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Recent research on Gulf War illness and other health problems in veterans of the 1991 Gulf War: Effects of toxicant exposures during deployment

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Abstract

Veterans of Operation Desert Storm/Desert Shield – the 1991 Gulf War (GW) – are a unique population who returned from theater with multiple health complaints and disorders. Studies in the U.S. and elsewhere have consistently concluded that approximately 25–32% of this population suffers from a disorder characterized by symptoms that vary somewhat among individuals and include fatigue, headaches, cognitive dysfunction, musculoskeletal pain, and respiratory, gastrointestinal and dermatologic complaints. Gulf War illness (GWI) is the term used to describe this disorder. In addition, brain cancer occurs at increased rates in subgroups of GW veterans, as do neuropsychological and brain imaging abnormalities.

Chemical exposures have become the focus of etiologic GWI research because nervous system symptoms are prominent and many neurotoxicants were present in theater, including organophosphates (OPs), carbamates, and other pesticides; sarin/cyclosarin nerve agents, and pyridostigmine bromide (PB) medications used as prophylaxis against chemical warfare attacks. Psychiatric etiologies have been ruled out.

This paper reviews the recent literature on the health of 1991 GW veterans, focusing particularly on the central nervous system and on effects of toxicant exposures. In addition, it emphasizes research published since 2008, following on an exhaustive review that was published in that year that summarizes the prior literature (RACGWI, 2008).

We conclude that exposure to pesticides and/or to PB are causally associated with GWI and the neurological dysfunction in GW veterans. Exposure to sarin and cyclosarin and to oil well fire emissions are also associated with neurologically based health effects, though their contribution to development of the disorder known as GWI is less clear. Gene-environment interactions are likely to have contributed to development of GWI in deployed veterans. The health consequences of chemical exposures in the GW and other conflicts have been called “toxic wounds” by veterans. This type of injury requires further study and concentrated treatment research efforts that may also benefit other occupational groups with similar exposure-related illnesses.

Keywords

Gulf War illness; Pesticide; Organophosphates; Sarin; Cyclosarin; Veterans’ health

1. Introduction

The 1991 Gulf War (GW) was fought by a multinational coalition that formed to oppose Iraq’s invasion of Kuwait in 1990. The coalition included nearly 700,000 U.S. troops as well

as military personnel from the United Kingdom, Canada, Australia, and France, with over 30 partnering countries. It began with a build-up of troops in the region (Operation Desert Shield) prior to the actual conflict (Operation Desert Storm), which included a six-week air campaign and four days of ground fighting before a ceasefire was declared on February 28, 1991. This was followed by the return of the majority of the troops by the spring of 1991. There were few casualties on the winning side. The GW was remarkable for the numbers of chemical exposures experienced by troops, including the low-level chemical warfare agents released by the destruction of Iraqi facilities, extensive spraying and use of pesticides, medications given prophylactically to protect troops against hazardous exposures, and hundreds of oil well fires set by the Iraqi troops as they withdrew from Kuwait.

Within a year of return from the GW, it became apparent that troops were suffering from a variety of symptoms that were difficult to explain by health care providers, who did not recognize a typical medical illness in the veterans. Initially dubbed “GW syndrome” by the press, this disorder appeared to affect many, but not all, GW veterans. Fatigue, widespread pain, cognitive and memory problems, skin rashes, gastrointestinal and respiratory difficulties were commonly reported, but not every veteran afflicted by GW illness (GWI) presented with identical symptoms. Intensive research was initiated to characterize the disorder, understand its prevalence, investigate likely causes, and explore possible mechanisms of disease. Although the troops and some health care providers immediately suspected that chemical exposures were the cause of the condition, others ascribed GWI to post-traumatic stress disorder (PTSD) or other psychiatric conditions, or to the usual consequence of all wars. Effective treatments for GWI have been elusive but recently a treatment research effort has begun to flourish.

This paper explores the characteristics of GWI, its definition and prevalence (Epidemiology of GWI), the conditions in theater that may have caused GWI and specific indictors of nervous system dysfunction (Persistent Health Effects in GW Veterans in Relation to Deployment Experiences and Exposures), physiological mechanisms underlying GWI (Neuropathology of GWI) and experimental models of GWI and its causation (Animal Models of GWI Etiology and Pathology). It also summarizes current evidence related to a variety of neurological outcomes in addition to GWI that have been significantly associated with self-reported or modeled chemical exposures encountered by veterans during the GW. The paper is based on a recent summary of GWI research, *Gulf War illness and the health of Gulf War veterans: Research update and recommendations, 2009–2013* (RACGWI, 2014), which our group authored. The paper and its tables focus on the literature appearing since 2008, with occasional briefer summaries or tables on research published prior to 2008.

2. The epidemiology of GWI

2.1. Case definitions and prevalence

Research on GWI has relied on a number of differing definitions of the disorder, including chronic multisymptom illness (CMI, Fukuda et al., 1998), the Kansas GWI definition (Steele, 2000), the Haley syndrome criteria (Haley, Kurt, & Hom, 1997) and adaptations of these approaches. CMI has been used the most commonly in epidemiologic research to date. GW veterans who meet criteria for CMI must report one or more symptoms that have been

ongoing for at least six months in two of three categories, which include musculoskeletal pain (symptom list: joint pain, joint stiffness, muscle pain); mood-cognition (feeling depressed, feeling moody, feeling anxious, trouble sleeping, difficulty remembering or concentrating, trouble with word finding), and fatigue. CMI can be categorized as "severe" if the veteran rates each defining symptom as severe or "mild-moderate" for milder complaints. This case definition was recommended for clinical use by a recent IOM panel (IOM, 2014). The Kansas definition of GWI requires that cases have moderately severe or multiple chronic symptoms in at least three of six categories: fatigue/sleep problems, pain, neurological/cognitive/mood symptoms, respiratory complaints, gastrointestinal problems or skin symptoms (Steele, 2000). Veterans who have severe psychiatric disorders or other medical conditions that might predict similar symptoms are excluded. The 2014 IOM report on GWI case definitions recommended that this definition be used for research purposes (IOM, 2014). The Haley syndromes were originally developed using factor analytic evaluation of symptom data from a Seabees unit and include three symptom complexes. Syndrome 1 (Impaired cognition) is characterized by problems with attention, memory, and sleep along with depression. Syndrome 2 (Confusion/ataxia) involves problems with thinking and balance. Syndrome 3 (Neuropathic pain), is defined by joint and muscle pain.

Each of these definitions has particular strengths and weaknesses. The mild form of CMI is broad and overly inclusive, resulting in high prevalence rates even in control populations, though the severe form appears to be more specific to GWI (Nisenbaum, Barrett, Reyes, & Reeves, 2000). The Kansas criteria predict GWI at rates that appear to be consistent with those seen across multiple GW populations but can potentially exclude veterans with some concurrent medical disorders who may also have GWI. The Haley syndromes are quite narrow and underestimate the occurrence of the disorder but may allow highly specific characterization of veterans who meet criteria for a syndrome. When used in research, use of one of these definitions at least provides a basis for understanding the health characteristics of GWI cases being described. Many studies have not included any clear definition of how GWI was diagnosed among cases, a serious problem for the literature on this disorder. The ultimate goal of a consensus case definition for GWI has been advocated, which would lead to greater clarity in GWI research (RACGWI, 2014).

Because the individual symptoms seen in GWI can occur commonly in the general population, it is important to identify the *excess* rates of such symptoms in the GW veteran population, that is, the proportion of 1991 GW veterans who experienced multiple chronic symptoms over and above the "background" rate of these symptoms seen in contemporary veterans who did not deploy to the GW theater. Using the definitions of GWI described above, the 2008 RAC report compared the rates of the symptoms of the disorder in deployed GW veterans with those seen in control groups to provide a consistent methodology for estimating the prevalence of symptomatic illness attributable to GW service across studies.

Table 1 provides prevalence data from nine investigations that used this approach and three studies that provide estimates only for GW veterans. Seven of ten estimates indicated excess rates of symptomatology to be in the 25–32% range across multiple populations when using the more general case definitions for GWI (CMI, Kansas), while the more narrowly focused factor analytic case definitions such as the Haley criteria produced lower estimates of the

disorder. Longitudinal studies have consistently indicated that GWI rates and symptom frequencies reported by veterans have remained fairly constant, with no overall improvement over time (Hotopf et al., 2003; Ozakinci, Hallman, & Kipen, 2006; Proctor et al., 1998; Wolfe, Proctor, Erickson, & Hu, 2002).

2.2. Neurological conditions

Rates of neurological conditions that have been evaluated among deployed GW veterans compared to nondeployed controls include amyotrophic lateral sclerosis (ALS), brain cancer, seizures, neuritis and neuralgia, migraine headaches, multiple sclerosis (MS) and Parkinson's disease (PD). The literature appearing on these disorders since 2008 is summarized in Table 2.

The neurological disorder that was first identified as occurring at increased rates in GW veterans was ALS. Prior to 2008, several studies had reported an excess rate of ALS among deployed GW veterans relative to nondeployed controls (Coffman, Horner, Grambow, & Lindquist, 2005; Horner et al., 2008). Some findings suggested that age of onset might be earlier in this population (Haley, 2003). However, Horner et al. (2008) reported that the increased rate of ALS in GW versus nondeployed veterans was maintained only for the first 10 years after the war, peaking in 1996, suggesting a time-limited ALS "outbreak" in GW veterans (Horner et al., 2008). ALS risk was also reportedly related to specific locations of affected troops in theater (Miranda, Galeano, Tassone, Allen, & Horner, 2008). Two studies appearing since 2008 have examined the occurrence of ALS. One paper compared the characteristics of ALS in GW-deployed and era nondeployed veterans, concluding that age, site of onset and symptom presentation were similar in the two groups but that ventilator-free survival time was shorter in the GW-deployed ALS patients (Kasarskis et al., 2009). A second study concluded that there was no excess mortality from ALS in deployed GW veterans compared to nondeployed era controls (Barth, Kang, Bullman, & Wallin, 2009).

Two studies have found excess rates of death due to brain cancers among GW veterans who were identified by Department of Defense (DoD) exposure models as having been possibly exposed to nerve gas agents during/following the demolition of the weapons depot in Khamisiyah, Iraq, in March of 1991 (Barth et al., 2009; Bullman, Mahan, Kang, & Page, 2005). Veterans exposed to the highest levels of contaminants from oil well fires were also reported to have increased rates of brain cancer deaths (Barth et al., 2009).

The VA's 2005 national longitudinal survey of nearly 9,000 GW era veterans published in 2009 (Kang et al., 2009) found that deployed veterans reported being diagnosed with repeated seizures, neuralgia or neuritis, and stroke at greater rates than nondeployed era controls. Most of these conditions had also been reported at excess rates by GW veterans in VA's 1996 national survey. Although these conditions were self-reported, medical record reviews for both the 1996 and 2005 VA national surveys indicated a high percent agreement (93–96%) between medical records and veteran-identified reasons for clinic visits and hospital stays (Kang et al., 2009; Kang, Mahan, Lee, Magee, & Murphy, 2000).

Increased rates of migraine headaches have been reported for some time among GW deployed veterans relative to controls (Gray, Reed, Kaiser, Smith, & Gastanaga, 2002; Kang

et al., 2000; Steele, 2000; Unwin et al., 1999). In GW veterans who met clinical criteria for chronic fatigue syndrome (CFS), 64% were diagnosed with migraine headaches, which is a rate similar to nonveteran subjects with CFS and significantly higher than that seen in sedentary controls (Rayhan, Ravindran, & Baraniuk, 2013).

There are no reliable data on incidence or prevalence of MS or PD among veterans of the 1991 GW specifically. As noted in Table 2, a paper published in 2009 (Barth et al., 2009) concluded that GW veterans, overall, did not have higher mortality rates due to these disorders, compared to non-deployed era veterans. A study of MS in veterans who served in the military between 1990 and 2007 and had applied for disability compensation identified increased MS rates in women, African Americans, and Army veterans compared to other groups but did not focus specifically on deployed veterans of the 1991 GW (Wallin et al., 2012). A later report indicated that rates of MS were not significantly different between GW veterans and nondeployed veterans in this convenience cohort (Wallin et al., 2014). Neither mortality data nor the number of veterans seeking disability benefits for MS provides a valid indication of whether GW veterans have been affected by excess rates of MS or most other neurological disorders since the war. Determining the impact of MS and other neurological disorders on GW veterans requires clear prevalence figures derived from well-designed research that utilizes population-based samples of GW veterans and appropriate comparison groups. It is also important to determine if rates of these disorders differ in GW veteran subgroups in connection with exposures or other deployment characteristics.

Reports summarizing the research on health problems in GW veterans have repeatedly emphasized that it is essential that studies intended to evaluate rates of illness and diagnosable diseases in GW veterans determine those rates in appropriate veteran subgroups, defined by particular exposures, locations in theater, or other relevant factors (RACGWI, 2008, 2014). It is now well understood that deployment exposures and experiences encountered by GW veterans were not uniform across theater. General analyses that combine all GW veterans into a single group will underestimate or completely obscure important findings associated with exposures that affected only a subgroup of veterans. This has been well illustrated, for example, by studies identifying excess rates of brain cancer mortality (Barth et al., 2009), brain structure and cognitive alterations (Chao, Abadjian, Hlavin, Meyerhoff, & Weiner, 2011; Heaton et al., 2007; Proctor, Heaton, Heeren, & White, 2006) and respiratory disease (Cowan, Lange, Heller, Kirkpatrick, & DeBakey, 2002) among veteran subgroups who had the greatest exposure to nerve agents or oil fire smoke during the GW.

2.3. Psychiatric and psychological disorders

Deployment related stress, PTSD and other psychiatric conditions were extensively studied in GW veterans immediately after their complaints of increased ill health became known. Population-based studies indicated that rates of diagnosed PTSD in GW veterans were about 3–6%, compared to a rate of 25–32% for GWI (RACGWI, 2008). When combat stressors, self-reported stress reactions and exposures to other stressful events in theater were quantified, these variables did not explain or predict diagnosis of GWI (RACGWI, 2008, p. 78). The 2010 IOM report on GWI concluded: “The excess of unexplained medical

symptoms reported by deployed GW veterans cannot be reliably ascribed to any known psychiatric disorder" (IOM, 2010, p. 109).

Research studies investigating PTSD since 2008 are summarized in Table 3. These studies have concluded that PTSD symptom severity was associated with poorer physical health after deployment (Hassija, Jakupcak, Maguen, & Shipherd, 2012), that exposure to war casualties was associated with greater mental health decline (Gade & Wenger, 2011) and that combat exposure was related to PTSD, depressive symptoms and alcohol abuse (Hassija et al., 2012). Problem drinking in the GW population was found to be associated with PTSD, major depression and multisymptom illness (Coughlin, Kang, & Mahan, 2011). National Guard/Reservists and troops on active duty scored higher on PTSD rating scales and reported increased perceived threats and difficult living and working environments while deployed than comparison service men and women (Vogt, Samper, King, King, & Martin, 2008).

The literature on neuroimaging and PTSD in deployed GW veterans mirrors PTSD findings in other veteran populations, including neuropathological and hormonal changes. GW veterans with PTSD were found in one study to have smaller hippocampal volumes on brain imaging than controls without PTSD (Apfel et al., 2011). Diminished hippocampal volume, metabolic activity changes and enhanced hormonal response to dexamethasone were reported in a second study of GW veterans diagnosed with PTSD (Yehuda et al., 2010). GW veterans diagnosed with combat-related PTSD showed smaller volume, area and thickness values in the hippocampal gyrus, superior temporal cortex, lateral orbital frontal cortex and pars orbitalis brain regions when compared to veterans without PTSD in a third investigation (Woodward, Schaer, Kaloupek, Cediel, & Eliez, 2009). Although these studies suggest that PTSD should be assessed and accounted for when evaluating neuroimaging outcomes in GW veterans, none of the reported studies controlled for potential nerve agents or other relevant environmental exposures that should also be assessed when evaluating magnetic resonance imaging (MRI) outcomes in this population.

Overall, research on PTSD and other psychiatric disorders among GW veterans shows lower rates of these conditions than are found in veterans of other wars and far lower than the prevalence of GWI. However, related physiology and predictors of PTSD occurrence and severity are similar.

3. Research on persistent health effects in GW veterans in relation to deployment experiences and exposures

Exposures in the GW theater that have been suspected of contributing to long-term health effects after the war include pesticides, depleted uranium munitions, airborne contaminants from the Kuwaiti oil well fires, chemical nerve agents, the anthrax vaccine and multiple vaccinations, widespread use of pyridostigmine bromide (PB) as a prophylactic measure against possible nerve agent exposure, chemical resistant coating (CARC) paint, and other hazards such as psychologically stressful conditions and heat. Military personnel commonly experienced multiple exposures in different combinations, for which possible interactive or synergistic effects have not been determined in human populations. One of the central

challenges in evaluating risk factors for GW-related health outcomes involves a paucity of data on the types and doses of exposures experienced by veterans in theater. Initial research efforts on exposure–outcome relationships in this population were forced to rely on self-report, which can be subject to bias. To address this concern, the U.S. DoD sponsored a number of intensive efforts to provide simulations, modeled estimates and detailed investigations in an effort to better characterize wartime exposures in different locations and military units. These include estimates of nerve agent exposures following demolitions at the massive munitions depot at Khamisiyah, Iraq, in March of 1991; modeled estimates of levels of airborne contaminants from the hundreds of Kuwaiti oil well fires; determinations of radiation and heavy metal exposures associated with depleted uranium munitions, and in-depth investigations that provided detailed information on the use of pesticides and PB in theater. The hazards that have been studied most extensively with regard to health outcomes in this population include psychological stressors, pesticides, PB, sarin/cyclosarin, vaccines, depleted uranium and oil well fires.

Early exposure-related studies in the deployed GW veteran population were often problematic, due to analytic limitations that led to errors in interpretation of study findings. Such problems arose when studies that assessed myriad potential risk factors for GWI failed to control for confounding due to effects of concurrent exposures. Such studies typically reported that all, or most, GW experiences and exposures evaluated were significantly associated with GWI (RACGWI, 2008). In contrast, studies that evaluated individual GWI risk factors, while controlling for effects of other exposures, invariably identified a limited number of significant risk factors for GWI. Across all studies and populations, when confounding effects of concurrent exposures are considered, pesticide and PB use during the GW have been consistently identified as significant risk factors for GWI.

3.1. Pesticide exposures

As detailed elsewhere (DOD, 2001), GW personnel were often exposed to high levels of a variety of pesticides and insect repellants in theater. After adjusting for effects of concurrent exposures, significant associations between self-reported pesticide exposure and GWI, variously defined, have been identified in six of the seven different GW veteran populations in which they have been evaluated (RACGWI, 2008; Steele et al., 2012). Pesticide exposures were associated with GWI as defined by the Haley syndrome criteria in veterans from a single Navy unit (Haley & Kurt, 1997), CMI in Air Force veterans (Nisenbaum et al., 2000), study-specific criteria among Navy Seabees (Gray et al., 2002), overall symptom severity among United Kingdom GW veterans (Cherry et al., 2001a, 2001b), and gastrointestinal and/or neuropsychological symptoms in Danish GW veterans (Ishoy, Suadicani, Guldager, Appleyard, & Gyntelberg, 1999; Ishoy, Suadicani, Guldager, Appleyard, Hein, et al., 1999; Suadicani, Ishoy, Guldager, Appleyard, & Gyntelberg, 1999). In a more recent study, Steele et al. (2012) also found an association between pesticide exposures and GWI for veterans who had served in different locations in theater. In addition, two studies have reported dose–response effects in the association between pesticide exposures and GWI (Cherry et al., 2001b; Haley & Kurt, 1997).

3.2. PB

The 1991 GW is the only conflict in which PB was widely used by military personnel as a prophylactic measure intended to protect against effects of possible nerve gas attacks (Golomb, 1999). Self-reported PB use has also been consistently linked to ill health in GW veteran populations (see Table 4). Use of PB and/or experiencing side effects from PB were significantly associated with Haley syndrome symptomatology (Haley, Kurt, et al., 1997), with study-specific criteria for GWI among Navy Seabees (Gray et al., 2002), CMI in U.S. Air Force (Nisenbaum et al., 2000) and Army (Wolfe et al., 2002) veterans, a study-specific diagnosis of GWI in Oregon veterans (Spencer et al., 2001), and overall symptom severity in U.K. GW veterans (Cherry et al., 2001b). In a more recent study, PB use was associated with a significantly elevated risk for GWI (OR = 3.5) among GW veterans who were located in forward areas in theater (Steele et al., 2012). Overall, self-reported PB use has been identified as a significant risk factor for GWI in all seven populations in which it has been evaluated, after adjusting for the effects of other exposures. Three studies have reported dose–response effects for GWI in relation to PB use (Cherry et al., 2001b; Spencer et al., 2001; Wolfe et al., 2002), and two have identified dose–response effects in relation to side effects from PB use (Cherry et al., 2001b; Haley & Kurt, 1997).

3.3. Chemical warfare agents

Several studies have linked sarin/cyclosarin exposure to central nervous system outcomes. The 2008 RAC report summarized studies from Boston investigators that examined the relationship between brain outcomes and DoD models of sarin/cyclosarin nerve gas agent exposures resulting from the demolition of the Khamisiyah, Iraq, weapons depot in March 1991. This modeling provided a dose exposure estimate across three days as well as identification of U.S. troops who were likely in the area. Investigators found that reduced performance on neurobehavioral tests (Proctor et al., 2006) and smaller white matter volumes on brain imaging (Heaton et al., 2007) were associated with nerve gas agent exposure in a dose-dependent manner, with higher exposures predicting poorer performance and less overall brain white matter.

The findings of associations between DoD models of sarin/ cyclosarin exposure and MRI and behavioral outcomes have received support from recent investigations. In the first, gray matter and hippocampal volumes were found to be smaller in Khamisiyah-exposed veterans versus non-exposed veterans, and reduced white matter volume measured on a 1.5 T MRI was associated with poorer performance on neurobehavioral tests of executive and visuospatial functions (Chao, Rothlind, Cardenas, Meyerhoff, & Weiner, 2010). A second study from Chao et al. using a 4.0 T MRI and a different study sample found that total gray and total white matter volumes were both significantly reduced in Khamisiyah-exposed veterans, though findings were inconsistent regarding exposure-related cognitive differences (Chao et al., 2011). An additional study evaluating neurobehavioral outcomes found slower motor function speeds among Khamisiyah-exposed veterans compared to non-exposed (Toomey et al., 2009).

Two studies have reported significantly increased rates of death due to brain cancer among veterans who were located within the nerve agent plume area defined by DoD models of the

Khamisiyah demolitions. The earlier study, reporting on mortality through 2000, identified a nearly two-fold increase in brain cancer deaths in exposed veterans (Bullman et al., 2005). The observed increase was further supported by a 2009 VA study that evaluated mortality rates through 2004, which found a nearly three-fold increase in brain cancer deaths among veterans with the highest level of exposure to the Kuwaiti oil well fires and nerve agents associated with the Khamisiyah plume (Barth et al., 2009).

In a large national study, Haley et al. (2013) explored the relationship between chemical agent exposures and GWI. This group reported an increased risk for GWI defined as CMI or the Haley syndromes associated with hearing chemical alarms in theater, a proxy for possible nerve agent exposure. A significant dose–response effect in which veterans who reported hearing more alarms had greater risk for GWI was reported in this study. In contrast, this study reported no association between GWI and modeled exposure to the Khamisiyah plume, which contained these agents. A study of Kansas City-area GW veterans did not reveal associations between hearing chemical alarms and risk for GWI (Steele et al., 2012).

In summary, the literature appearing prior to 2008 and since then clearly supports a link between adverse neurological outcomes and sarin/cyclosarin in populations of GW veterans with exposure to these agents. The link between such exposures and GWI remains unclear, perhaps because studies on the issue over time have assessed nerve gas agent exposure in different ways (self-report, chemical alarms, Khamisiyah models) and defined GWI differently.

Only limited evidence is available regarding exposures to and health effects of other chemical warfare agents known to have been present in theater. A study published in 2013 tracked meteorological patterns in the region and indicated that U.S. troops may have been exposed to both nerve and blister agents as fallout from the Coalition bombing of chemical storage sites in 1991, during the early days of the air campaign (Tuite & Haley, 2013). This possibility had previously been raised by multiple sources, including Czech and other Coalition partners who reported chemical detections in northern Saudi Arabia in January of 1991, with related evidence summarized in a 2004 report from the U.S. Government Accountability Office (U.S. Department of Defense Office of the Special Assistant for Gulf War Illnesses, 1998; U.S. General Accounting Office, 2004). Chemical detection monitors used during the war had limited capabilities for detecting mustard gas, but government reports have verified the presence of mustard gas at chemical manufacturing and storage sites in Iraq (U.S. Central Intelligence Agency, Persian Gulf War Illnesses Task Force, 2002) and in munitions stored at the Khamisiyah weapons depot (U.S. Department of Defense Office of the Special Assistant for Gulf War Illnesses, 2002). A 2012 study described a mechanism by which mustard gas may have interacted with other exposures in theater in contributing to long-term health effects in GW veterans (Brimfield, 2012). However, there are no reports in the literature providing systematic evaluation of the effects of mustard gas on the health of GW veterans.

3.4. Other exposures and chemical mixtures

Previous evidence that links GWI to individual vaccines and/or the total number of vaccines received by GW veterans is quite limited (Research Advisory Committee, 2008). Prior to 2008, one study identified a significant association between GWI and the number of vaccines received after controlling for the effects of other exposures in theater (Cherry et al., 2001b). A 2009 Australian study reported a weak association between health symptoms affecting GW veterans and the number of vaccines received, but no associations with vaccines reported in military records (Kelsall et al., 2009). Similarly, no associations between GWI and vaccines received in theater were reported in a 2012 study of Kansas City-area veterans (Steele et al., 2012). Some investigators have suggested that certain vaccines used during the GW contained squalene, which potentially gave rise to antibodies that might be associated with GWI (Asa, Cao, & Garry, 2000). However, a 2009 study found no association between diagnosis of CMI and the presence of squalene antibodies in Navy Seabees who served in the GW (Phillips et al., 2009).

Earlier studies provided mixed conclusions on the long-term health effects of exposures resulting from the hundreds of Kuwaiti oil well fires that burned between February and November, 1991, but close proximity to oil well fires was not ruled out as a risk factor for GWI (Research Advisory Committee, 2008). Two recent studies have provided additional evidence supporting long-term health effects in veteran subgroups that were most highly exposed to oil well fire smoke. A study of Kansas City-area GW veterans identified a significantly increased risk for GWI among GW veterans exposed to oil well fire smoke among personnel in forward areas in theater (Steele et al., 2012). Exposure to airborne pollutants from the Kuwaiti oil well fires has also been associated with increased risk for death due to brain cancer (Barth et al., 2009).

Multiple investigations have identified a high degree of overlap or clustering among GW exposures, indicating that personnel with some exposures (e.g., certain pesticides) were also much more likely to have additional exposures of concern (e.g., other pesticides, PB Boyd et al., 2003; Cherry et al., 2001b; Fricker et al., 2000; Steele et al., 2012). Most veterans experienced exposures to chemical mixtures in theater, and a large body of research using animal models has demonstrated persistent effects from combinations of GW exposures not seen with individual exposures. However, effects of these complex exposures have been minimally evaluated in GW veterans and remain unknown. Improved modeling of the contributions of individual and combined exposures would inform the assessment of mixed exposures as causes of GWI, as would the development of biomarkers of past exposures to specific chemicals of interest.

3.5. Genetic factors

Genetic vulnerabilities to chemicals present in theater likely played a role in the post-deployment health of individual veterans (IOM, 2010; RACGWI, 2014). A recently published population study of 304 GW veterans identified a significant gene–exposure interaction in a subgroup of veterans with GWI. This study found that veterans with less active genetic variants of the butyrylcholinesterase enzyme were at substantially greater risk

for GWI if they used PB compared to veterans with these genotypes who did not use PB (Steele, Lockridge, Gerkovich, Cook, & Sastre, 2015).

4. Neuropathology of GWI

Because the most prominent symptoms of GWI are so clearly related to nervous system function and because GW veterans were exposed to several well-known neurotoxicants in theater, research has focused on the nervous system in attempts to identify the underlying neuropathological mechanisms of the disorder. Other systems, including the immune, respiratory, and gastrointestinal systems, have also received attention, though to a lesser extent. We will focus here on the known neuropathological and neurofunctional correlates of GWI, mentioning other systems when they are found on the pathway to nervous system effects.

4.1. Neuroimaging

Early research using MRI and electroencephalography (EEG) methods tended to compare ill and healthy GW veterans and to use insensitive clinical visual interpretation of images, finding few differences (Amato et al., 1997; Haley, Hom, et al., 1997; Lee, Bale, & Gabriel, 2005; Levine et al., 2006; Newmark & Clayton, 1995). Since 2008, 16 additional peer-reviewed EEG and neuroimaging papers have appeared, with more sophisticated methodology and closer attention to exposure–outcome relationships. Table 5 summarizes two papers that describe exposure-related neuroimaging findings in GW veterans. Table 6 summarizes 13 additional studies that utilized imaging and EEG to characterize structural and functional alterations in relation to symptomatic illness in GW veterans.

Research prior to 2009 using magnetic resonance spectroscopy reported lower levels of several metabolites (choline, creatine, N-acetylaspartate [NAA]) using proton magnetic resonance spectroscopy (H-MRS) in the brainstems and basal ganglia in GW veterans who met Haley criteria for diagnosis of GWI (Haley et al., 2000) and lowered NAA/creatine ratios in basal ganglia (Meyerhoff, Lindgren, Hardin, Griffin, & Weiner, 2001) and hippocampus (Menon, Nasrallah, Reeves, & Ali, 2004). Research conducted by Weiner (2005) identified brain metabolic abnormalities in choline/creatine ratios in GW veterans meeting Haley Syndrome 2 (Confusion-ataxia) criteria for GWI (Weiner, 2005). However, a later study (Weiner et al., 2011) failed to confirm this finding: NAA, creatine and choline levels did not differ significantly in symptomatic versus asymptomatic GW veterans (Weiner et al., 2011). Rayhan, Raksit, et al. (2013), Rayhan, Ravindran, et al. (2013) and Rayhan, Stevens, et al. (2013) assessed lactate metabolite levels in the prefrontal cortex prior to and after an exercise challenge in ill GW veterans, finding that pre-exercise lactate level was associated with memory performance pre-and post-exercise. A single-photon emission computer tomography (SPECT) method that injects a radioactive tracer to produce a 3-D representation of metabolic activity in the brain was used to evaluate cerebral blood flow in 21 subjects diagnosed with Haley Syndrome 2 (Confusion-ataxia) compared to 17 military controls; significantly lower cerebral blood flow in the caudate, globus pallidus, putamen and posterior hypothalamus was seen in the ill veterans (Haley et al., 2009).

Because exposures experienced by GW veterans in theater included many chemicals that act on the cholinergic system (sarin, cyclosarin, organophosphates – OPs, PB; Golomb, 2008), one approach to imaging in this population employed physostigmine infusions to challenge the cholinergic system and evaluate the challenge effects. Table 6 summarizes three recent investigations utilizing physostigmine challenge. Using MRS probes, Li et al. (2011) detected abnormal cerebral blood flow through the hippocampus before the physostigmine challenge, and after the challenge veterans with Haley Syndromes 2 (Confusion-ataxia) and 3 (Neuropathic pain) showed significantly abnormal *increases* in regional cerebral blood flow in the hippocampus of both hemispheres. A second physostigmine challenge study failed to find any decrease in brain activity in symptomatic GW veterans; instead, GWI patients showed either no change or increased cerebral blood flow after physostigmine injection, with changes being statistically significantly different from sedentary control veterans. Differences were most significant in the hippocampus, amygdala, caudate and thalamic areas after physostigmine injection (Liu et al., 2011). Similar elevated cerebral blood flow results with physostigmine challenge were also reported in a study using SPECT methodology (Haley et al., 2009).

Reduced white and gray matter volumes in cortical areas have been consistently reported in structural MRI studies of ill GW veterans (Chao et al., 2011, 2010; Rayhan, Stevens, et al., 2013; Rosenzweig, Bodi, & Nashef, 2012). Reduced signaling was also seen in the thalamus, caudate, hippocampus, globus pallidus and putamen (Calley et al., 2010; Haley et al., 2009; Li et al., 2011). As noted above and in Table 6, Chao et al. (2011) found that GWI and CMI diagnoses significantly predicted volume changes in sarin and cyclosarin-exposed subjects.

Several studies have used functional MRI (fMRI) to assess functional anomalies and white matter integrity using diffusion tensor imaging (DTI). For example, Rayhan, Raksit, et al. (2013), Rayhan, Ravindran, et al. (2013) and Rayhan, Stevens, et al. (2013) reported that fatigue, pain and hyperalgesia were associated with diminished white matter integrity in GW veterans with CMI or CFS (Rayhan, Stevens, et al., 2013). Axial diffusivity in the right inferior fronto-occipital fasciculus specifically predicted CMI diagnosis in this study. In addition, civilian controls and ill GW veterans exposed to exercise revealed two distinct GWI phenotypes. One subgroup displayed orthostatic tachycardia while the other developed hyperalgesia. Imaging results on both groups showed signs of brain atrophy when compared to controls and altered working memory compensation in brain areas that were different from controls. In a second study, fMRI scanning of 53 symptomatic GW veterans showed significant signal changes in the thalamic and caudate regions in Haley Syndrome 2 (Confusion-ataxia) subjects when compared to other symptomatic veterans and healthy controls. Furthermore, the Haley Syndrome 2 group's performance on a semantic learning task was associated with signal change in the caudate areas bilaterally (Calley et al., 2010).

Responses to an innocuous heat stimulus in symptomatic and control GW veterans was investigated using fMRI methodology in a study by Gopinath et al. (2012). Compared to Haley Syndrome 3 (Neuropathic pain) patients and controls, patients with Haley Syndromes 1 (Impaired cognition) and 2 (Confusion-ataxia) showed significantly reduced brain activity in the insula, somatosensory areas S1 and S2, the medial prefrontal cortex, supplementary

motor area, premotor cortex and dorsolateral prefrontal cortex. An investigation using a working memory challenge task during fMRI concluded that symptomatic GW veterans showed distinctive prefrontal cortical activity when compared to civilian controls consistent with impairments in central executive processing (Hubbard et al., 2013).

Using an EEG task that measures hyperarousability, (Tillman et al., 2012) significant associations were found between P1 latency and amplitude in veterans with Haley Syndrome diagnoses 2 (Confusion-ataxia) and 3 (Neuropathic pain) when compared to healthy controls and Haley Syndrome 1 (Impaired cognition) subjects. GW veterans with Syndromes 1 and 2 showed P3a amplitudes that were significantly different from controls and Syndrome 3 subjects. In a follow-up study, significantly lower P3b amplitudes were seen in all three syndrome groups when compared to controls (Tillman et al., 2013).

As a group, studies that utilize imaging and EEG probes when investigating veterans with GWI defined in various ways and when assessing GW veterans with sarin/cyclosarin exposure consistently identify structural and electrical abnormalities in the central nervous system: 14 of the 15 papers published since 2008 and summarized in Tables 5 and 6 support this conclusion.

4.2. Neurocognition

GWI symptoms commonly include complaints about memory and concentration as well as dysregulated mood. These symptoms have been systematically investigated in this population through neuropsychological assessments in order to provide objective, quantified and standardized measurements of specific brain and behavioral functions. Early research comparing deployed GW veterans and nondeployed era veterans found that affective and mood complaints often differentiated the two groups, with greater dysphoria among the deployed veterans. However, overall comparisons between deployed and nondeployed era veterans generally failed to reveal cognitive differences in the two groups. Significant differences tended to emerge only in research that compared deployed veterans with and without GWI and that compared veterans who experienced specific exposures in theater to deployed veterans who did not experience these exposures.

Several investigations published prior to 2009 concluded that visuospatial and motor skills were poorer and greater dysphoria was evident in deployed veterans with GWI compared to healthy GW veterans (Anger et al., 1999; Axelrod & Milner, 1997; Binder et al., 1999; Bunegin, Mitzel, Miller, Gelineau, & Tolstykh, 2001; Lange, Van Niekerk, & Meyer, 2001; Storzbach et al., 2000; Storzbach, Rohlman, Anger, Binder, & Campbell, 2001; Sullivan et al., 2003). A subgroup of GW veterans who were markedly slower on psychomotor tasks was identified in one study, suggesting that there may be subgroups within the GWI population who are markedly impaired (Anger et al., 1999; Storzbach et al., 2001). Self-reported exposure to PB was found to be associated with poorer performance on tests assessing executive function and with greater mood complaints (Sullivan et al., 2003; White et al., 2001). Self-reported exposure to chemical and biological warfare agents predicted greater difficulty on neuropsychological tests that assess memory and attention as well as poorer affective function among deployed veterans (White et al., 2001). And modeled sarin and cyclosarin exposure experienced by GW veterans in relation to the Khamisiyah

demolition was associated with poorer performance on tests of psychomotor speed and visuospatial skills (Proctor et al., 2006).

Table 7 lists four neuropsychological assessment studies published since 2008. Toomey et al. (2009) identified differences between deployed and nondeployed veterans in a large study (N = 1061 deployed, N = 1128 nondeployed), with deployed veterans showing slower motor speed and worse attention. Also noted in this study was poorer performance on neuropsychological tests within certain domains that was associated with specific self-reported exposures. Sustained attention was poorer in veterans with self-reported exposure to contaminated food and water, verbal memory performance was worse among veterans who reported being at Khamisiyah (and presumably exposed to sarin/cyclosarin), visual memory was poorer in veterans with self-reported CARC paint exposure, and motor speed was slower among veterans who reported being near SCUD missiles (Toomey et al., 2009). As already summarized, Chao et al. found relationships between modeled exposure to nerve gas agents from the Khamisiyah demolition and cognition in one study that was related to volumetric MRI measures (Chao et al., 2010) but cognitive findings from a second investigation were inconsistent (Chao et al., 2011; see Table 6). A small investigation that assessed 25 deployed and 16 nondeployed veterans reported no differences in cognitive outcomes, but measures assessing quality of life and mood did differentiate the two groups (Wallin et al., 2009). This study must be viewed with caution given low power to detect differences between groups. In another study, a GO-NOGO task was administered while veterans with self-reported cognitive problems underwent EEG and results were compared to control GW veterans; the veterans with cognitive complaints were less able to inhibit inappropriate responses than the controls (Tillman et al., 2010). A face-name paradigm was used by Odegard et al. (2013) to compare performance among GW veterans with the Haley syndromes and healthy controls. Haley Syndrome 3 (Neuropathic pain) veterans performed worse than those with Haley Syndrome 1 (Impaired cognition) and healthy controls.

4.3. Autonomic nervous system (ANS)

ANS dysregulation in GW veterans was noted in several early studies reviewed in the 2008 RAC report. Findings included significant differences between symptomatic and healthy veterans in relation to 24-h heart rate variability (HRV; Haley et al., 2004; Stein et al., 2004), increased HRV in symptomatic veterans after exposure to diesel vapors (Fiedler et al., 2004), differential blood pressure, heart rate, and symptomatic responses with tilt table testing (Clauw, 2001; Davis, Kator, Wonnett, Pappas, & Sall, 2000; Lucas, Armenian, Debusk, Calkins, & Rowe, 2005; Sastre & Cook, 2004) and blunted blood pressure response to cognitive stressors (Peckerman et al., 2003, 2000). No statistical differences were identified in tests of sympathetic skin response and airway pressure response (Sharief et al., 2002).

A more recent study identified several significant ANS differences between GW veterans meeting criteria for the three Haley syndromes and controls. GW veterans meeting any of the three syndrome criteria scored worse than controls on the Autonomic Symptom Profile questionnaire, due to higher self-reports of gastrointestinal distress, sleep and urinary dysfunction and orthostatic intolerance. They also received higher Composite Autonomic

Severity scores, and Syndrome 2 (Confusion-ataxia) veterans showed significantly reduced sweat response. This study also found diminished night-time HRV in all three syndrome groups (Haley et al., 2013).

4.4. Neuroendocrine function

Although clinical neuroendocrine disorders have not typically been observed in GW veterans, a series of studies conducted by Golier and colleagues investigated hypothalamic-pituitary-adrenal (HPA) axis parameters in GW veterans for over a decade. This work revealed that cortisol suppression in response to dexamethasone was significantly related to musculoskeletal symptoms and was more pronounced in GW veterans reporting PB use (Golier, Legge, & Yehuda, 2006; Golier, Schmeidler, Legge, & Yehuda, 2006). In addition, this line of research consistently revealed patterns of HPA-axis functioning in GW veterans that are distinct from those seen in other conditions, including depression, PTSD and CFS (Golier, Caramanica, & Yehuda, 2012; Golier, Schmeidler, Legge, & Yehuda, 2007; Golier, Schmeidler, & Yehuda, 2009). Preliminary findings relevant to other hypothalamic–pituitary parameters were recently reported by clinical investigators in the U.K., who identified a variety of abnormalities in blood hormone levels, most prominently gonadotropin releasing hormone, in a small series of symptomatic GW veterans (Wakil, Sathyapalan, & Atkin, 2011).

4.5. Mitochondrial dysfunction

Some GW-related exposures, such as organophosphates (OPs), can be toxic to mitochondria, producing symptoms such as fatigue and brain, muscle, gastrointestinal (GI), sleep and autonomic dysfunction, all symptoms that are seen in GWI (Odegard et al., 2013). Phosphocreatine is a back-up energy source for muscle that is depleted during exercise, and the speed of recovery is dependent on the rate of mitochondrial ATP synthesis. Post-exercise phosphocreatine recovery rate (PCr-R) assessed using 31-phosphorus magnetic resonance spectroscopy has been confirmed as a robust measure of mitochondrial defects *in vivo* (Thompson, Kemp, Sanderson, & Radda, 1995). A case–control study compared PCr-R in veterans with GWI and in age-, sex- and ethnicity-matched controls. A significant PCr-prolongation indicating delayed recovery was seen in the veterans with GWI, supporting the study hypothesis that mitochondrial dysfunction is a mechanism of GWI (Koslik, Hamilton, & Golomb, 2014).

5. Animal models of GWI etiology and pathology

Animal studies have identified biological effects of GW exposures and combinations of exposures that were previously unknown. The evidence concerning these effects has burgeoned since 2008, with new animal models of GWI evaluating persistent and delayed effects of exposures in theater. It is axiomatic that animals are not humans and conclusions from animal studies must be used as clues that can be further investigated in appropriate human research. However, the outcomes from animal studies are important because data on exposure–outcome relationships can be collected rapidly and efficiently to provide mechanistic insights.

Animal models have been used to characterize the effects of pesticides, PB, insect repellants, nerve agents and stress, either administered alone or in combination. Multiple studies published prior to 2008 established that neurobiological effects of low-dose sarin exposure resulted in delayed and persistent effects in animals (Henderson et al., 2002; RACGWI, 2008). Early animal models of PB established that this drug can adversely affect nerve function (Drake-Baumann & Seil, 1999; Hudson, Foster, & Kahng, 1985) and can also have gastrointestinal (Kluwe, Page, Toft, Ridder, & Chung, 1990), muscular (Adler, Deshpande, Foster, Maxwell, & Albuquerque, 1992), immune (Peden-Adams et al., 2004) and cardiovascular (Bernatova, Babal, Grubbs, & Morris, 2006) effects. Rodents given PB over time showed a number of locomotor, learning and behavioral deficits (Abou-Donia, Dechkovskaia, Goldstein, Bullman, & Khan, 2002; Abou-Donia et al., 2001; van Haaren et al., 2001), despite showing no overt signs of cholinergic toxicity or illness. Three studies in rodent models found that the adverse effects of PB were enhanced by stressors (Abdel-Rahman, Abou-Donia, El-Masry, Shetty, & Abou-Donia, 2004; Abdel-Rahman, Shetty, & Abou-Donia, 2002; Friedman et al., 1996). Other studies showed reduced levels of acetylcholin-esterase (AChE) in the brains of animals given PB and exposed to stressors (Baireddy, Mirajkar, Nallapaneni, Singleton, & Pope, 2007; Sinton, Fitch, Petty, & Haley, 2000). PB administered with the nerve agent sarin produced locomotor deficits (Abou-Donia et al., 2002; Scremin et al., 2003), EEG abnormalities (van Helden et al., 2004), changes in HRV (Scremin et al., 2003) and increased markers of oxidative stress in urine (Shih, Hulet, & McDonough, 2006).

Since 2008, a large number of animal studies have built on earlier findings, further elaborating relationships between GW theater exposures and the symptoms of GWI. This work is summarized in Table 8. It has focused on behavior, cognition, neurotransmission and intracellular signaling; molecular and cellular disruptions of axonal transport, and genomic and proteomic profiling to identify previously unknown targets of GW exposures.

5.1. Altered behavior, cognitive function, neurotransmission and intracellular signaling

OPs have been shown to inhibit the enzyme AChE and can covalently bind organophosphorylate serine residues throughout the body. Mice exposed to low doses of PB, a carbamate medication that is also an AChE inhibitor, and permethrin (PER; a pyrethroid-based pesticide) showed elevated levels of the reservoir compounds necessary for acetylcholine synthesis (Abdullah et al., 2013). Ten days of chlorpyrifos (CPF) exposure in combination with PB and PER increased basal acetylcholine levels in the brains of six-month old mice. Within the dentate gyrus, exposed mice had reduced immunostaining for a marker of immature neuronal cells and a synaptic vesicle protein (Ojo et al., 2013). In addition, there was an increase in astrogliosis within the prefrontal cortex and a reduction in several vascular injury markers within the whole brain homogenates in exposed mice compared to controls. Animal models also showed impairments in spatial navigation and memory after GWI-related exposures (Parihar, Hattiangady, Shuai, & Shetty, 2013). Combined stress and pesticide exposure chronically over four weeks produced significant increases in glial-related inflammation, reduced neuronal growth in the hippocampus and reduced overall hippocampal volume at testing two months post-exposure (Parihar et al., 2013).

Hippocampal synaptic transmission and reduced neuronal spine density were observed at three months post CPF exposure by Speed et al. (2012). These data support the hypothesis that acute exposures to CPF at low dosages can produce long lasting changes to brain areas involved in cognition without producing obvious signs of cholinergic toxicity. Exposure to CPF, PER and PB produced changes in K^+ channel kinetics and excitability in muscle pain receptors, even though no behavioral changes were seen (Nutter, Jiang, & Cooper, 2013). Exposure of mice to PB and DEET for two weeks followed by exposure to the sarin surrogate, diisopropylfluorophosphate (DFP), or exposure to one week of CPF, resulted in deficits in signaling through glutamatergic receptors in the striatum (Torres-Altoro et al., 2011). Exposure of mice to DFP also results in neuroinflammation in multiple brain areas, effects which are markedly exacerbated by prior exposure to corti-costerone as a stressor surrogate (O'Callaghan, Kelly, Locker, Miller, & Lasley, 2015). Taken together, evidence from animal studies suggests that subtle brain changes at the neuronal signaling and structural levels could underlie some of the symptoms experienced by GW veterans. Month-long exposures to permethrin, PB and DEET with and without a brief exposure to restraint stress produced mood and cognitive changes in animal models and was consistent with neuro-inflammatory changes in hippocampal brain areas (Parihar et al., 2013).

OPs have been shown to disrupt multiple functions beyond those linked strictly to AChE. While AChE inhibition from exposures that occurred in the GW (e.g., sarin and CPF) have been implicated in the etiology of GWI (Golomb, 2008), other studies have identified additional secondary pathways of OP effects apparently unrelated to inhibition of AChE (see review; Terry, 2012). A notable non-cholinergic target of OPs is the process of axonal transport, a key nervous system function for transporting molecules (e.g., RNA and proteins) and subcellular organelles (e.g., mitochondria and synaptic vesicles) through the cytoplasm of axons (Terry, 2012). OPs can affect axonal transport directly through altering microtubule structure by binding to tubulin required for transport function (Grigoryan et al., 2008). This and similar covalent interaction of OPs with proteins to alter their function is not limited to binding to serine residues, because tyrosine is also bound by OP esters (Grigoryan et al., 2009), suggesting effects on energy metabolic/mitochondrial function at dosages too low to inhibit AChE. The direct consequences of OP binding (e.g., CPF) on transport has been visualized *in vitro* and shown to affect movement of mitochondria within the axon at concentrations below those that inhibit AChE (Middlemore-Risher, Adam, Lambert, & Terry, 2011). Effects of OPs on axonal transport were accompanied by changes in behavior associated with impairments in attention, memory and other aspects of cognition after exposure of rats to the OP CPF and the sarin surrogate DFP (Terry, 2012). Thus, axonal transport disruption by OPs relevant to exposures in the 1991 GW can result in deficits in cognition in animal models that resemble symptoms in ill veterans. As with most animal models of GWI studied to date, future evaluations of GW exposures on axonal transport would benefit from combined exposures at low levels. Nevertheless, studies that have been conducted since 2008 clearly indicate that low levels of OPs can adversely affect a key CNS process that may serve as a partial mechanistic explanation for symptoms associated with GWI.

Chronic exposures to PB and PER and to PB, PER, DEET and restraint stress to recapitulate exposures that occurred in the GW were applied in a in a mouse model by Abdullah and colleagues (Abdullah et al., 2011, 2012, 2013). Results revealed novel effect domains. Phospholipids key to lipid metabolism, axonal transport and endocrine and immune function were implicated. These effects were accompanied by behavioral findings indicating sensory, motor and memory impairments as well as subtle effects on glial morphology suggestive of underlying neuropathology and/or neuroimmune alterations. Together these data show the value of obtaining a broader perspective of the effect domains associated with exposure to GW-related agents. These studies serve as a template to discover additional pathways and systems disrupted by GW-related exposures.

In summary, animal models of GW-relevant exposures to individual chemicals, chemical mixtures, and chemicals plus other stressors have demonstrated alterations in nervous system outcomes (behavior, cognition, neurotransmission, intracellular signaling, molecular and cellular disruptions of axonal transport); liver and cardiovascular function; genomic, proteomic, lipidomic and metabolomic profiles, and mitochondrial changes. These studies have confirmed hypotheses that exposures are important in the development and expression of GWI symptomatology, that health effects due to exposures and exposure mixtures are often delayed and that persistent effects can be seen long after exposure has ended.

6. Conclusions/discussion

6.1. Prevalence and case definitions of GWI and other disorders affecting GW veterans

The disorder known as GWI has been investigated systematically since the early 1990's. Prevalence has been most validly characterized as the *excess* of diagnostic indicators of the disorder in deployed GW veterans relative to veterans who served during the same period but did not deploy to the GW. The two most commonly used case definitions are CMI (Fukuda et al., 1998) and the Kansas definition (Steele, 2000). Using these two definitions, prevalence of GWI is estimated to be about 25–32% in deployed GW veterans (RACGWI, 2008, 2014). Application of the more narrowly defined Haley criteria (Haley, Kurt, et al., 1997) tends to result in much lower prevalence estimates for GWI. Although these definitions have frequently been characterized as "symptom-based" and not related to known medical diagnoses, GWI symptoms are consistent with those seen in chemically induced toxic injuries and residual encephalopathies (Baker et al, 1985) and are associated with a range of objectively-measured biological alterations. Prognosis for recovery is understudied but appears to be poor.

Neurological disorders also occur in GW veterans. They may occur in connection with GWI (e.g., migraine headaches, neuritis or neuralgia) or as separate disorders, possibly occurring on a continuum with GWI. ALS, stroke, brain cancer and seizures have been identified at excess rates in deployed GW veterans, and brain cancer has been related to specific chemical exposures in theater. Given the presence of white matter anomalies in some subgroups of GW veterans, there has been concern that MS might also occur at higher rates in this population. However, the data required to draw valid conclusions about MS have not been systematically collected or analyzed. Because PD is also sometimes seen in patient

groups with chemical exposures, this disorder also remains a condition of concern; the status of knowledge about GW deployment-related PD is similar to that of MS.

Studies evaluating psychiatric disorders among deployed GW veterans have consistently shown that combat and other psychological stressors are associated with PTSD, anxiety, depression and alcohol abuse. However, psychological stressors are not significant predictors of GWI diagnosis and PTSD occurs at much lower rates in the deployed GW population than GWI. While some patients with GWI report dysphoria and sleep problems, these may reflect neuropathological effects of GW exposures (organic affective symptoms) and/or the consequences of being chronically ill with a debilitating condition for many years.

6.2. Etiology of GWI and neurological dysfunction

Across all studies and populations and since the earliest findings appeared linking self-reported exposures to diagnosis of GWI, two types of theater-related exposures have been consistently identified as risk factors for the disorder: exposures to pesticides and PB use. In research controlling for concurrent exposures, pesticide exposures were significantly associated with GWI in six of seven GW populations evaluated, and PB exposure was significantly associated in all seven of the populations studied. In addition, research that assessed the relationship between degree of exposure to pesticides and PB has consistently identified significant positive dose–effect relationships between degree of exposure and likelihood of GWI diagnosis (greater exposure is associated with higher likelihood of GWI diagnosis). Further evidence on the long-term residual effects of pesticides and PB carried out many years after the war using neurocognitive and neuroendocrine assays suggests significant sequelae of these exposures: neurocognitive research has shown that higher exposures to PB and pesticides are associated with decrements in cognitive function and they are also associated with alterations in HPA parameters in investigations of neuroendocrine function. Multiple studies using animal models of PB and pesticide exposure (individually and in combination with other exposures) have identified persistent and delayed structural changes in the brain and CNS as well as neurobehavioral dysfunction that are consistent with the symptomatology associated with GWI. And the profiles of symptoms and decrements in neurocognitive function identified in GW veterans parallel those seen in dozens of studies of occupational groups exposed to pesticides and pesticide mixtures. Taken together, these multiple lines of evidence suggest that exposure to pesticides and PB use are causally associated with GWI and other neurological consequences in GW veterans.

Research evaluating the relationship between exposure to the nerve agents sarin and cyclosarin and ill health in deployed veterans has consistently shown that modeled exposure to these agents is associated with structural brain differences on MRI (especially total white and grey matter volumes), with neurocognitive outcomes and with mortality due to brain cancer. The limited evidence on the relationships between these exposures and diagnosis of GWI has been inconsistent and inconclusive. More research on these exposures is needed to determine if they are causative for GWI.

Exposure to oil well fire smoke has also been less well studied and may be linked to GWI, respiratory disorders and brain cancer mortality, but more research is needed to make conclusions. The research to date on vaccines is also limited, with inadequate evidence to persuasively support a link between GWI and specific types of vaccines or the number of vaccines received.

6.3. Pathobiology of GWI and neurological and neuroimmune function in GW veterans

Because GWI is a multi-system illness, human studies on pathobiology have been difficult to pursue, particularly with regard to basic underlying mechanisms that may induce multiple symptoms and types of dysfunction. There is clear neurological pathology in this population. Studies of veterans with GWI defined in various ways and in veterans exposed to nerve gas agents that utilize varying imaging and EEG probes consistently identify structural and electrical abnormalities in the central nervous system: 14 of the 15 papers published since 2008 support this conclusion, as does a sizable literature published earlier. Similarly, neurocognitive research on GW veterans has consistently revealed exposure-related dysfunction among deployed GW veterans and differences between ill and healthy GW veterans suggestive of structural and functional CNS pathology.

Some GWI symptoms imply ANS involvement and early research consistently suggested that ANS dysfunction was prominent in GWI. This has been less well studied recently, but remains a likely contributing factor in the pathobiology of the disorder.

Neuroendocrine and immune dysregulation have also been reported in a number of studies, including those using protocols that demonstrate pronounced differences after exercise and other challenges. Specific patterns of altered HPA-axis functioning that are quite distinct from other conditions, including PTSD, have been reported in a long line of research. And one recent study has provided evidence of significant mitochondrial dysfunction in veterans with GWI. Further studies are warranted to determine the exact nature of identified alterations, which may lead to treatment options.

6.4. Animal models of GWI and theater exposures

Research on animal models of GW exposures and of GWI has contributed a great deal to our understanding of the exposure–outcome relationships and underlying mechanisms of GWI and other health issues in deployed GW veterans. These studies have examined the acute, chronic, and lasting residual effects of single and mixed exposures to PB, OPs, permethrin, DEET, nerve gas agents and experimental stressors on CNS outcomes. Results have shown both delayed and persistent effects (including effects seen an extended time after exposure has ended) on behavior, cognition, neurotransmission, intracellular signaling, and molecular and cellular transport in the CNS as well as liver and cardiovascular function, mitochondrial function, and genomic, proteomic, lipidomic and metabolomic profiles. Genomic and proteomic surveys have implicated phospholipids essential to lipid metabolism, axonal transport and endocrine and immune function. These effects were seen in the context of sensory, motor and memory impairments and changes in glial morphology. Taken together, the animal research supports the plausibility of the occurrence of multi-system health complaints existing long after exposure as well as underlying neuropathological and

neuroimmune mechanisms of GWI and other disorders and dysfunctions in exposed GW veterans.

6.5. The bottom line

The research data to date on health in GW veterans converge to support these conclusions:

- Between one-fourth and one-third of deployed GW veterans are affected by a disorder characterized by chronic symptoms involving multiple body systems; this condition is best identified by the term GWI.
- This disorder was caused by toxicant exposures, individually or in combination, that occurred in the GW theater. At present, research most clearly and consistently links pesticide and PB exposures to GWI, while exposures to low-level nerve gas agents, contaminants from oil well fires, multiple vaccinations, and combinations of these exposures cannot be ruled out.
- In addition to GWI, deployed GW veterans suffer from a variety of neurological disorders, alone or in combination with GWI. ALS, brain cancer, stroke, migraine headaches, neuritis and neuralgia have all been reported as occurring at higher rates in this population. Rates of disorders such as MS and PD are unknown and further intensive research is needed to determine whether they are elevated in GW veterans. This should include studies focused on GW veteran subgroups classified by individual exposures or geographic locations in theater.
- Neurological disorders as well as alterations in brain structure and function have been linked to specific exposures in theater, including nerve gas agents, PB and oil well fires
- The state of knowledge on the health of deployed GW veterans supports the conclusion that they are suffering from persistent pathology due to chemical intoxication (sometimes referred to by veterans as “toxic wounds”).
- Further research into the mechanisms and etiology of the health problems of GW veterans is critical to developing biomarkers of exposure and illness and preventing similar problems for military personnel in future deployments; this information is also critical for developing new treatments for GWI and related neurological dysfunction.
- Given the similarity of the health problems of GW veterans and those of other occupational groups with OP exposures (e.g., insecticide applicators, farmers, sheep dippers, nursery workers, chemical plant workers), the identification of treatments for the GW veteran population will have far-reaching implications for treating other groups of ill patients for whom no effective treatments have been identified.

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Table 1

Population-based prevalence estimates: chronic symptomatic illness in 1991 Gulf War veterans and nondeployed era veterans.

Study	Gulf War veterans assessed	Year(s) of assessment	Case definition used	Prevalence in Gulf War veterans	Prevalence in nondeployed veterans	Excess illness in Gulf War veterans
Fukuda et al., 1998	1,155 Air Force veterans	1995	CMI	45%	15%	30%
Unwin et al., 1999	4,428 U.K. male veterans	1998	CMI (modified)	62%	36%	26%
Steele, 2000	1,548 Kansas veterans	1998	Kansas GWI CMI	34% 47%	8% 20%	26% 27%
Proctor, Harley, Wolfe, Heeren, & White, 2001	180 New England Army veterans	1994–1996	CMI (modified)	65%	33%	32%
Unwin et al., 2002	226 U.K. female veterans	1998	CMI (modified)	64%	35%	29%
Blanchard et al., 2006	1,035 U.S. veterans	1999–2001	CMI (modified)[a]	29%	16%	13%
King, King, Bolton, Knight, & Vogt, 2008	357 U.S. veterans	2001	CMI	54%	not evaluated	–
Kang, Li, Mahan, Eisen, & Engel, 2009	6,111 U.S. veterans	2005	VA-defined multisymptom illness[b]	37%	12%	25%
Kelsall et al., 2009	1,381 Australian veterans	2000–2002	Australian factor definition	26%	16%	10%
Iannacchione et al., 2011	5,699 U.S. veterans	2007–2009	Haley factor definition (3 syndromes combined)	14%	4%	10%
Smith et al., 2012	317 U.S. veterans	2001	CMI	50%[c] 34%[c]	not evaluated	–
Steele, Sastre, Gerkovich, & Cook, 2012	646 Kansas City area veterans	2000	CMI	45%	not evaluated	–

Abbreviations: CMI = chronic multisymptom illness, as defined in Fukuda et al. (1998); Kansas GWI = Kansas Gulf War illness as defined in Steele (2000); VA = Department of Veterans Affairs.

[a] CMI modification replaced fatigue criterion with fatigue lasting >24 h after exertion.

[b] Unexplained multisymptom illness defined as multiple types of symptoms occurring together, not explained by medical/psychiatric diagnoses.

[c] Unweighted sample prevalence = 50% (prevalence estimate weighted to reflect general population = 34%).

(Table adapted from RACGWI, 2014).

Table 2

Studies reporting on diagnosable neurological conditions in Gulf War veterans.

Study	Groups studied	Outcome(s)	Key findings
Barth et al., 2009	621,902 GWV, 746,248 NDV	Mortality due to brain cancer, MS, PD, and ALS	GWV potentially exposed to nerve agents over multiple days and GWV with greatest exposure to oil well fires had significantly higher rates of brain cancer mortality. Overall, mortality due to brain cancer, PD, MS, ALS similar in GWV and NDV.
Kang et al., 2009	6,111 GWV, 3,859 NDV	Diagnosed medical conditions reported by veterans	Compared to NDV, GWV reported significantly higher rates of repeated seizures, neuralgia/neuritis, and stroke.
Kasarskis et al., 2009	43 deployed GWV with ALS, 66 nondeployed GWV with ALS	ALS age of onset, site of onset, atypical symptom features, ventilator-free survival time	No differences between ALS symptoms, age and site of onset similar for deployed GWV versus nondeployed. Ventilator-free survival time post-diagnosis was significantly shorter in deployed GWV.
Wallin et al., 2012	2,691 veterans who served in the military between 1990 and 2007, and had applied for VA benefits for MS	MS incidence by age, sex, race and branch of service	No determination of MS rates specifically in relation to 1991 Gulf War era or deployment. MS incidence was significantly higher in females than males, blacks versus other races, and in Air Force and Army veterans versus other branches.
Rayhan, Raksit, et al., 2013; Rayhan, Ravindran, et al., 2013; Rayhan, Stevens, et al., 2013	50 symptomatic GWV, 39 CFS patients, 45 sedentary controls	Structured headache evaluation	Statistically similar proportions of GWV (64%) and CFS (82%) patients affected by migraines; both significantly greater than controls (13%).
Wallin et al., 2014	387 GWV and 1,454 NDV who filed for disability benefits due to MS and ODD	MS incidence in GW-era veterans by age, sex, race and branch of service	MS incidence estimates (using entire active duty population of GWV and NDV as denominators), indicated no significant MS differences between GWV and NDV.

Abbreviations: GWV = Gulf War veterans; NDV = nondeployed veterans; ALS = amyotrophic lateral sclerosis; PD = Parkinson's disease, MS = multiple sclerosis; CFS = chronic fatigue syndrome, ODD = other demyelinating disease.

(Table adapted from RACGWVI, 2014).

Table 3

Studies reporting on psychiatric and psychological disorders in Gulf War veterans.

Study	Groups studied	Outcome(s)	Key findings
Vogt et al., 2008	81 active duty GWV and 230 NG/R GWV	DRRI, PTSS	High PT and DLWE scores on the DRRI and PTSS were significantly stronger for active duty women and NG/R men.
Woodward et al., 2009	50 PTSD+ (13 GWV and 37 VV) and 47 PTSD− (23 GWV and 24 VV)	Cortical volume measured using MRI	Subjects with combat-related PTSD showed significantly smaller cerebral cortical volume, thickness and area compared to PTSD-controls.
Yehuda et al., 2010	12 PTSD + GWV and 9 PTSD-GWV	Plasma ACTH changes, declarative memory, MRI, PET, DST	PTSD + group showed significantly greater cortisol and ACTH suppression. Hippocampal volume difference and greater hippocampal metabolic activity seen in PTSD + GWV. No memory differences were seen.
Apfel et al., 2011	82 GWV with lifetime PTSD, 44 GWV with current PTSD, 38 GWV with MDD, 80 PTSD-GWV	Hippocampal volume measured using MRI	GWV with chronic PTSD had smaller hippocampal volume than GWV without current PTSD. Current PTSD symptoms were associated with significantly reduced hippocampal volume.
Coughlin et al., 2011	6,111 deployed GWV, 3,859 nondeployed veterans	Alcohol use, PTSD, MDD	Problem drinking was significantly and positively associated with PTSD and MDD
Gade & Wenger, 2011	1035 GWV, 3452 VV	MCS	Exposure to war casualties but not combat overall was associated with mental health decline. Negative effects of combat were larger for GWV compared to VV.
Hassija et al., 2012	87 GWV and 43 OIF/OEF veterans	PSS, DSS, alcohol misuse	Combat exposure was significantly associated with PSS, DSS and alcohol misuse.
Wachen et al., 2013	317 GWV	PSS, PCL, PHS	Significant associations between post-deployment physical health and PSS in all symptom categories. PSS score was more strongly related to physical health for subjects with lower warzone exposures, but also significant for high warzone exposures.

Abbreviations: GWV = Gulf War veterans; MDD = major depressive disorder; PTSD = post-traumatic stress disorder; PTSD+ = meets the criteria for current PTSD resulting from one or more military trauma; PTSD− = did not meet criteria for PTSD, either current or lifetime; MRI = magnetic resonance imaging; MSI = multisymptom illness; MCS = Mental Component Summary; VV = Vietnam veterans; OEF = Operation Enduring Freedom; OIF = Operation Iraqi Freedom, PSS = post-traumatic stress disorder symptom severity; DSS = depressive symptom severity; PTSS = post-traumatic stress symptomatology; DRRI = Deployment Risk and Resilience Inventory; PT = perceived threat; DLWE = difficult living and working environment; NG/R = National Guard/Reserve; PCL = Post-traumatic Stress Disorder Checklist; PHS = physical health symptoms; ACTH = adrenocorticotropic hormone; PET = positron emission tomography; DST = dexamethasone suppression test.

(Table adapted from RACGWVI, 2014).

Table 4

Association of pyridostigmine bromide and pesticide exposures with symptomatic illness in Gulf War veteran populations.

Study	Gulf War veterans studied	Symptomatic illness evaluated	Association of exposure with symptomatic illness (adjusted for effects of other exposures)		Additional information
			PB	Pesticides, repellants	
Haley & Kurt, 1997	249 GWV Navy Seabees	Haley syndromes	+[1]	+	PB side effects “dose response” effect; DEET dose response effect
Ishoy, Suadicani, Guldager, Appleyard, & Gyntelberg, 1999	686 Danish GWV	Gastrointestinal and/or neuropsychological symptoms	na	+	
Nisenbaum et al., 2000	1,002 Air Force GWV	CMI	+	+	
Cherry et al., 2001b	7,971 U.K. GWV	Overall symptom severity	+[2]	+	PB dose response effect; Pesticide dose response effect
Spencer et al., 2001	1,119 GWV from Washington, Oregon	Gulf War unexplained illness (study defined)	+	−	PB dose response effect; DEET was only pesticide evaluated in model
Gray et al., 2002	3,831 GWV Navy Seabees	Gulf War illness (study defined)	+	+	
Wolfe et al., 2002	945 Army GWV	CMI	+	na	PB dose response effect
Steele et al., 2012	304	Kansas GWI	+	+	PB association most pronounced in forward deployed GWV

Abbreviations: PB = pyridostigmine bromide; GWV = Gulf War veterans; CMI = chronic multisymptom illness, as defined in Fukuda et al. (1998); Kansas GWI = Kansas Gulf War illness as defined in Steele (2000); DEET = NIN-diethyl-meta-toluamide.

+ = statistically significant association; − = association not statistically significant; na = not assessed.

Notes:

[1] association with PB side effects only,

[2] association with PB use and PB side effects.

(Table adapted from RACGWVI, 2008).

Table 5

Studies assessing exposures associated with health outcomes in Gulf War veterans.

Study	Groups studied	Exposure(s)	Method(s)	Key findings
Neurological and neuropsychological				
Toomey et al., 2009	1,061 deployed GWV; 1,128 nondeployed veterans	PB, pesticides, vaccines, IG injections, oil well fire smoke	Neuropsychological testing	Deployed GWV had significantly lower scores on tests of verbal memory, verbal learning, motor speed, and attention than nondeployed. Specific exposure in Khamisiyah was negatively correlated with motor speed.
Chao et al., 2010	40 exposed GWV, 40 unexposed GWV	Sarin and cyclosarin	MRI, neuropsychological testing	Significantly reduced gray matter and hippocampal volumes in sarin and cyclosarin exposed subjects. White matter volume was associated with executive function and visuospatial abilities in exposed veterans.
Chao et al., 2011	64 exposed GWV, 64 unexposed GWV	Sarin and cyclosarin	MRI, neuropsychological testing	Sarin/cyclosarin exposed GWV showed sign. reduced total gray and white matter volumes compared to unexposed controls. GWI/CMI diagnosis sign. predicted gray and white matter volumes in sarin/cyclosarin exposed subjects. Exposed GWV performed sign. worse on a continuous performance test of attention, but better on psychomotor function (Trailmaking Test A and Grooved Pegboard).
Cancer mortality				
Barth et al., 2009	621,902 GWV, 746,248 nondeployed veterans	Sarin/cyclosarin Oil well fire contaminants	Brain cancer mortality, brain cancer, ALS, MS, PD	Significant increase in brain cancer mortality among GWV in sarin exposure area ≥ 2 days; sign. dose response effect for number of days of exposure. Oil fire associated with sign. increase in brain cancer mortality among exposed Army GWV, compared to non-exposed. No interaction found between oil well fires and sarin exposure.
Health status				
Kelsall et al., 2009	698 Australian GWV	Vaccines	Total symptom number, SF-12 physical component, GHQ-12 case status	Number of self-reported vaccines weakly associated with total number of symptoms and poorer health; relationship not seen with recorded vaccination number.
Genotyping				
Steele et al., 2015	144 GWI cases, 160 GWV controls	Exposures or exposure indicators with possible cholinergic effects (PB, pesticides, hearing chemical alarms)	Association of BChE genotype with GWI gene–exposure interactions	No association of BChE genotype overall with GWI; significant gene–exposure interaction for PB only; GWV with less active BChE variants (KK, A, F heterozygotes) who used PB had significantly greater GWI risk (OR = 40.0) than GWV with more active UU & UK genotypes (OR = 2.7)
GWI and CMI				
Phillips et al., 2009	175 male U.S. Navy Seabees GWV	Vaccines (squalene antibodies)	CMI	Similar proportions of CMI (55%) and healthy (51%) GWV were positive for squalene antibodies (p = .71).
Steele et al., 2012	304 Kansas City area GWV	PB, pesticides, vaccines, oil well fire smoke, chemical alarms	GWI	Pesticide use significantly associated with GWI for veterans who were in Iraq or Kuwait and for veterans in support areas. Use of PB, close proximity to exploded SCUD missile and exposure to oil well fire smoke significantly associated with GWI for

Study	Groups studied	Exposure(s)	Method(s)	Key findings
				personnel in forward areas only; GWI not associated with serving in combat, hearing che
				personnel in forward areas only; GWI not associated with serving in combat, hearing che
Haley et al., 2013	8,020 GWV	Chemical alarms, DoD-modeled Khamisiyah exposure area	GWI	GWI was significantly associated in a dose–response manner with hearing chemical alarms but not with exposure to Khamisiyah plume

Abbreviations: GWV = Gulf War veterans; GWI = Gulf War illness; PB = pyridostigmine bromide pills; MRI = magnetic resonance imaging; IG = immunoglobulin; ACTH = adrenocorticotropic hormone; CRF = corticotrophin-releasing factor; CMI = chronic multisymptom illness; SF-12 = Short-Form Health Survey 12 items; PCS = Physical Component Summary Score; GHQ-12 = General Health Questionnaire; DoD = Department of Defense, ALS = amyotrophic lateral sclerosis; PD = Parkinson's disease; MS = multiple sclerosis; SCUD = Subsonic Cruise Unarmed Decoy; BChE = butyrylcholinesterase.

(Table adapted from RACGWVI, 2014).

Table 6

EEG and brain imaging findings in symptomatic Gulf War veterans.

Study	Groups studied	Method(s)	Key findings
MRI and SPECT			
Haley et al., 2009	21 GWV with Haley syndromes, 17 veteran controls	SPECT	Syndrome 2 showed significantly lower resting nrCBF compared to controls and other syndrome groups. Reduction most apparent in caudate head, globus pallidus, putamen and posterior thalamus. Subjects with Syndrome 2 showed elevated nrCBF while other groups showed reduced nrCBF after physostigmine stimulation.
Weiner et al., 2011	81 symptomatic GWV, 101 intermediate GWV, 97 deployed veteran controls	MRI, MRS	No significant differences in NAA and NAA metabolites in the basal ganglia and pons between symptomatic and control veterans.
Rayhan, Raksit, et al., 2013; Rayhan, Ravindran, et al., 2013; Rayhan, Stevens, et al., 2013	15 symptomatic GWV, 11 veteran and civilian controls	fMRI, MRS	Prefrontal lactate levels prior to exercise predicted whether symptomatic GWV showed increased or decreased memory test scores.
Physostigmine challenge test			
Li et al., 2011	35 GWV with Haley syndromes, 13 veteran controls	MRI-based ASL	Abnormal hippocampal CBF persists in symptomatic GWV at baseline. Patients with Syndromes 2 and 3 showed significantly increased bilateral rCBF in hippocampi after physostigmine stimulation.
Liu et al., 2011	33 GWV with Haley syndromes, 14 nonsymptomatic veteran controls	MRI-based ASL	Expected physostigmine decrease in CBF was absent in symptomatic GWV, who showed either no change or increased CBF after cholinergic challenge. Physostigmine response differences between GWV and controls most pronounced in amygdala, hippocampus, caudate and thalamus.
Structural MRI			
Calley et al., 2010	53 GWV with Haley syndromes, 16 nonsymptomatic deployed GWV	fMRI	Significant signal change increase in the thalamic region and signal change decrease in the caudate in Syndrome 2 subjects compared to Syndrome 1 and controls. Syndrome 2 subjects showed significantly positive association between reaction time on SORT task and percent signal change in bilateral caudate heads. Syndrome 1 and 3 subjects performed significantly worse on SORT compared to deployed controls.
Chao et al., 2011	64 GWV with suspected sarin or cyclosarin exposure matched to 64 unexposed GWV	MRI	Sarin and cyclosarin exposed GWV showed significantly reduced total gray and white matter volumes compared to unexposed controls. GWI/CMI diagnosis significantly predicted gray and white matter volumes in sarin and cyclosarin exposed subjects. No dose–response relationships seen.
fMRI			
Gopinath et al., 2012	40 GWV with Haley syndromes, 14 veteran controls	fMRI	In response to innocuous heat, subjects with Syndromes 1 and 2 showed significantly reduced activation in the insula, S1, S2, SMA, medial PPC, IPL, premotor cortex and DMPFC in compared to controls. Syndrome 1 and 2 exhibited significantly more activation to innocuous heat in the ventral anterior cingulate.
Hubbard et al., 2013	96 symptomatic GWV, 44 matched controls	fMRI	Significant differences were seen between groups for prefrontal cortex activity during a working memory task, indicating that GWVs allocate high demand working memory loads differently from controls.
Rayhan, Raksit, et al., 2013; Rayhan, Ravindran, et al., 2013; Rayhan, Stevens, et al., 2013	28 symptomatic GWV, 10 civilian controls	fMRI	The GWI post-exercise orthostatic tachycardia subgroup showed brainstem atrophy and baseline working memory compensation in the vermis. The other GWI subgroup exhibited hyperalgesia in response to exercise, and had baseline working memory compensation in the basal ganglia when compared to controls. GWV showed impaired working memory compared to controls.
Rayhan, Raksit, et al., 2013; Rayhan, Ravindran, et al.,	31 GWV with CFS and CMI, 12 sedentary control veterans	fMRI	In GWV diagnosed with CMI or CFS, white matter integrity loss was identified in cortico-cortical and corticospinal areas. Changes in axial diffusivity in the IFOF significantly different between controls and CFS/CMI GWV.

Study	Groups studied	Method(s)	Key findings
2013; Rayhan, Stevens, et al., 2013			
EEG			
Tillman et al., 2012	20 GWV with Haley syndromes, 8 deployed asymptomatic GWV	ERP from EEG	Haley syndrome group predicted P1 amplitude, P1 latency, with longer latencies in syndromes 2 and 3 compared to controls and Syndrome 1. Mean P3a amplitudes significantly different between syndromes 1 and 2 compared to controls and syndrome 3.
Tillman et al., 2013	22 GWV with Haley syndromes, 8 deployed asymptomatic GWV	ERP from EEG	Significantly lower P3b amplitudes in 3 syndrome groups compared to controls in an oddball attention task.

Abbreviations: GWV = Gulf War veterans; PTSD = post-traumatic stress disorder; SORT = Semantic object retrieval test; MRI = magnetic resonance imaging; fMRI = functional magnetic resonance imaging; GWI = Gulf War illness; CMI = chronic multisymptom illness; CSF = cerebrospinal fluid; S1 = Primary somatosensory cortex; S2 = Secondary somatosensory cortex; SMA = supplementary motor area; PPC = posterior parietal cortex; IPL = inferior parietal lobule; DMPFC = dorsomedial prefrontal cortex; SPECT = Single Photon Emission Computed Tomography; nrCBF = normalized regional cerebral blood flow; rCBF = regional cerebral blood flow; ASL = arterial spin labeling; CFS = chronic fatigue syndrome; IFOF = inferior fronto-occipital fasciculus; MRS = magnetic resonance spectroscopy; MS = multiple sclerosis; EEG = electroencephalogram; ERP = event related potential; NAA = N-acetyl aspartate; VV = Vietnam veterans; PHG = parahippocampal gyrus; STC = superior temporal cortex; OFC = orbital frontal cortex; PO = pars orbitalis.

Table 7

Neurocognitive findings in Gulf War veterans.

Study	Groups studied	Key findings
Odegard et al., 2013	10 GWV Haley Syndrome 1; 12 GWV Haley Syndrome 2; 11 GWV Haley Syndrome 3; 14 GWV well controls	Control GWV and GWV with Haley Syndrome 1 provided significantly more recall responses to face-name items than GWVs with Haley Syndrome 3. Memory performance was related to activation in the left hippocampus.
Tillman et al., 2010	25 GWV with major cognitive complaints; 23 matched GWV controls	The experimental group had significantly more false positives and significantly fewer hits than the control group suggesting inhibition difficulties. The mean P3 amplitude of the patient group was significantly lower than the control group, and also demonstrated a condition effect with decreased amplitude during the NOGO condition.
Toomey et al., 2009	1,061 deployed GWV; 1128 nondeployed GWV	Eight factors were generated accounting for 68% of variance including verbal memory, attention/working memory, visual memory, executive functioning, perceptual motor speed, visual organization, motor speed, and sustained attention. With a cutoff of 2 SD below the mean the deployed group performed worse on motor speed and sustained attention. The deployed group performed significantly worse on Trails B compared to the nondeployed group. Self-reported exposure to contaminated food or water was a significant predictor of performance in sustained attention. Khamisiyah exposure was a significant predictor of verbal memory performance, CARC/paint and receipt of IG were significant predictors of visual memory performance, and SCUD missiles and vaccines of motor speed performance.
Wallin et al., 2009	25 deployed GWV with CDC defined GWI; 16 deployed GWV without CDC defined GWI	No significant differences were found between GWI cases and controls in assessed cognitive domains. GWI cases and controls mean scores were both within normal limits compared to population based normative samples. GWI cases mean scores were all lower than controls. GWI cases were significantly more impaired on measures of mood and quality of life.

Abbreviations: GWV = Gulf War veteran; CARC = chemical agent resistant coating; IG = immunoglobulin; SD = standard deviation; CDC = Centers for Disease Control.

(Table adapted from RACGWVI, 2014).

Table 8

Studies using animal and *in Vitro* models of Gulf War illness and related diseases.

Study	Model	Parameter(s) evaluated exposure	Key findings
Abdullah et al., 2011	Mouse	PB, PER	Exposed mice demonstrated significantly increased anxiety behavior, memory impairment and psychomotor dysfunction. After 150 days of exposure, significant increases in astrogliosis were seen in exposed mice. Proteomic analysis showed significant expression alterations for proteins that regulate lipid metabolism, molecular transport, and endocrine and immune function.
Abdullah et al., 2012	Mouse	PB, PER, DEET, stress	Significant increases in ether-containing PC, diacyl, PC and SM lipids, indicating altered transport, uptake, storage and synthesis in ACh pathways in the brain. Anxiety-like behavior was increased in exposed mice, especially in females. Sensorimotor deficits were also significantly associated with exposure, as was astrogliosis.
Abdullah et al., 2013	Mouse	PB, PER	Exposed mice had elevated brain levels of PC and SM phospholipid species, particularly those containing ether PC. Brain catalase staining was higher in exposed than control mice. Lyso-platelet activating factors (precursors of inflammatory lipid mediators) were decreased in the brain and blood from exposed compared to control mice.
Bozkurt et al., 2010	Rat	CPF	Single CPF dose led to significant short term (12 h) changes in glial and neuronal markers in serum. Immediate significant changes in body weight and temperature persisted for approximately 168 h.
Cardona et al., 2006	Rat	CPF	CPF significantly inhibited AChE and APF enzymatic activity even when signs of acute toxicity were absent. Striatum and brainstem areas showed slowed AChE recovery after CPF exposure.
Corbel et al., 2009	Insect and mouse cultured tissue	DEET	DEET application to insect CNS neuronal preparation produced significant initial increase in neuronal electrophysiological activation, followed by a significant decrease, indicating changes in synaptic transmission and inhibition of cholinesterase activity.
Grigoryan et al., 2008	Bovine protein isolate	Sarin, soman, CPO, DFP, FP-biotin	Pesticide agents bind covalently to tubulin, a protein required for neuronal transport, putatively creating axonal transport deficits.
Grigoryan et al., 2009	Bovine, human, porcine and murine protein isolate	FP-biotin	OP esters bind to tyrosine in proteins across different species. OP-reactive proteins include enzymes with and without active serine sites.
Grigoryan et al., 2009	Bovine, human, porcine, murine protein isolate	DFP, CPO	OP esters covalently bind to lysine in albumin, keratin, actin, tubulin and transferrin in a number of mammalian species.
Jiang et al., 2010	Mouse	CPF, CPO	Microtubules isolated from brain tissue from exposed mice showed fewer associated proteins than control mice, and microtubules from exposed mice were significantly smaller in comparison to controls. Mice brains show CPO-labeled tubulin after injections of nontoxic doses of CPF or CPO.
Middlemore-Risher et al., 2011	Rat	CPF, CPO	Mitochondrial length, number and axonal movement were decreased in central nervous system neurons in rats exposed to CPF or CPO when compared to controls.
Nutter et al., 2013	Rat	CPF, PER, PB	After exposure, K^+ channel kinetics were altered in vascular pain receptors, with significant increases in electrophysiological excitability. No behavioral differences were noted between exposed and control animals, nor were significant effects seen in Na^+ channel activity.

Study	Model	Parameter(s) evaluated exposure	Key findings
O'Callaghan et al., 2015	Mouse	DFP, DEET, CORT	Pretreatment with CORT greatly increased neuroinflammatory responses to DFP. Minocycline (anti-inflammatory) suppressed DFP + CORT neuroinflammation.
Ojo et al., 2013	Mouse	CPF, PB, PER	Exposure to CPF alone or in combination with PB and PER reduced synaptic function by reducing hippocampal synaptophysin and impairing cell differentiation in the dentate gyrus, with altered basal ACh levels throughout the brain.
Parihar et al., 2013	Rat	DEET, PER, PB, stress	Exposure to low doses of DEET, PER and PB increased disordered mood and cognitive behaviors. Rats exposed to pesticides and stress showed significantly reduced hippocampal volume and neuron growth, and increased CNS inflammation.
Speed et al., 2012	Mouse	CPF	Mice injected with CPF showed a short term increase in synaptic transmission in the CA3–CA1 hippocampal region. After three months, decreased spine density in the hippocampus and reduced synaptic activity was seen in exposed versus control mice.
Torres-Altoro et al., 2011	Mouse	CPF, sarin, PB, DEET, DFP	CPF and PB altered dopaminergic and glutamatergic synaptic transmission *in vivo* and slice preparations. Combined PB/DEET/DFP exposure stimulated aberrant brain specific protein expression in the striatum and hippocampus.

Abbreviations: PB = pyridostigmine bromide; PER = permethrin; DEET = *N*,*N*-diethyl-meta-toluamide; PC = phosphatidylcholine; SM = sphingomyelin; ACh = acetylcholine; DU = depleted uranium; CPF = chlorpyrifos; CNS = central nervous system; CPO = chlorpyrifos oxon; DFP = diisopropylfluorophosphate; FP-biotin = 10-fluoroethoxyphosphinyl-*N*-biotinamidopentyldecanamide; OP = organophosphorus; AChE = acetylcholinesterase; APF = acylpeptide hydrolase; LV = left ventricular; TH = tyrosine hydroxylase; PC = phosphatidylcholine; SM = sphingomyelin; DU = depleted uranium; ROS = reactive oxygen species; CORT = corticosterone.

(Table adapted from RACGWVI, 2014).