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Word-finding impairment in veterans of the 1991 Persian Gulf War

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ABSTRACT

Approximately one quarter of 1991 Persian Gulf War Veterans experience cognitive and physiological sequelae that continue to be unexplained by known medical or psychological conditions. Difficulty coming up with words and names, familiar before the war, is a hallmark of the illness. Three Gulf War Syndrome subtypes have been identified and linked to specific war-time chemical exposures. The most functionally impaired veterans belong to the Gulf War Syndrome 2 (Syndrome 2) group, for which subcortical damage due to toxic nerve gas exposure is the suspected cause. Subcortical damage is often associated with specific complex language impairments, and Syndrome 2 veterans have demonstrated poorer vocabulary relative to controls. 11 Syndrome 1, 16 Syndrome 2, 9 Syndrome 3, and 14 age-matched veteran controls from the Seabees Naval Construction Battalion were compared across three measures of complex language. Additionally, functional magnetic resonance imaging (fMRI) was collected during a covert category generation task, and whole-brain functional activity was compared between groups. Results demonstrated that Syndrome 2 veterans performed significantly worse on letter and category fluency relative to Syndrome 1 veterans and controls. They also exhibited reduced activity in the thalamus, putamen, and amygdala, and increased activity in the right hippocampus relative to controls. Syndrome 1 and Syndrome 3 groups tended to show similar, although smaller, differences than the Syndrome 2 group. Hence, these results further demonstrate specific impairments in complex language as well as subcortical and hippocampal involvement in Syndrome 2 veterans. Further research is required to determine the extent of language impairments in this population and the significance of altered neurologic activity in the aforementioned brain regions with the purpose of better characterizing the Gulf War Syndromes.

1. Introduction

An estimated one quarter of the 700,000 veterans of the Persian Gulf War experience chronic physiological and psychological symptoms of unknown etiology (Binns et al., 2004). Affected veterans largely report distressing multisymptom complaints that significantly impair daily functioning (Anger et al., 1999; Coker, Bhatt, Blatchley, & Graham, 1999; Fukuda et al., 1998; Gray, Reed, Kaiser, Smith, & Gastanaga, 2002; Haley & Kurt, 1997; Lange et al., 2001). Through extensive epidemiological

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investigation of hundreds of Gulf War veterans, Haley and colleagues used factor analysis of symptoms to develop a working research definition of Gulf War illness that includes three syndrome subtypes, or variants, referred to as the Gulf War syndromes (Haley, Kurt, & Hom, 1997), which they cross-validated with structural equation modeling, first in a clinical sample (Haley, Luk, & Petty, 2001) and later in a large national random sample (Iannacchione et al., 2011). They identified unique war-time chemical exposures that are associated with each syndrome (Haley & Kurt, 1997). Syndrome 1 is referred to as "impaired cognition" and is associated with exposure to pesticides in flea and tick collars used by soldiers to deter insects. It is characterized by sleep disturbance, attention and memory difficulties, and migraine headaches. Syndrome 2 is referred to as "confusion-ataxia" and is strongly associated with low-level sarin exposure and unusually severe side effects of the pyridostigmine anti-nerve gas medication soldiers were ordered to take. It is characterized by more profound cognitive difficulties involving confusion and difficulty processing information, as well as motor abnormalities and psychological symptoms. Syndrome 3, referred to as "central neuropathic pain," is associated with use of high-concentration DEET and more severe side effects of pyridostigmine. It is characterized by pain and weakness in the joints and muscles of the body as well as milder cognitive complaints. Although veterans in all three syndrome groups show some degree of functional impairment, those with Syndrome 2 are the most cognitively and functionally impaired, and they are 12.5 times more likely to be unemployed than veterans from other syndrome groups (Haley, Maddrey, & Gershenfeld, 2002; Haley et al., 1997; Iannacchione et al., 2011).

Sarin nerve gas, associated with Syndrome 2, is an organophosphate that produces immediate poisoning by binding to and thereby inactivating acetylcholinesterase, allowing build-up of acetylcholine at cholinergic synapses. It produces long-term neuropsychiatric symptoms and deficits by mechanisms not yet understood. Henderson et al. (2002) exposed rats to low levels of sarin nerve gas over an extended period of time, causing no immediate overt clinical symptoms of poisoning. One month post-exposure, the rat brains exhibited significant reductions of acetylcholinesterase in the basal ganglia, and additionally in the hippocampus when sarin exposure was coupled with heat-induced stress. In a similar study, rats that were treated with pyridostigmine bromide (PB) in combination with shock-induced stress demonstrated lower acetylcholinesterase activity in the basal ganglia and basal forebrain (Beck et al., 2001). These animal data provide a working model of the long-term effects of sarin nerve gas on the brain.

Veterans ill with Gulf War syndromes also exhibit changes in the basal ganglia and hippocampus, most consistent and severe in those with Syndrome 2. Magnetic resonance spectroscopy (MRS) data identified biochemical changes in basal ganglia bilaterally (Haley et al., 2000), with Syndrome 2 veterans showing the greatest reduction in the *N*-acetylaspartate-to-creatine ratio (NAA/Cr), indicating reduced functional neuronal mass in this region. Decreased NAA/Cr ratios in the left basal ganglia of this sample of veterans are also associated with altered central dopamine production, signifying additional neurotransmitter changes present in Syndrome 2 veterans (Haley et al., 2000). Reduction of NAA/Cr was also noted in hippocampus of another sample of ill Gulf War veterans (Menon, Nasrallah, Reeves, & Ali, 2004). Cholinergic challenge by intravenous infusion of physostigmine in a 1998 study produced abnormal changes in regional cerebral blood flow (rCBF), measured by single-photon emission computed tomography (SPECT), compared with controls (Haley et al., 2009). The most marked difference from controls was a paradoxical increase in rCBF in Syndrome 2 in the hippocampus, caudate and amygdala; less marked differences were seen in the right putamen in Syndrome 1, and in the left thalamus in Syndromes 1 and 3. In a repeat of the cholinergic challenge study of the same veterans a decade later, rCBF measured by MRI arterial spin labeling (ASL) showed the same paradoxical reversal in the hippocampus in Syndrome 2, but now also in the Syndrome 3 group (Li et al., 2011). One theory regarding these paradoxical changes posits that the increases in activity noted in Syndromes 2 and 3 veterans reflect hyperactivity of the cholinergic system as a downstream effect of sarin-induced cellular damage (Allon et al., 2011). Rats exposed to low-levels of sarin nerve gas exhibit chronic changes to the inhibitory muscarinic-2 cholinergic receptors of the hippocampus, thereby reducing their affinity. In this way, one could similarly interpret the observed activity increases in Syndromes 2 and 3 veterans as chronic disinhibition of hippocampal processes resulting from cholinergic receptor damage.

One of the symptoms most characteristic of Gulf War illness is difficulty finding previously familiar words, e.g., "coming up with the right word" (Haley et al., 1997, 2001) or "trouble finding words" (Fukuda et al., 1998). Previous research has documented that word generation increases activity in the basal ganglia and that basal ganglia disturbances are associated with impairment of complex verbal functions (Henry & Crawford, 2004). Crosson et al. (2003) demonstrated that covert word generation tasks evoked basal ganglia activity bilaterally in normal subjects. Further, Copland and colleagues demonstrated that patients with dominant non-thalamic basal ganglia lesions perform significantly worse than normal controls on complex language tasks including word fluency, sentence generation, interpretation of ambiguous sentences, and definition of words (Copland, Chenery, & Murdoch, 2000). Veterans with Gulf War syndromes also demonstrate impaired performance on the Vocabulary subtest of the Wechsler Adult Intelligence Scale in comparison to controls (Hom, Haley, & Kurt, 1997). These findings led us to question whether (1) the verbal impairments noted in ill Gulf War veterans extend beyond the reduced ability to correctly define words, (2) vary in presentation or severity across syndrome subtypes, and (3) are associated with basal ganglia pathology.

Hence, the current study compared veterans with Gulf War syndromes to control veterans on a short neuropsychological battery of word fluency tasks and on a word fluency task during functional magnetic resonance imaging (fMRI). Given the previous evidence of basal ganglia abnormalities in this sample of Gulf War veterans, most severe in the Syndrome 2 group, and the prominence of their word-finding problems, we expected veterans with Gulf War illness to perform worse than the control veterans, with Syndrome 2 veterans demonstrating the lowest performance across all tasks. Similarly, given the reduction in NNA/Cr in the basal ganglia as an indicator of reduced basal ganglia function, we expected veterans with Gulf War illness to exhibit reductions in brain activity primarily in the basal ganglia during a covert word generation task, with Syndrome 2 veterans exhibiting the greatest difference in activity when compared to control veterans. We also included the left and right thalamus in our analyses due to their significant interconnections with the structures of the basal ganglia (Alexander, DeLong, & Strick, 1986; Middleton & Strick, 2000) as well as the hippocampus because of its apparent involvement in Gulf War syndromes (Haley et al., 2009; Li et al., 2011; Liu et al., 2011; Menon et al., 2004).

2. Methods

2.1. Participants

The subjects included 50 right-handed male Gulf War-era veterans, all members of the Twenty-Fourth Reserve Naval Mobile Construction Battalion (Seabees), selected on the basis of a