Memory and Functional Brain Differences in a National Sample of U.S. Veterans with Gulf War
Illness

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1. Introduction (5150 Words)

Of the 697,000 U.S. military personnel who served in operations Desert Shield and Desert Storm in the 1991 Persian Gulf War, 26-32% report suffering from chronic health problems, including muscle and joint pain, chronic fatigue, attention problems, memory and other cognitive deficits, sleep disorders, and headaches. The incidence of these self-reported symptoms is greater among Gulf War veterans (GWV) than control groups (Centers for Disease Control and Prevention, 1995; Fukuda et al., 1998; Haley et al., 1997; Iowa Persian Gulf Study Group, 1997; Steele, 2000), and self-reports of these symptoms have shown to be linked to structural and functional brain abnormalities (Chao et al., 2011; Hom et al., 1997; Proctor et al., 2006; White et al., 2001).

Service-related exposure to neurotoxins (Binns et al., 2008) has been hypothesized to cause the elevated rates of self-reported symptoms and central nervous system abnormalities in Gulf War Illness (GWI). Such neurotoxins include sarin gas and pyridostigmine bromide (PB) tablets, anti-nerve agent pills pharmacologically similar to sarin but that are reversible cholinesterase inhibitors taken as a pretreatment to nerve gas exposure. Recent epidemiological studies, as well as meteorological and intelligence data on chemical weapons fallout from bombing early in the war, have assisted in confirming exposure of GWV to low-level sarin nerve gas (Haley and Tuite, 2013; Tuite and Haley, 2013). Research conducted in animal models demonstrates that low-dose exposure to sarin and similar organophosphates negatively impacts the central nervous system (Abdel-Rahman et al., 2002; Abdel-Rahman et al., 2004a; Abdel-Rahman et al., 2004b; Henderson et al., 2001; Speed et al., 2012), and results in behavioral and cognitive abnormalities (Abdel-Rahman et al., 2004b; Gardner et al., 1984; Lamproglou et al., 2009).

These data suggest that ill GWV are at an elevated risk of experiencing cognitive and behavioral symptoms, but limited research has verified the symptoms they report. Memory impairment, for example, is commonly reported, but ill GWV sometimes do not demonstrate impaired memory performance relative to appropriate control participants on standardized memory tests (Chao et al., 2010; 2011; Hom et al., 1997; Haley and Kurt, 1997; White et al., 2001). The inconsistencies in the memory findings are perplexing given that ill GWV exhibit abnormalities in the basal ganglia and hippocampus, both of which are critical components of learning and memory circuits in the brain (Haley et al, 2009; Li et al., 2011; Liu et al., 2011; Menon et al., 2004). To better understand the memory problems reported by GWV and their potential neurobiological basis, we previously evaluated episodic memory performance and brain function in a small sample of veterans who served in a construction battalion (Seabees) during the 1991 Gulf War (Odegard et al., 2013). Relative to unaffected GWV, ill GWV demonstrated impaired performance on a face-name memory task; performance was correlated with brain activation in the left hippocampus during the memory test. A similar relationship was observed between memory performance and hippocampal blood flow elicited by a cholinergic challenge with physostigmine performed during a separate resting-state scan performed on the same cohort of Seabees GWV (Li et al., 2011).

These initial results better characterize the memory deficits experienced by ill GWV and their associated neurobiological correlates, but Odegard et al. (2013) used a sample of male veterans who had served in the same construction battalion, which raises questions about the extent to which these findings would replicate in a nationally representative sample of GWV. Additionally, the small sample size limited the ability to detect potential differences in memory performance and brain function across different groups of ill GWV. These points are critical

given that ill GWV are known to be a heterogeneous group reporting a range of symptoms. The Fukuda or Centers for Disease Control classification of GWI, for example, describes GWI as a complex multi-symptom illness associated with service in the first Gulf War that is defined by the presence of two or more of the following symptoms for 6 months or longer: general fatigue, mood abnormalities, cognitive problems, and musculoskeletal pain (Fukuda et al., 1998). Based on these criteria, only sub-groups of ill GWV report memory problems, and a GWI diagnosis can be made in the absence of reported memory problems.

The heterogeneity inherent to ill GWV was addressed in the previous study (Odegard et al., 2013) by classifying participating GWV into three syndrome types based on their self-reported symptoms. The syndrome types were originally defined based on the symptoms reported by 249 Seabees GWV (Haley and Kurt, 1997; Haley et al., 1997; Haley et al., 2001) and later validated with a national sample of 8020 GWV (Iannacchione et al., 2011) from which the participants for the current study were obtained. Syndrome 1 (“impaired cognition”) is characterized by self-reported problems with executive function; Syndrome 2 (“confusion-ataxia”), by confusion and ataxia, problems with declarative memory, and emotional disturbances; Syndrome 3 (“central pain”), by widespread bodily pain and abnormalities in bodily sensation (Haley et al., 1997). Memory and cognitive problems were reported by all three major syndrome types, but more often by GWV classified as having Syndromes 1 and 2 (Haley et al., 1997).

To address the issue of generalizability and to better compare memory and brain function across groups of GWV, a larger cohort of Persian Gulf War veterans with age and gender distributions and other demographics representative of all U.S. GWV (Iannacchione et al., 2011) participated in the current study. The participating ill GWV were classified based on the

syndrome type system described above, and brain function was measured using functional magnetic resonance imaging (fMRI) while each participant completed a face-name memory task. It was predicted that veterans classified as Syndrome types 1 or 2 would present with memory deficits relative to controls (GWV-C), and that the same might be true of Syndrome 3, given that GWV classified as suffering from Syndrome 3 were observed to have decreased memory performance relative to control participants in the prior study (Odegard et al., 2013). It was also predicted that differences in brain function measured during the memory task would be observed between ill and well GWV, and that the different syndrome types would show unique spatial patterns of regional brain activation relative to GWV-C. As an extension to Odegard et al. (2013), the present study will also investigate the potential impact of deployment on memory and brain function by using separable GWV-C groups, both deployed and nondeployed.

A subsequent memory paradigm was implemented to 1) characterize the processes supporting successful memory of face-name pairs across the GWV groups, and 2) detect group differences in patterns of brain activation during such encoding. These paradigms have been used to operationally define successful encoding activity with well over 100 studies to date investigating memory function in healthy adults (for a meta-analysis see Kim, 2011) and to characterize memory deficits and differences in encoding in aging and disease states (Dannhauser et al., 2008; Guedj et al., 2011; Hulst et al., 2012; Trivedi et al., 2008; Weis et al., 2011). The associative memory paradigm used in this study may allow ill GWV's complaints to be objectively validated and potential differences in underlying patterns of brain activation evoked during encoding to be observed, providing insights into central nervous system abnormalities of GWI.

2. Methods

2.1. Design

The experiment conformed to a 2 (Item Type: Face-Name, Face-Only) X 5 (Group: Nondeployed GWV-C, Deployed GWV-C, GWV-1, GWV-2, GWV-3) mixed factors design. At study, participants viewed faces (face-only items) and faces with names (face-name items). At test, participants were presented with faces that had been face-name items at study and faces that had been face-only items at study. For each face presented on the test, participants made one of three memory responses: (1) "recall" when they explicitly remembered the name paired with the face, (2) "know" when they knew the face had been paired with a name but could not remember the specific name, and (3) "face-only" when the face had been presented without a name during the study phase. The "recall" and "know" responses are considered associative memory judgments, and the "face-only" response is considered to be a non-associative judgment. The face-only items provided a basis to correct associative memory judgments made to face-name pairs for response bias (i.e., guessing).

2.2. Participants

A nested case-control sample (N=89) of U.S. military veterans of the 1991 Persian Gulf War era was selected from a nationally representative sample of Gulf War-era veterans (N=8020) who completed a comprehensive computer-assisted telephone interview (CATI) questionnaire; the survey and sample selection methods have been described in detail elsewhere (Iannacchione et al., 2011; Haley et al., 2013). Participating veterans gave written informed consent and volunteered to participate in this study in exchange for monetary compensation, in accordance with a protocol approved by an institutional review board. Due to incomplete data or technical error, 8 participants were excluded from analyses. Demographics and co-morbidity measures were obtained by clinical interview (see Table 1). Post-Traumatic Stress Disorder

(PTSD) was assessed using the clinician administered PTSD scale (CAPS; Blake et al., 1990; Blake et al., 1995; Weathers et al., 2001). The structured clinical interview for DSM-IV Axis I disorders (SCID; First et al., 1996), which includes modules containing question prompts and scoring for the majority of Axis I and Axis II disorders, was used to measure major depressive disorder (MDD), alcohol abuse or dependence, and drug abuse. These are important to assess due to their high prevalence rates in veteran populations.

The participating veterans were housed and monitored at the institution's clinical research center while undergoing a week-long study; the project was conducted in 2009-2010. Of the ill GWV, 19 met the Haley et al. (1997) criteria for GWI Syndrome 1, 20 met criteria for GWI Syndrome 2, and 18 met criteria for GWI Syndrome 3. In addition, age-sex-education-matched control GWV who did not present with GWI (10 deployed and 14 not deployed to the Gulf War theater) were included. The two GWV-C groups were compared for differences rather than pooled because deployed control veterans, unlike non-deployed control veterans, were likely exposed to the same elements (e.g., sarin and PB tablets) of the war as those who later presented with GWI. The groups did not differ in age, gender, race, or ethnicity.

2.3. fMRI stimuli

Visually presented fMRI stimuli consisted of 144 grayscale pictures of Caucasian faces (72 male, 72 female) and 144 names (72 male, 72 female). There were a total of six study lists; each contained 24 items, 8 faces and 16 face-name pairs. Examples of the study items are provided in Figure 1. Each study list was followed by a memory test of the 24 faces that had been presented on the previous study list (Figure 1).

2.4. Presentation of stimuli

Research personnel blind to whether or not a GWV was ill or well administered the protocol. Participants completed two study lists and accompanying memory tests for training purposes prior to scanning and four study lists and four memory tests while inside the MR scanner. There was no overlap between the practice and scanner stimuli. Each stimulus appeared on the screen for 2 s followed by a variable inter-stimulus interval (ISI) averaging 6 s (range 4-8 s) during study (Figure 1). Immediately after the presentation of each study list, participants completed a memory test. At test, participants were presented with the same faces that they had seen on the study list (Figure 1). Each face was presented for 4 s followed by a variable ISI averaging 6 s (range 4-8 s). Participants were asked to identify which faces had been presented with a name at study and which had not. To do so, participants made one of three responses. If participants knew that a name had been presented with a face at study and they were able to recall the name, they were to make a *recall* judgment. In contrast, if participants knew that a face had been presented with a name at study but were unable to recall the name, they were to make a *know* judgment. Participants were instructed to respond *face-only* if they thought the face had not been accompanied by a name at study. Test responses were recorded using a four-button fiber optic response box, and participants were instructed not to actually say aloud the names they recalled when they were inside the scanner.

2.5 Associative memory response bias correction

To accommodate differences in response bias, associative memory data were corrected using the two-high threshold correction of signal detection theory (Snodgrass and Corwin, 1988), which is a simple method used to correct for response bias by subtracting the proportion of false alarms (i.e., noise) from the proportion of hits (i.e., signal). For the present data, the proportion of *recall* responses given to faces was subtracted from the proportion of *recall* responses given to

face-name pairs to correct for response bias in making *recall* responses. To correct for response bias in making *know* responses, the proportion of *know* responses given to faces was subtracted from the proportion of *know* responses given to face-name pairs.

2.6. Functional imaging parameters

Scanning was performed on a 3T Siemens Trio Total Imaging Matrix scanner with a 12-channel radio frequency head coil. A high-resolution T1-weighted structural 3D MP-RAGE sequence (flip angle = 9° ; TE = 3.96 ms; TR = 2250 ms; TI = 900 ms; in-plane resolution = 0.94 x 0.94 mm; slice thickness = 0.9 mm; matrix size = 256 x 240; 176 sagittal slices; acquisition time = 4.5 min) was acquired for anatomic reference.

For fMRI, a series of T2*-weighted echo planar image (EPI) sequences with flip angle = 90° , TE = 18 ms, TR = 2000 ms, 220 mm field of view, matrix size = 74 x 74, in-plane resolution = 2.97 x 2.97 mm, slice thickness = 3 mm, and 42 axial slices, were collected using GeneRalized Autocalibrating Partially Parallel Acquisitions with an acceleration factor of 2. EPI data were acquired during the four study lists and four memory tests. A total of 105 volumes were collected during the presentation of each study list and 129 volumes were collected during the completion of each memory test. Total acquisition time for all of the fMRI runs was roughly 45 min.

2.7. fMRI data analysis

The functional data were processed and analyzed with Analysis of Functional Neuroimages (AFNI) software (Cox, 1996). The first three volumes of each run acquired prior to magnetization equilibrium were discarded. The EPI images were corrected for temporal differences in slice acquisition and for head motion, by aligning all volumes to the first EPI volume collected using a three-dimensional rigid body registration. Linear drift was removed,

and the four study EPI runs were concatenated into a single file. Finally, the EPI data were spatially smoothed with an isotropic 6 mm full-width half maximum Gaussian filter.

For the fMRI data, a general linear model was created for each participant to model hemodynamic response functions (HRF) for five different events of interest: (1) faces presented at study that subsequently received *know* responses at test; (2) faces presented at study that subsequently received *face-only* responses at test, (3) face-name pairs presented at study that subsequently received *recall* responses at test presentation of the face, (4) face-name pairs presented at study that subsequently received *know* responses at test presentation of the face, and (5) face-name pairs presented at study that subsequently received *face-only* responses at test presentation of the face. Furthermore, any face-only presented at study that received a *recall* response at test, as well as any face or face-name pair presented at study that did not receive any response at test, were modeled but not further analyzed due to low occurrence (*all Ms* < 0.04, *all SDs* < 0.07). A second model with four events of interest was also conducted that combined face-name *recall* and *know* (*recall+know*) responses (see section 2.8 fMRI associative memory modeling for details). Each onset time was convolved with a canonical HRF to produce the predicted BOLD signal by modeling the peak and undershoot of the impulse response. Finally, the resulting activation maps for each of the events of interest were aligned to Talairach space (Talairach & Tournoux, 1988).

2.8. fMRI associative memory modeling

The proportion of *recall* responses were low ($M = 0.15$, $SD = 0.13$ [9.43/64]¹), so *recall* responses were combined with *know* responses ($M = 0.53$, $SD = 0.14$ [33.84/64]) to increase the number of observations available to model the activation evoked by successful associative

¹ Average Observations/Trials. Brackets include observation by trial calculations depicting average response type observations for participants divided by the 64 face-name trials.

memory encoding (*recall+know*; $M = 0.68$, $SD = 0.12$ [43.27/64]). Analyses were performed using the mean amount of brain activation evoked by the presentation of face-name pairs during study that later received an accurate associative memory response at test (i.e., judged *Recall* or *Know*) after accounting for brain activation evoked for face-name study items that were not accurately remembered at test (i.e., judged as *face-only*). To do so, we calculated the difference in activation evoked at encoding by face-name pairs that subsequently received a *recall* or *know* response and activation evoked by face-name pairs that subsequently received a *face-only* response. This new coefficient was entered into between group t-tests in order to identify differences between controls (deployed and nondeployed controls separately due to activation differences between these groups, see Table 3) and each GWV group as well as amongst GWV with the different syndrome classifications. For these comparisons the critical t value was set to a level that resulted in an uncorrected alpha value of 0.01 for each of the contrasts. A spatial threshold of 35 contiguous voxels of touching faces ($RMM = 1$) was used to correct for multiple comparisons, resulting in a spatially corrected $p < 0.05$ as determined by Monte Carlo simulation computed using AlphaSim (Cox, 1996).

3. Results

First, the mean accuracy on the associative memory test was compared among the different groups of veterans. All participants achieved at least 85% accuracy on overt *recall* responses provided during the practice phase², which is a proxy of their *recall* performance during the fMRI session. Then, the mean amount of brain activation evoked by the presentation of face-name pairs during study that later received an accurate response at test was compared

² A practice phase of the associative memory task was conducted outside of the scanner prior to beginning the fMRI session. When participants gave a *recall* response, they verbally provided the name being recalled to the face. These responses were recorded by the researcher on a response sheet next to that item in the list. Overt recall responses were scored and a proportion of accurate recalls was calculated for each participant by dividing the number of accurate names recalled to the total number of recall responses given to the faces of face-name pairs.

between the well GWV and the three different syndrome types. All analyses were conducted using a coding system that blinded the researchers as to whether participants were well or ill.

3.1. Memory performance

The mean proportion of *recall*, *know*, and *recall+know* responses given to face-name pairs presented on the memory tests performed while participants were in the MR scanner are presented in Table 2. Initial *t*-tests were conducted to compare performance between the two control groups (deployed vs. nondeployed) on each of the associative memory responses (i.e., *recall*, *know*, *recall+know*) corrected for response bias. No significant differences were found between the nondeployed and deployed controls on *recall*, *know*, or *recall+know* scores, $t(27) = -0.66, p = 0.55$; $t(27) = 1.64, p = 0.12$; $t(27) = 1.03, p = 0.32$. The same *t*-tests were conducted on uncorrected responses, and were also found to be non-significant, all $ps > 0.41$. Therefore, all subsequent memory analyses were conducted with these two groups combined into a single control group, GWV-C. Additionally, a series of ANCOVAs were conducted to test for any effect of PTSD, MDD, and age on differences observed between the groups of veterans. A diagnosis of current MDD and PTSD provided by the SCID and CAPS, respectively, were used as covariates in the ANCOVA analyses. None of these variables significantly affected the observed differences. Therefore, the results observed using reduced models are presented.

Pair-wise comparisons revealed that GWV-1 ($M = 0.07, SD = 0.13, p = 0.01$) and GWV-2 ($M = 0.09, SD = 0.07, p = 0.04$) had significantly lower *recall* scores than GWV-C ($M = 0.15, SD = 0.13$). GWV-2 ($M = 0.12, SD = 0.12, p = 0.01$) also had significantly lower *know* scores than GWV-C ($M = 0.23, SD = 0.16$; See Figure 2). All three syndrome groups, GWV-1 ($M = 0.22, SD = 0.21, p = 0.003$), GWV-2 ($M = 0.21, SD = 0.13, p = 0.001$), and GWV-3 ($M = 0.26, SD = 0.15, p = 0.02$) had significantly lower *recall+know* scores than GWV-C ($M = 0.38, SD =$

0.19). There were no significant differences observed between the GWV-1, GWV-2 and GWV-3 syndrome groups for any of the memory scores (*recall*, *know*, *recall+know*), all pairwise *ps* > 0.27.

3.2. fMRI associative memory encoding results

Group activation differences in face-name *recall+know* encoding are presented in Table 3 and Figure 3. Nondeployed controls showed greater activation in the left insula and the right posterior temporal gyrus than deployed controls (Table 3, Figure 3D). The left insula cluster also included the putamen, inferior frontal gyrus, and pars opercularis. The right posterior temporal gyrus cluster also included the right middle occipital gyrus. GWV-1 and GWV-3 did not differ from nondeployed controls in the amount of activation associated with *recall+know* encoding. However, GWV-2 (Table 3, Figure 3B) exhibited less activation in regions of the left medial frontal gyrus, which encompassed the superior medial and anterior cingulate gyri, when compared to nondeployed controls. GWV-1 and GWV-2 exhibited significantly greater activation relative to deployed controls in the left insula and putamen (Table 3, Figure 3A,B). GWV-3 did not differ from deployed controls. Comparisons between the GWV syndrome types revealed GWV-2 to have greater activity in the left insula, encompassing the superior temporal gyrus, than GWV-1. GWV-3 had greater activity in the brainstem, which included the mammillary body and red nucleus, than GWV-1 (Table 3, Figure 3E). There were no observed differences between GWV-2 and GWV-3.

In an attempt to further identify potential differences in brain activation between ill and well GWV, we also compared 1) all well GWV (i.e., deployed and nondeployed controls) to each syndrome type separately, 2) and all well GWV to all ill GWV. The first set of analyses revealed only GWV-3 to differ from controls. Specifically, GWV-3 had greater activation than

well GWV in a cluster of voxels in the brainstem that again included the mammillary body and red nucleus (Table 3, Figure 3C). For the second set of analyses, comparing pooled control activation to pooled ill GWV activation, no differences were observed.

4. Discussion

The purpose of this study was threefold. First, the study was conducted to extend previous research with a smaller cohort of Seabees that showed memory differences between ill and well GWV (Odegard et al., 2013). The current study also observed ill GWV to demonstrate less accuracy on an associative memory task of episodic memory relative to well GWV. The second goal of the study was to investigate if memory deficits are exclusive to those GWV groups that are more likely to self-report problems with memory and cognition or if they are observed in all ill GWV groups. In the previous Seabees study, ill GWV had impaired memory performance relative to well GWV regardless of syndrome type. The current study extended this finding to a national sample of GWV, showing that all three syndrome types (GWV-1, GWV-2, and GWV-3) showed deficits in associative memory, especially combined *recall+know* scores, relative to GWV-C. However, it should be noted that GWV-3 veterans, who do not complain about cognitive or memory deficits, had significantly less accurate memory relative to GWV-C only when the *recall* and *know* scores were combined.

The third goal of this study was to investigate the extent to which ill GWV would exhibit differences in brain function during the memory task, as measured by BOLD fMRI, when compared to well GWV. The previous study of GWV, which used the same memory paradigm (Odegard et al., 2013), observed brain activation during encoding to be positively correlated with subsequent memory performance. However, the smaller number of subjects in that study limited the detection of potential differences in brain activation between groups. The current study was

able to detect differences in brain activation evoked during the encoding phase of the associative memory task between the different groups. Additionally, the previous study did not categorize study items based on subsequent memory performance. In the current study we used brain activation measured when veterans were viewing face-name pairs to which an accurate memory response would later be given after correcting for activation to face-name pairs that were later forgotten. This provides a way to investigate if the different groups of veterans use different brain regions to foster successful associative memory encoding, or, in another perspective, where there might be breakdown in the network that supports successful memory.

The fMRI analyses revealed GWV-1 and GWV-2, the two groups with the most cognitive complaints, to be the more functionally different ill GWV groups. Specifically, GWV-1 and GWV-2 showed heightened insula activity relative to deployed controls, with GWV-2 insula activity more posterior and significantly higher than GWV-1. Similar to the GWV-1 and GWV-2, a separate posterior insula cluster differentiated the control groups, with activation being greater in nondeployed than deployed controls. The insula is involved in a variety of processes ranging from sensation and perception to emotion and cognitive integration (Augustine, 1996; Craig 2009; Phan et al., 2002; Stephani et al., 2011). GWV-2 also had lower activity in the medial frontal gyrus compared to nondeployed controls. Recently, this region has been shown to be more active in healthy controls relative to patients with mild cognitive impairment (MCI) when performing an episodic memory task prior to being treated with a cholinesterase inhibitor (Risacher et al., 2013). Following treatment, MCI patients showed increase connectivity of their medial temporal lobes (including the hippocampus) to the medial frontal gyri relative to healthy controls, which was positively related to memory performance. It would appear that GWV-2 (and GWV-1 to a lesser degree) are over-activating the insula, an area

highly involved in awareness, and under-activating the medial frontal gyrus, an area known to support the encoding of information that is later remembered. While insula activity in the deployed controls was lower than several GWV groups, it may not be negatively impacting their associative memory performance overall.

Lastly, for the syndrome groups, GWV-3, while not traditionally thought to struggle cognitively, performed lower than controls in this task. The only cluster of significant difference between GWV-3 and the other groups was in the brainstem, where GWV-3 activated more than GWV-1 and pooled GWV-C. While one of the functions of the brainstem is pain sensitivity control and GWV-3 have central pain complaints, recently the mammillary body included in this cluster has shown involvement in recollective memory (Vann, 2010). Of note, previous results from this research team also observed cerebral blood flow abnormalities in the same brainstem region during cholinergic challenge among veterans with GWI, further suggesting this region to be important in Gulf War-associated chronic encephalopathy (Haley et al., 2009).

Nondeployed controls also showed greater insula activation than deployed controls during successful encoding. Nondeployed controls also exhibited greater activity than deployed controls in the posterior middle temporal gyrus, a brain region implicated in processes from object recognition to memory integration (Cabeza and Nyberg, 2000; Chao et al., 1999; Galvert, 2001; Klingberg and Roland, 1998; Mesulam, 1998). Though hippocampal activation differences between GWV and controls were expected, hippocampal activation differences were not observed for any comparison. It is possible that response differences in the hippocampus (and other regions) could have been masked by 1) fitting the whole brain to a typical HRF peak and undershoot within 4-7 s post-stimulus, lacking biphasic or delayed transient features sometimes reported for hippocampus (Meltzer et al., 2008), and 2) added noise introduced into the BOLD

signature by unequal variances due to differing response rates among the groups (Friston et al., 2005).

A final aspect of the study that helps better inform our understanding of GWI is its ability to provide insight into competing explanations of GWI and the potential exacerbating effects of deployment on veterans. There were about twice as many veterans in the national sample cohort of this paper than in the Seabees cohort (Odegard et al., 2013), which provided sufficient power to investigate potential effects of PTSD, MDD, and aging on an objective test of memory ability, as well as to look for potential differences between deployed and nondeployed controls on behavior and brain function. The popular psychological stress hypothesis takes the perspective that GWI can be explained primarily by psychiatric and medical conditions unrelated to neurotoxin exposure (Binns et al., 2008). Considering PTSD and MDD had no significant effects on memory performance adds to a growing body of evidence (Gopinath et al., 2012; Li et al., 2011; Odegard et al., 2013; Tillman et al., 2013) supporting the neurotoxin exposure hypothesis, which posits that GWI is primarily caused by exposure to one or more neurotoxins during the war. The fMRI data show differences in brain function among the three major syndrome types, even when only looking at the activation at encoding evoked by items that received accurate memory judgments, providing further construct validity for the syndrome classification system (Haley and Kurt, 1997; Haley et al., 1997; Haley et al., 2001; Iannacchione et al., 2011). Although these differences may shed light onto differential brain function between groups, medication use cannot be ruled out as a potential confound. Up to 27% of ill GWV were on one form of psychotropic medication (e.g., anti-depressant, anti-seizure, or anti-anxiety), which could modify their BOLD response.

Our data also show encoding activation differences between the two groups of GWV controls, suggesting that deployment status is also an important factor to consider. It may be that exposure to service-related neurotoxins, and taking PB tablets, in the deployed controls plays a role in this difference between the two control groups. Interestingly, 74-85% of each ill GWV group as well as 50% of the deployed controls in this sample self-reported taking PB tablets, hearing chemical alarms (i.e., sarin warning), or both, during their service, but deployed controls do not present with GWI (see Table 1). The deployed controls may have sustained less damage than ill GWV from the same neurotoxic exposures, possibly due to lower inherent genetic susceptibility. The data in the present study offer objective measures of memory impairment in addition to functional brain differences that could be indicative of a mixture of nerve-agent exposure and susceptible genotypes among the GWV groups.

Moving forward, it will be important for future studies to keep deployed and nondeployed control groups separate (unless statistically equivalent for the measures reported), and to investigate specifically what it is about the deployed controls that make them different from nondeployed controls. No control veteran in the current study presented with PTSD or MDD, but it is possible that, due to their deployment, these veterans experienced stress-related effects of serving in the war, but not at a diagnosable level. Future studies could investigate the role of psychological well-being, across a dimension of sub-threshold conditions, as well as investigate the effects of neurotoxin exposure rates (Haley and Tuite, 2013; Tuite and Haley, 2013) and genetic factors (Haley et al., 1999) that might provide additional insight into and validation of the putative etiologies of GWI.

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Table 1. Demographic and co-morbidity measures in controls and Gulf War Illness groups.

	Non-Deployed Control	Deployed Control	GWV-1	GWV-2	GWV-3
No. Participants	14	10	19	20	18
Age, mean years, (SD)	51.50 (7.80)	45.60 (7.41)	49.16 (8.84)	49.95 (8.39)	51.44 (8.15)
No. Left-handed/ambidextrous (%)	1 (7)	0 (0)	2 (11)	2 (10)	1 (6)
Female (%)	3 (21)	1 (10)	6 (32)	6 (30)	3 (17)
Race/Ethnicity					
Caucasian (%)	12 (86)	6 (60)	13 (68)	16 (80)	13 (72)
Afr. Amer (%)	2 (14)	3 (30)	2 (11)	3 (15)	3 (17)
Hispanic (%)	0 (0)	1 (10)	1 (5)	1 (5)	1 (6)
Other (%)	0 (0)	0 (0)	3 (16)	0 (0)	1 (6)
Education scale, mean (SD)	5.21 (2.19)	4.80 (1.90)	5.68 (1.67)	4.74 (1.70)	4.94 (2.13)
MOS SF-12 Mental Component t-Score, mean (SD)	57.83 (3.64)	57.73 (9.21)	36.45 (10.75)	49.45 (9.42)	46.66 (10.71)
MOS SF-12 Physical Component t-Score, mean (SD)	53.44 (5.97)	54.92 (2.26)	36.47 (12.13)	26.45 (7.52)	32.21 (9.66)
MDD Active, SCID (%)	0 (0)	0 (0)	4 (21)	1 (5)	3 (17)
Antidepressant Use(%)	0 (0)	0 (0)	8 (42)	9 (45)	2 (11)
Alcohol abuse or dependence, active, SCID (%)	2 (14)	0 (0)	5 (26)	8 (40)	5 (28)
Drug abuse or dependence, active, SCID or admission urine test (%)	1 (6.70)	0 (0)	1 (5)	3 (15)	1 (6)
PTSD Active, CAPS (%)	0 (0)	0 (0)	8 (42)	8 (40)	5 (28)
Antianxiety use No. (%)	0 (0)	0 (0)	4 (21)	4 (20)	1 (6)
Endorse PB Tablet Use, No. (%)	0 (0)	5 (50)	16 (84)	17 (85)	15 (83)
Endorse hearing chemical alarms, No. (%)	0 (0)	5 (50)	14 (74)	17 (85)	15 (83)

SD, standard deviation; CAPS, Clinical Administered PTSD Scale; MDD, Major Depressive Disorder; PTSD, Post-traumatic Stress Disorder; SCID, Structured Clinical Interview for DSM-IV Disorders

Table 2. Mean proportion of *recall* and *know* judgments made to faces and face-name pairs as a function of group membership.

	Veteran Group					
	Sample Size					
	Nondeployed Control	Deployed Control	GWV- Control	GWV-1	GWV-2	GWV-3
Face-Names						
Recall	0.16 (0.15) [10.50/64]	0.20 (0.10) [12.60/64]	0.18 (0.03) [11.38/64]	0.09 (0.12) [5.79/64]	0.14 (0.14) [9/64]	0.17 (0.13) [11.17/64]
Know	0.57 (0.14) [36.71/64]	0.53 (0.14) [33.60/64]	0.55 (0.04) [35.42/64]	0.54 (0.13) [34.47/64]	0.50 (0.15) [32.10/64]	0.52 (0.16) [33/64]
Faces						
Recall	0.02 (0.03) [0.79/32]	0.03 (0.03) [0.80/32]	0.02 (0.01) [0.79/32]	0.02 (0.03) [0.74/32]	0.05 (0.09) [1.70/32]	0.07 (0.11) [2.17/32]
Know	0.30 (0.11) [9.57/32]	0.36 (0.16) [11.60/32]	0.33 (0.03) [10.42/32]	0.39 (0.14) [12.47/32]	0.38 (0.16) [12.20/32]	0.37 (0.14) [11.72/32]

Note. Standard Deviations are provided in parentheses; Average Observations/Trials are provided in brackets.

Table 3. Brain regions in which GWV groups showed differences in activation to face-name pairs presented during study that subsequently received *Recall+Know* judgments at test after correcting for face-name pairs that received *Face-Only* judgments. Positive t-values correspond to the 1st listed group having greater activation. Negative t-values correspond to the 2nd listed group having greater activation.

Region	TLRC coordinates (x, y, z)	Brodmann area (BA)	# of voxels	t value
Syndrome 1 vs. Nondeployed Control				
None				
Syndrome 2 < Nondeployed Control				
Left Medial Frontal Gyrus (Superior Medial Gyrus, Anterior Cingulate Gyrus)	-1, 53, 5	10/32	35	-3.01
Syndrome 3 vs. Nondeployed Control				
None				
Syndrome 1 > Deployed Control				
Left Insula (Putamen)	-31, 5, 5	13	39	3.63
Syndrome 2 > Deployed Control				
Left Insula (Putamen)	-31, 5, 2	13	35	3.45
Syndrome 3 vs. Deployed Control				
None				
Syndrome 1 vs. All Controls				
None				
Syndrome 2 vs. All Controls				
None				
Syndrome 3 > All Controls				
Left/Right Brainstem (Mammillary body, Red nucleus)	-4, -10, -13	NA	41	3.05
All Syndrome Types vs. All Controls				
None				
Deployed < Nondeployed Controls				
Left Insula (Putamen, Inferior Frontal Gyrus, Pars Opercularis)	-40, 2, 11	13/44	66	-3.27
Right Posterior Middle Temporal Gyrus (Middle Occipital Gyrus)	41, -70, 17	39/19	40	-4.49

Syndrome 1 < Syndrome 2

Left Insula (Superior Temporal Gyrus)	-43, -7, -1	13/22	39	-3.66
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Syndrome 1 < Syndrome 3

Right/Left Brainstem (Mammillary body, Red nucleus)	5, -10, -13	NA	65	-2.85
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Syndrome 2 vs. Syndrome 3

None

Note. Areas in parenthesis are additional regions included in the cluster.

Figure 1. Depiction of study and test phases of face-name task.

Figure 2. Graphical depiction of corrected face-name memory performance as a function of group by item type.

Figure 3. Brain regions in which GWV groups showed differences in activation to face-name pairs presented during study that subsequently received *Recall+Know* judgments at test after accounting for face-name pairs that received *Face-Only* judgments. A) Deployed controls having greater activity than GWV-1; B) Nondeployed controls having greater activity than GWV-2, but GWV-2 having greater activation than deployed controls; C) All GWV-C having greater activity than GWV-3; D) Nondeployed controls having greater activity than Deployed controls; and E) GWV-2 and GWV-3 having greater activity than GWV-1. ROI colors denote greater activation for a given group in the comparison of interest: Yellow = Nondeployed controls, Blue = Deployed controls, Green = pooled GWV-C group, Magenta = GWV-2 greater than GWV-1, and Cyan = GWV-3 greater than GWV-1. Images are in neurological orientation with the right side of the brain to the right and the left side to the left.