction effects, additional variables that may influence the slope of the outcome variable can be controlled for in the analyses. In the present analyses, variables on which group differences were found (described above) were used as covariates (age, Hispanic ethnicity, IQ as estimated by the North American Adult Reading Test, correct guess of exposure type, and pre-session Profile of Mood States Scale total negative mood score for each session). Although baseline group differences were not found for the Daily Stress Inventory, changes in the Daily Stress Inventory over sessions as a function of exposure condition were found. Therefore, pre-session Daily Stress Inventory ratings (for each session) were also included as a covariate. The final model included the following predictors: the covariates, main effect of trial, main effect of session, covariate interactions (two-way interactions), exposure by session and trial (two-way interaction), each contrast by trial (two-way interaction), each contrast by session (two-way interaction), each contrast by exposure and session (three-way interaction), and each contrast by exposure and trial (three-way interaction). The statistical significance of the overall model, as well as statistically significant individual predictors are presented.

Results: Groups did not differ significantly for mean tracking error as a function of session, trial, or exposure condition. **Table I** presents the raw means and SDs of the subgroup values presented by exposure status (JP-8 or sham clean air) for mean central and mean peripheral reaction times. For mean central reaction time, although the overall model was significant [$F(118,400) = 10.25, p < 0.0001, R^2 = 0.75$], there were no significant three-way interactions. However, a two-way interaction for exposure by trial, collapsed across group and session [$F(1,400) = 3.97, p < 0.05$], was found. Veterans receiving JP-8 exhibited a greater decrease in slope from pre- to post-trial (faster central reaction times) than veterans receiving clean air sham. A two-way interaction collapsing across session and exposure for contrast 2 by trial was also found. Unhealthy veterans with CI exhibited a greater decrease in slope from pre- to post-trial (faster central reaction times) than the unhealthy veterans without CI [$F(1,400) = 4.12, p < 0.04$; **Fig. 1**]. No statistically significant differences were found for contrasts 1 and 3.

For mean peripheral reaction time, the overall model was significant [$F(104,414) = 14.84, p < 0.0001, R^2 = 0.79$]. All three contrasts were also significant for three-way interactions of group by exposure by session (**Fig. 2**). For the contrast between the unhealthy veterans with CI vs. the unhealthy veterans without CI (**Fig. 2A**), the slope increased over sessions for both groups in the sham condition, indicating longer mean peripheral reaction time scores, while the slope decreased in the JP-8

TABLE I. RAW MEANS AND SDS FOR GROUP BY EXPOSURE TYPE BY SESSION.

Group	Session 1		Session 2		Session 3	
	JP-8	Sham	JP-8	Sham	JP-8	Sham
Mean Central Reaction Time (ms)						
Unhealthy GW veterans with CI	1.02 ± 0.40	0.76 ± 0.46	0.96 ± 0.59	0.93 ± 0.59	1.07 ± 0.74	0.90 ± 0.58
Unhealthy GW veterans without CI	0.67 ± 0.53	0.69 ± 0.29	0.68 ± 0.48	0.72 ± 0.33	0.82 ± 0.36	0.74 ± 0.36
Healthy GW veterans	0.70 ± 0.37	0.66 ± 0.15	0.71 ± 0.37	0.61 ± 0.24	0.69 ± 0.35	0.59 ± 0.22
Healthy GW-era veterans	0.59 ± 0.31	0.66 ± 0.38	0.65 ± 0.35	0.81 ± 0.48	0.57 ± 0.41	0.58 ± 0.28
Mean Peripheral Reaction Time (ms)						
Unhealthy GW veterans with CI	1.30 ± 0.37	1.19 ± 0.19	1.27 ± 0.38	1.18 ± 0.21	1.21 ± 0.38	1.22 ± 0.26
Unhealthy GW veterans without CI	1.26 ± 0.24	1.04 ± 0.18	1.15 ± 0.20	1.05 ± 0.17	1.12 ± 0.19	1.13 ± 0.23
Healthy GW veterans	1.10 ± 0.24	1.22 ± 0.25	1.09 ± 0.25	1.08 ± 0.24	1.03 ± 0.18	1.10 ± 0.31
Healthy GW-era veterans	1.13 ± 0.18	1.04 ± 0.33	1.04 ± 0.19	0.96 ± 0.26	1.02 ± 0.26	0.99 ± 0.27

GW = Gulf War, CI = chemical intolerance.

condition, indicating shorter mean peripheral reaction time scores, with the greatest rate of change over sessions occurring in the unhealthy veterans without CI [F (1,414) = 3.87, $p < 0.05$].

In the contrast between the healthy Gulf War veterans and the healthy Gulf-era veterans (Fig. 2B), slopes decreased for all groups, indicating faster mean peripheral reaction times over sessions [F (1,414) = 5.16, $p < 0.02$]. However, the healthy Gulf War veterans in the sham condition showed the greatest decrease, followed by Gulf-era veterans in the JP-8 condition. In general, the Gulf-era veterans in the JP-8 exposure condition had lower mean peripheral reaction time scores across sessions, indicating faster mean peripheral reaction time scores. In the third contrast (Fig. 2C), unhealthy veterans in the sham condition (with and without CI, combined) showed an increase in the slope over time, indicating a slower performance over sessions on their mean peripheral reaction time scores, while the three remaining groups all showed a decrease in slope, indicating faster performance over sessions, although the unhealthy veterans in the JP-8 group were slower overall [F (1,414) = 6.89, $p < 0.01$].

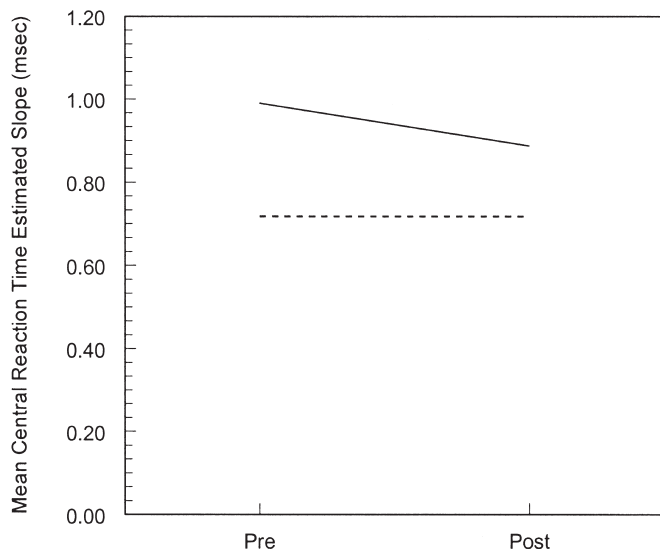


Fig. 1. Estimated slopes of pre- to post-session mean central reaction times in unhealthy Gulf veteran subgroups with and without chemical intolerance (CI). The solid line represents unhealthy Gulf veterans with CI, the dashed line unhealthy Gulf veterans without CI.

DISCUSSION

Time-dependent sensitization is the progressive amplification of host responses to repeated intermittent exposures to a foreign substance or stressor (2). Consistent with time-dependent sensitization to low-level exogenous exposures (2,61), JP-8 exposed veterans in this study exhibited faster peripheral reaction times over time (sessions) compared with unexposed veterans. Unhealthy veterans with CI showed faster central reaction times in comparison with other unhealthy veterans without CI from pre- to post-session assessments.

The slope findings suggest that certain subgroups showed less change (Fig. 1) or even shifted in the opposite direction from other subgroups over time (Fig. 2A and 2C). Two possible factors may have contributed to these observations: 1) subgroups were already at their respective ceiling or floor for the central or peripheral reaction time performance; and/or 2) individual differences in prior exposure histories and degrees of current sensitivity influenced the direction of change from the laboratory exposures. Antelman's group has demonstrated in animals that the direction of sensitized responses varies as a function of either the intensity of the original, initiating exposure (4) and/or the number of prior eliciting exposures (3,25).

These data are similar to those seen in a previous civilian study in our laboratory (9) in which mean central reaction times became faster over two sessions in persons with CI, especially those individuals with associated lifestyle changes (e.g., diet, home environment). In the latter investigation, the chemicals were galaxolide, a perfume constituent, and propylene glycol, a common solvent; no noise stimuli were given with the exposures in the previous study. However, it is possible that the current unhealthy Gulf veterans without CI (Fig. 1) began the study at a floor for possible changes in central reaction time, thus making it difficult to observe any potential decreases in mean central reaction time that might have otherwise occurred in those subjects.

A limitation of the present study is that the delivered JP-8 concentration was confirmed periodically, but not at each session. Therefore, it is possible that there were some random fluctuations in levels during the study. However, the fact that the test bags were freshly prepared for each session using the same procedures, and

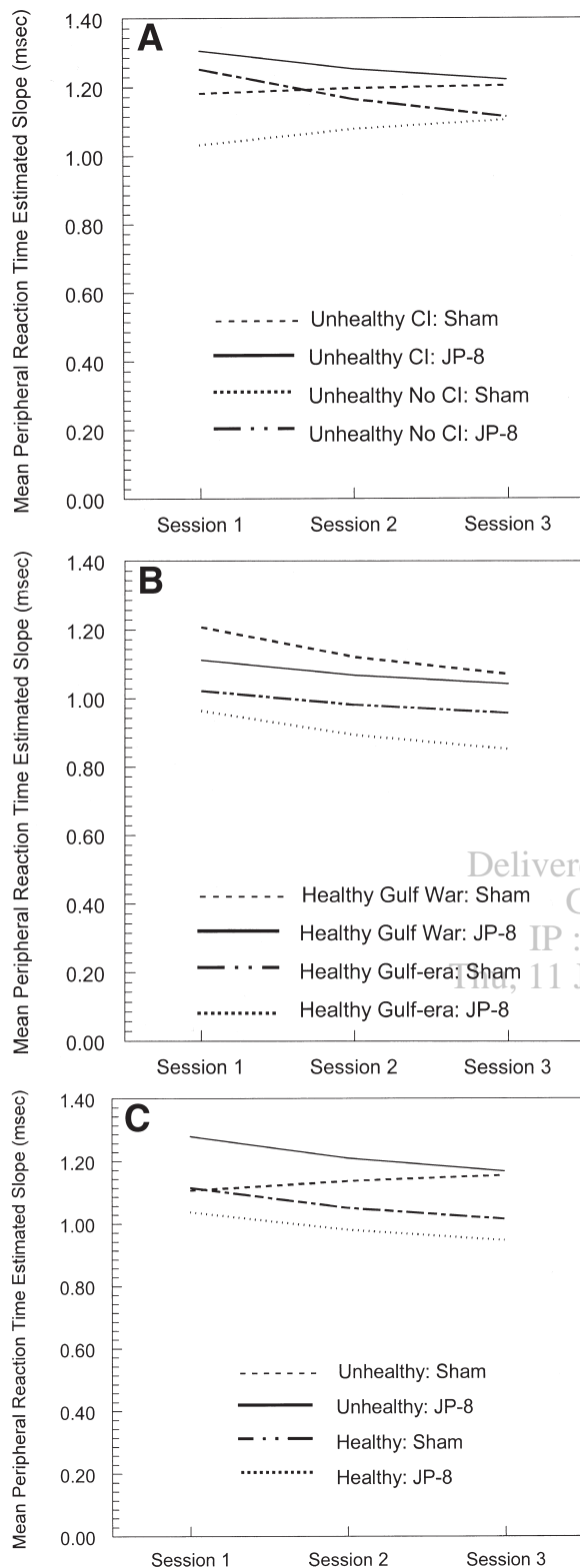


Fig. 2. Estimated slopes of changes in mean peripheral reaction time over time showing planned comparisons of subgroups with one another, each exposed to either JP-8 jet fuel or clean air sham by inhalation. A) Unhealthy Gulf veterans with vs. without CI. B) Healthy veterans, Gulf vs. non-Gulf-era service. C) Unhealthy Gulf veterans (combined CI and non-CI) vs. healthy veterans (combined Gulf and Gulf-era).

the subjects in the groups were run in all sessions under the same randomized, double-blind protocol would be expected to expose all of the groups and subgroups

equally and randomly to any such fluctuations in exposure levels. The exposure findings would thus not have been subject to any systematic bias.

In the earlier human study (9), within three successive divided attention tests in a 12-h time period (vs. the 7-d lag of the current design), the civilians with CI and lifestyle changes (presumably sicker individuals) showed a type of oscillatory phenomenon—first faster, then slower performance on mean peripheral and central reaction times—while persons with CI but no lifestyle changes (presumably healthier individuals) showed progressive slowing in the same brief time frame. Oscillatory processes (reversals of direction) are reported in animal models of time-dependent sensitization (25), and may occur at the physiological limits of the organism in its capacity to continue to sensitize. Thus, it remains an open question as to whether or not veterans with the most severe degree of CI would eventually show an oscillatory reversal in the direction of change in their reaction time performance after additional laboratory chemical exposures and a longer period of time.

In the present study, the definitions of “unhealthy” and “healthy” were derived from validated self-report scales. The groups were deliberately defined using non-overlapping cut-offs of the Quick Environmental Exposure and Sensitivity Inventory and Chemical Intolerance Index to ensure separation, albeit arbitrary, in their clinical pictures. Although it would have been desirable to define the groups by “objective” laboratory test criteria, this has not been possible clinically for a large subset of Gulf War veterans who report acquired deteriorations of health as a result of their military service (17). In the field of health psychology, use of the symptomatic definitions and/or self-report scale scores is a widely applied and acceptable strategy for examining individual differences in outcomes. Even if one assumes the skeptical stance that the unhealthy Gulf veterans are “merely” somatizers, then it remains an important question as to whether or not “somatizers” have objective neuropsychological performance differences from non-somatizers under double-blind JP-8 exposure conditions. The evidence to date suggests that, at least for 1991 Gulf War veterans with subjective complaints, cognitive function alterations beyond psychological distress are present under specific exposure conditions (16). Factors that alter central vs. peripheral reaction times on the visual divided attention test merit additional study.

The current findings suggest that reaction time performance on a divided attention task can accelerate over time under certain, intermittent chemical exposure conditions using very low levels of JP-8 jet fuel. The present findings differ from those of Fiedler et al. (33), who found no average differences in divided attention test performance of ill Gulf veterans with CI vs. healthy Gulf veterans in a single exposure session using 5 ppm JP-8 (comparable to occupational exposure levels during jet re-fueling procedures). Possible explanations of the divergence in findings include a previously demonstrated non-linear neurobehavioral dose-response pattern to JP-8 exposures in animal studies (58) (the current

JP-8 concentration was very low at 0.00057 ppm), the lack of repeated intermittent exposure sessions or sham controls in the Fiedler et al. study as contrasted with the three spaced sessions and clean air sham controls in the current investigation, and different subject samples in the two studies. The current study had two additional groups as compared with Fiedler et al., i.e., ill Gulf veterans without CI and healthy Gulf-era veterans.

As discussed earlier, previous research on time-dependent sensitization indicates that the individual's past exposure history and current sensitivity can affect the direction of subsequently elicited responses over repeated exposures (3,4). The relative speeding of central reaction time performance in the present study occurred in individuals with CI vs. those without CI (Fig. 1), where CI might serve as a proxy variable for heightened susceptibility to undergoing sensitization. Within the unhealthy veteran subgroups, repeated JP-8 exposures led to negative slopes (i.e., faster performance), whereas repeated sham clean air exposures led to positive slopes (i.e., slower performance), in peripheral reaction times (Fig. 2A). In the latter case, the contents of the laboratory-based exposures influenced the direction of change. Time-dependent sensitization is a process that involves, in part, dopaminergic mesolimbic pathways in the brain involved in reward and appetitive behaviors (6,31,61,65,69,70). Stimulant-like arousal effects of the JP-8 are also a possible factor in the current findings (6), in addition to nonlinear dose-response patterns (58). JP-8 jet fuel is a complex mixture of aliphatic and aromatic hydrocarbons, including various solvents. These environmental agents can cross-sensitize with known dopaminergic agents such as cocaine and apomorphine (25,26,31,57). Specific tests of mesolimbic dopamine status have not as yet been reported in Gulf War veterans.

Notably, in chronically ill 1991 Gulf War veterans, Haley's group has already demonstrated abnormalities of central dopaminergic metabolites associated with reduced neuronal mass of the left basal ganglia, another major dopaminergic region of the brain (38). A recent study reported that a buspirone challenge test in civilian women with fibromyalgia [a prevalent polysymptomatic condition in Gulf War veterans (30) in which CI is a common comorbidity (8,64)] produced an enhanced prolactin response compared with controls. Prolactin responsivity, regulated by the tuberoinfundibular dopaminergic pathway, was considered a biomarker of increased dopaminergic D2 receptor sensitivity or density (48). Furthermore, civilians with CI exhibit electroencephalographic α frequency sensitivity (12,32), a finding previously shown to be associated with increased mobilization of mesolimbic dopaminergic D2 receptors in animals (31,69). Although beyond the scope of the present study, the convergence of the current JP-8-related alterations in divided attention test performance of Gulf veterans, animal evidence for time-dependent sensitization to JP-8 (61), and the role of mesolimbic and prefrontal dopamine in sensitization (58,73) and attention (27,36) together provide a basis for future research on the possible involvement of various dopaminergic pathways in ill Gulf veterans, especially those with CI.

In conclusion, the current observations warrant further investigation. Visual divided attention testing under repeated, intermittent low-level jet fuel vs. sham clean air exposures differentiates veterans with various chronic health status outcomes. Design considerations should include assessments of longitudinal sensitization, comparisons of divided attention test performance differences in central vs. peripheral reaction times, and nonlinear dose-response relationships that focus on concomitant changes in brain biology and behavior.

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