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Associations between the self-reported frequency of hearing chemical alarms in theater and regional brain volume in Gulf War Veterans

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ABSTRACT

Background: We previously reported evidence of reduced cortical gray matter (GM), white matter (WM), and hippocampal volume in Gulf War (GW) veterans with predicted exposure to low-levels of nerve agent according to the 2000 Khamisiyah plume model analysis. Because there is suggestive evidence that other nerve agent exposures may have occurred during the Gulf War, we examined the association between the self-reported frequency of hearing chemical alarms sound during deployment in the Gulf War and regional brain volume in GW veterans.

Methods: Ninety consecutive GW veterans (15 female, mean age: 52 ± 8 years) participating in a VA-funded study underwent structural magnetic resonance imaging (MRI) on a 3 T scanner. Freesurfer (version 5.1) was used to obtain regional measures of cortical GM, WM, hippocampal, and insula volume. Multiple linear regression was used to determine the association between the self-reported frequencies of hearing chemical alarms during the Gulf War and regional brain volume.

Results: There was an inverse association between the self-reported frequency of hearing chemical alarms sound and total cortical GM (adjusted $p = 0.007$), even after accounting for potentially confounding demographic and clinical variables, the veterans' current health status, and other concurrent deployment-related exposures that were correlated with hearing chemical alarms. Post-hoc analyses extended the inverse relationship between the frequency of hearing chemical alarms to GM volume in the frontal (adjusted $p = 0.02$), parietal (adjusted $p = 0.01$), and occipital (adjusted $p = 0.001$) lobes. In contrast, regional brain volumes were not significantly associated with predicted exposure to the Khamisiyah plume or with Gulf War Illness status defined by the Kansas or Centers for Disease Control and Prevention criteria.

Conclusions: Many veterans reported hearing chemical alarms sound during the Gulf War. The current findings suggest that exposure to substances that triggered those chemical alarms during the Gulf War likely had adverse neuroanatomical effects.

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1. Introduction

Military personnel of the 1990–1991 Persian Gulf War (GW) encountered numerous potentially hazardous substances during deployment, including oily black smoke generated by burning oil well fires, low-levels of chemical nerve agents such as sarin and cyclosarin, pyridostigmine bromide (PB) pills taken by U.S. and some coalition forces to protect against the acute effects of nerve agents, excessive use of pesticides and insect repellants, munitions containing depleted uranium, receipt of numerous vaccines, chemical resistant coating paint, and other potential hazards (Steele et al., 2012; White et al., 2015). Although exposures to these substances have been suspected of contributing to long-term ill health effects in GW veterans, it has proved difficult to thoroughly evaluate the consequences of these exposures because of the lack of measured data about who was exposed to what during the GW, and at what levels. Despite this ambiguity, we know that at least some GW veterans were exposed to low levels of chemical nerve agents when a munitions storage site at Khamisiyah, Iraq was destroyed in early March 1991. This is because a United Nations Special Commission inspection team that inspected the site in October 1991 found samples that tested positive for sarin and cyclosarin (Haley and Tuite, 2013).

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After the GW ended, the Presidential Advisory Committee and the National Security Council requested the Department of Defense (DOD) and Central Intelligence Agency (CIA) to model potential chemical warfare agent release events during the GW, including those associated with detonation of the munitions storage site at Khamisiyah (Presidential Advisory Committee on Gulf War Veterans' Illnessess, 1996). This lead to simulations that: (1) approximated the direction and extent of these releases using meteorological data and estimates of atmospheric transport and diffusion, (2) approximated the exposure dose across the three days in March 1991 when exposure was deemed likely, and (3) attempted to identify U.S. troops whose units may have been exposed by overlaying the geographical coordinates of the modeled plume with the geographical positions of U.S. military units in the theater on the dates in question. The simulations indicated that no military units were in the "first noticeable effect" area, defined as exposure at levels equal to or greater than 1 mg min/m^3 by the US Army (McNamara and Leitnaker, 1971) and the Centers for Disease Control and Prevention (CDC, 1988). However, 98,910 military personnel were identified to have been in the "low level exposure" area, defined as exposure at levels equal to or greater than the general population limit (i.e., 0.01296 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, 1997). 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 (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, 2002). This second plume model identified an additional 2942 military personnel, for a total of 101,752 GW veterans with potential low-level exposure to sarin/cyclosarin.

In a review of the Khamisiyah plume models, the United States General Accounting Office (2004) cited a number of problems, including inaccuracies in the source terms (e.g., quantity and purity of nerve agent), underestimation of explosion plume heights, unrepresentative conditions of field tests, and wide divergence of plume patterns from the various computer plume. This lead the U. S. General Accounting Office to conclude that the plume models did not reliably indicate which troops were exposed to nerve agent, if any was released from the demolitions.

Despite the uncertainty associated the Khamisiyah plume models, we and others have reported evidence of impaired neurobehavioral function (Chao et al., 2010; Proctor et al., 2006; Toomey et al., 2009) as well as reduced total brain gray matter (GM) (Chao et al., 2010, 2011) and white matter (WM) (Chao et al., 2011; Heaton et al., 2007) volume in Khamisiyah-exposed veterans compared to non-exposed GW veterans. We have also found evidence of reduced total hippocampal (Chao et al., 2010) and hippocampal subfield (i.e., CA2, CA3, and dentate gyrus) volumes (Chao et al., 2014) as well as WM microstructural changes (Chao et al., 2015) as measured by diffusion tensor imaging (DTI) in GW veterans with predicted Khamisiyah plume exposure compared to matched, unexposed GW veterans. These findings in GW veterans with predicted Khamisiyah plume exposure are reminiscent of the reports of long-term neurobehavioral (Miyaki et al., 2005; Nishiwaki et al., 2001) and brain (e.g., hippocampal, insula and neighboring white matter atrophy and WM microstructural abnormalities (Yamasue et al., 2007)) changes that have been described in victims of the 1995 Tokyo subway sarin attack, a terrorist attack that exposed more than 5500 civilians to sarin gas (Suzuki et al., 1995).

The DOD/CIA plume models only focused on exposures associated with the Khamisiyah demolitions. However, it has been suggested that other nerve agent exposures may have occurred during the Gulf War (Committee on Banking, 1994; Haley and Tuite, 2013; Office of the Special Assistant for Gulf War Illnesses, 1996; Tucker, 1997; Tuite and Haley, 2013). Therefore, the present study sought to examine whether there are associations between the frequency of hearing chemical alarms in theater and regional brain volumes in GW veteran. Due to the dearth of information on the types and doses of exposures experienced by GW veterans in theater, we relied on self-reports to evaluate possible exposure to chemical nerve agents, as previous epidemiologic studies have done (e.g., Haley and Tuite, 2013; Steele et al., 2012). Based on our findings of reduced hippocampal (Chao et al., 2010, 2014) and total brain GM volume (Chao et al., 2010, 2011) and our (Chao et al., 2011) and Heaton et al. (2007) finding of reduced total brain WM volume among Khamisiyah-exposed veterans, we hypothesized there would be an inverse association between the self-reported frequency of hearing chemical alarms sound during deployment and hippocampal, total brain GM and WM volumes. We also investigated the association between self-reports of hearing chemical alarms sound and the volume of the insula because Yamasue et al. (2007) had reported reduced insular volumes in victims of the 1995 Tokyo subway sarin attack. Finally, because Haley and Tuite (2013) reported a dose-response relationship between the number of times nerve agent alarms sounded in a veteran's immediate area and the risk of having Gulf War illness (GWI), we examined the frequency of GWI cases among GW veterans who did and did not reports of hearing chemical alarms sound during deployment.

2. Methods

2.1. Participants

We examined the neuroimaging data of 90 consecutive GW veterans who were recruited from 2014–2015 at the San Francisco Veterans Affairs Medical Center (VAMC) as part an on-going, VA-funded study on the effects of predicted exposure to sarin and cyclosarin from the Khamisiyah plume exposure on brain structure and brain function. All participants gave written informed consent, approved by the Institutional Review Boards of the University of California, San Francisco and the San Francisco Veterans Affairs Medical Center.

2.2. Study protocol and measures

The complete study protocol included self-report questionnaires about physical and mental health status, Gulf War military history, a psychological diagnostic interview, a battery of neuropsychological tests, magnetic resonance imaging (MRI) on a 3 T scanner, and optional saliva sampling for apolipoprotein E (APOE) genotyping. Results of the neuropsychological assessments will be reported elsewhere. The current report focuses on evaluation of associations between self-reports of hearing chemical alarms during deployment and volumetric MRI data.

2.2.1. Exposure measures

We used the Kansas Military History and Health Questionnaire (Steele, 2000) to query veterans about 19 specific experiences or exposures of interest during their deployment in the Gulf War. The questions emphasized the veterans' experiences rather than their impressions of their exposures. For example, rather than asking veterans if they had been exposed to depleted uranium, which many are unlikely to know, the questionnaire asked if veterans had contact with destroyed enemy vehicles, an experience required for nearly all personnel directly exposed to depleted uranium. The