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Memory and functional brain differences in a national sample of U.S. veterans with Gulf War Illness

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ABSTRACT

Roughly 26–32% of U. S. veterans who served in the 1991 Persian Gulf War report suffering from chronic health problems. Memory complaints are regularly reported by ill Gulf War veterans (GWV), but limited data verify their complaints. This study investigated episodic memory and brain function in a nationally representative sample of GWV, using a face-name memory task and functional magnetic resonance imaging during encoding. A syndrome classification system was used to subdivide ill GWV into the three major Gulf War Illness syndrome types, "impaired cognition" (GWV-1), "confusion ataxia" (GWV-2), and "central pain" (GWV-3). Memory and brain function of ill GWV were contrasted to deployed and non-deployed well GWV controls (GWV-C). Ill GWV exhibited impaired memory function relative to GWV-C but the patterns of functional brain differences varied. Brain activation differentiated the GWV-C from the ill GWV. The different syndrome types also differed from one another in several brain regions. Additionally, the current study was the first to observe differences in brain function between deployed and nondeployed GWV-C. These results provide (1) evidence of memory impairment in ill GWV and differentiate the syndrome types at a functional neurobiological level, and (2) the role of deployment in the war on brain function.

1. Introduction

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., 2010, 2011; Hom et al., 1997; 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, 2004a, 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

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appropriate control participants on standardized memory tests (Chao et al., 2010; Hom et al., 1997; Haley and Kurt, 1997; White et al., 2001). The inconsistences 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, 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