COGNITIVE AND PHYSIOLOGICAL IMPAIRMENTS OF PERSIAN GULF WAR VETERANS

By

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To my loving family

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Following the 1991 Gulf War, approximately one quarter of 690,000 returning veterans developed physiological and psychological symptoms not attributed to post-traumatic stress disorder. Three syndrome subtypes were identified: Haley Syndrome 1 (HS1), 2 (HS2), and 3 (HS3). HS2 veterans are the most cognitively impaired; however, little is known about the neurological basis of these impairments. The objective of this study was to elucidate the neurological mechanisms that may be responsible for these cognitive impairments. Forty-four 1991 Gulf War veterans (7 HS1, 15 HS2, 9 HS3, and 13 healthy deployed veterans) underwent neuropsychological testing and functional magnetic resonance imaging (fMRI) during which participants performed a covert category generation task. We hypothesized, based on previous evidence of basal ganglia damage, that the HS2 group would perform worse than all other groups on each neuropsychological measure, as well as produce an abnormal pattern of activity compared to healthy controls in response to the category generation task. Verbal fluency scores were compared among the four groups. The healthy and HS1 groups significantly outperformed the HS2 and HS3 groups on two of three measures. No

significant fMRI differences between HS2 and healthy veterans existed in brain areas where activity correlated with performance. Although behavioral differences exist, our study did not find significant differences in brain activity between the healthy and the most cognitively impaired group. Overall, the behavioral and neuroimaging data suggest that HS2 and HS3 veterans are impaired on verbal executive functions perhaps due to difficulties restricting controlled attentional processes to areas of the brain that are important for verbal fluency. Disruptions of fronto-striatal loops may be to blame for these difficulties and should be the focus of future research with this population.

CHAPTER 1
INTRODUCTION

Unexplained Illness Following Persian Gulf War

Following the 1991 Persian Gulf War, an estimated one quarter of the 700,000 Gulf War veterans developed a diversity of physiological and psychological symptoms unexplained by any single medical diagnosis. Specifically, Gulf War veterans largely reported multisymptom complaints most often involving fatigue, muscle weakness, joint pain, problems with attention and memory, and depression. In fact, in 1999 one study conducted by the Ministry of Defence in London (Coker, Bhatt, Blatchley, & Graham, 1999) medically and psychologically assessed 1,000 Gulf War Veterans and found that 49% of all patients were experiencing affective difficulties (mood swings, personality change, depression), 42% of patients were experiencing significant fatigue, 40% of patients were experiencing joint and muscle pain, and 26% were experiencing difficulties with cognition (difficulty concentrating, short term memory problems). Further, similar studies out of the United States reported comparable findings, specifically that 19% of the 20,000 Gulf War veterans assessed were experiencing musculoskeletal difficulties, 18% were experiencing mental disorders such as tension headache, major depressive disorder and prolonged posttraumatic stress disorder, and 18% were experiencing various signs and symptoms of undefined conditions. Compared to veteran groups from previous wars (World War II, the Vietnam War, and the Korean War) a significantly larger proportion of veterans from the Persian Gulf War have been considered disabled by disorders resulting from their military experience (Haley, 2003).

A Case Definition of Gulf War Illness (GWI)

Puzzled by the disproportionately high number of Gulf War veterans reporting post-war symptomatology, researchers suspected the presence of a specific Gulf War Illness. In order to test this hypothesis, researchers used various methods to develop case definitions of what might constitute Gulf War Illness. For example, a multidisciplinary team of investigators at the Portland Environmental Hazards Research Center (Anger, et al., 1999) identified cases of unexplained Gulf War Illness based on the self-reported presence of at least one of the following: cognitive or psychological changes (memory loss, difficulty concentrating, mood swings), gastrointestinal distress, fatigue, muscle and joint pain, or skin rashes. Once a respondent endorsed one or more of these symptoms they were referred to medical specialists and excluded from the study if their symptoms could be accounted for by a known medical diagnosis (i.e. diabetes mellitus, head injury, abnormal thyroid hormone levels). Of the final 152 veteran participants involved in this study, 65% were identified as cases and 35% were identified as controls. A second study out of the Centers for Disease Control and Prevention (Fukuda, et al., 1998) compared a symptom-based case definition to a case definition derived from factor analysis of self-reported symptoms and concluded that the two methods were essentially equivalent. Because the symptom-based case definition would be easier to apply in a clinical setting, the research team utilized this method on their sample and cases were thereby identified by the presence of one or more chronic symptoms from at least two of three categories (fatigue, mood-cognition, and musculoskeletal). Among the 1155 deployed veteran participants of this study, 45% were identified as cases. These and other findings illustrated that a significant portion of Gulf War veterans were suffering from some chronic unexplained Gulf War Illness. As

such, researchers sought to comprehensively define what factors differed between those with and without Gulf War Illness.

Psychological and Neuropsychological Profiles of GWI

Once differentiation between ill and healthy veterans was made by applying a case-definition of Gulf War Illness to each sample, various studies identified the breadth of psychological and neuropsychological findings unique to Gulf War Illness. A consistent finding across many studies was that veterans with Gulf War Illness reported significantly decreased overall functioning and well-being (Fukuda, et al., 1998; Anger, et al., 1999; Lange, et al., 2001; Gray, Reed, Kaiser, Smith, & Gastanaga, 2002; Haley & Kurt, 1997). Specific to neuropsychological findings, veterans with Gulf War Illness showed deficits in attention, concentration, and information processing, as well as abstraction and conceptualization (Anger, et al., 1999; Lange, et al., 2001). In regards to purely psychological findings, Gulf War veterans were generally shown to have higher rates of posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) when compared to veterans deployed elsewhere. Still, the rates of PTSD and MDD among Gulf War veterans were no higher than the national averages (Wolfe, et al., 1999). When separated into healthy and ill veteran groups, previous research is mixed with respect to the incidence of psychological pathology between groups. Fukuda et al. (1998) found no difference in the rate of PTSD, though they did report a difference in the rate of MDD with the Gulf War Illness group reporting more depression than the healthy Gulf War veterans in the sample. Further, a study conducted by Ismail et al. (2002) determined through structured clinical interviews on a random sample of veterans with Gulf War Illness, that the rate of PTSD among veterans was both low and comparable to that of the veteran control group. In contrast, other studies (Anger, et al.,

1999; Lange, et al., 2001) showed that those with Gulf War Illness reported significantly higher levels of PTSD, depression, and anxiety. In order to evaluate the influence these psychological difficulties may have on the reporting of cognitive and physical complaints common to Gulf War Illness, a number of studies controlled for psychological status (i.e. PTSD and depression) in their analyses. Two such studies, Wolfe et al. (2002) and Lange et al. (2001) determined that neuropsychological performance and reported health symptoms could not be explained by psychological status alone. In summary, related research indicates that a purely psychological origin of GWI is unlikely, potentially indicating the role of biological factors such as environmental toxins.

Unique Gulf War Syndromes

With the intention of uncovering potentially unidentified syndromes that could better describe Gulf War veterans' symptoms, a number of researchers (Everitt, Ismail, David, & Wessely, 2002; Haley, Kurt, & Hom, 1997; Knoke, Smith, Gray, Kaiser, & Hawksworth, 2000) employed factor analytic methods on the veterans' self-reported post-war symptoms. One research team at the University of Texas Southwestern Medical Center (UTSW) identified three unique syndrome subtypes (Haley, Kurt, & Hom, 1997) among Persian Gulf War veterans using factor analysis. Beginning in 1994, investigators at UTSW distributed a comprehensive epidemiological survey to members of the Twenty-fourth Reserve Naval Mobile Construction Battalion also commonly referred to as the Seabees. The survey was designed to measure both symptoms and risk factors common to veterans of the Gulf War and ultimately included fifty-two symptom items that the veterans could endorse if appropriate. Using a two-stage factor analysis on data from 249 veteran respondents, the investigators identified three strong factors representing unique syndrome subtypes each consisting of its own combination

of symptom loadings. A second study from UTSW (Haley & Kurt, 1997) then utilized logistic regression analyses to determine which war-time chemical exposures were associated with each identified syndrome (Table 1-1). The first extracted factor consisted of the following symptom loadings: distractibility, short and long-term memory problems, depression, excessive daytime sleepiness, slurred speech, confusion, middle and terminal insomnia, and migraine headaches. These symptoms were conceptualized as representing an “impaired cognition” syndrome referred to as Haley Syndrome 1 (HS1). HS1 was found to be associated with the use of flea-and-tick collars during the war. The second extracted factor consisted of the following symptom loadings: difficulty processing information, confusion, ataxia, problems with memory, impotence, and physician diagnoses of posttraumatic stress disorder and liver disease. This factor was conceptualized as representing a “confusion-ataxia” syndrome referred to as Haley Syndrome 2 (HS2). HS2 was found to be associated with sarin nerve gas exposure as well as adverse side effects from ingested pyridostigmine bromide tablets. The third extracted factor consisted of the following symptom loadings: joint pain, generalized muscle weakness, excessive muscle exhaustion, myalgia, and numbness/tingling in the extremities. This third factor was conceptualized as representing an “arthro-myo-neuropathy” syndrome referred to as Haley Syndrome 3 (HS3). HS3 was found to be associated with the use of government issued insect repellant containing diethyltoluamide (DEET) as well as adverse side effects from ingested pyridostigmine bromide tablets. Similarly constructed factor analytic studies on larger samples of Gulf War veterans have since confirmed the presence of these three symptom factors.

Table 1-1. Gulf War Syndrome subtypes

Syndrome Subtype	Associated Symptoms	Associated Exposures
Haley Syndrome 1: (Impaired cognition)	distractibility short-term memory problems long-term memory problems depression excessive daytime sleepiness slurred speech confusion middle and terminal insomnia migraine headaches	Flea and tick collars
Haley Syndrome 2: (Confusion-ataxia)	difficulty processing information confusion ataxia memory problems impotence diagnosis of PTSD diagnosis of liver disease	Sarin nerve gas Pyridostigmine bromide
Haley Syndrome 3: (Arthro-myo-neuropathy)	joint pain generalized muscle weakness excessive muscle exhaustion myalgia numbness in extremeties	DEET insect repellant Pyridostigmine bromide

Haley Syndrome 2

Haley Syndrome 2 veterans are the most cognitively and functionally impaired, and are 12.5 times more likely to be unemployed than the other syndrome groups (Haley, Kurt, & Hom, 1997). Still, few studies have focused specifically on this population. As previously described, the chemical exposure associated with HS2 is sarin nerve gas. In 1991 the US ground troops bombed a weapons storage site in Iraq, releasing both mustard gas and sarin nerve gas into the surrounding area and exposing estimates of 100,000 soldiers to the nerve toxin (Office of the Special Assistant for Gulf War Illness, US Department of Defense, 1996). Despite the large number of veterans

exposed to sarin as a consequence of the bombing event, only a small proportion developed HS2. In an effort to uncover the mechanism behind this phenomenon, a study was designed comparing veterans who fell ill to those who remained healthy (Haley, Billecke, & La Du, 1999). The results of this study identified a genetic susceptibility in the veterans who developed HS2. Specifically, HS2 veterans had lower blood levels of the PON1 Type Q allozyme, an enzyme known to hydrolyze compounds similar to sarin nerve gas.

Sarin is a toxic nerve agent that affects both the central and peripheral nervous systems. Sarin nerve gas is an organophosphate that impedes the proper operation of acetylcholinesterase (AChE), a necessary enzyme for nerve function in humans. Essentially, organophosphates bind to AchE and prevent it from breaking down acetylcholine at the nerve synapse. Although acute effects of sarin nerve gas exposure have been well documented, long-term effects are not well understood. However, multiple studies have followed populations of survivors from the Tokyo sarin attack with the intention of documenting any long term effects. Acutely, sarin gas exhausts the nervous system and can cause anything from a runny nose, watery eyes, and blurred vision at one end of the spectrum, to confusion, weakness, convulsions, and respiratory failure at the other extreme. Regarding long-term effects, sarin and other organophosphate poisonings produce multiple permutations of symptoms in humans including deficits in psychomotor performance (requiring motor persistence, sustained attention, and visuomotor coordination), decreased intellectual functioning, deficits in abstraction and flexibility of thinking, subjective language and memory complaints, increased reports of depression, irritability, and confusion, abnormal EEG findings, and

increased reports of PTSD up to 8 months post-exposure (Savage, Keefe, Mounce, Heaton, Lewis, & Burcar, 1988; Murata, et al., 1997; Yokoyama, et al., 1998). However, as noted by Henderson et al. in a 2002 article, the exposure situation (the Tokyo sarin attack) common to the previous human-based studies is notably different from the Gulf War exposure since Gulf War veterans experienced subclinical reactions to the nerve gas as opposed to the Tokyo survivors who experienced immediate symptoms of toxic nerve gas poisoning. As a result, Henderson et al. (2002) designed a study using a rat model wherein they exposed rats to low levels of sarin nerve gas thereby causing no overt clinical symptoms of poisoning. They intended to determine whether this method of exposure could cause long-term health effects in the rats. One month after the exposure, investigators examined the rat brains and found reductions in AchE in the cerebral cortex, basal ganglia, olfactory bulb, and hippocampus. Overall, they determined that repeated exposures to low levels of sarin nerve gas causes physical changes in the brain that could be associated with cognitive dysfunction and problems with memory.

The Basal Ganglia

The basal ganglia are a complex group of deep-brain structures thought to influence both movement and cognition through circuits connecting them with various areas of the cortex (Alexander, DeLong, & Strick, 1986). HS2 is suspected to involve damage to these basal ganglia structures. First, many of the symptoms inherent in HS2 also co-occur in the early stages of known degenerative basal ganglia diseases such as Huntington's disease (characterized by ballistic movements of the extremities and incipient cognitive decline) and Fahr's disease (characterized by progressive paralysis, cognitive decline, and psychosis) (Lauterbach, Cummings, & Duffy, 1998). Additionally,

the basal ganglia have a high concentration of cholinergic neurons, which are affected by organophosphate exposures. Studies utilizing specific brain imaging techniques have supported this theory. One such research study (Haley, Marshall, McDonald, Daugherty, Petty, & Fleckenstein, 2000) measured the N-acetylaspartate-to-creatine (NAA/Cr) ratio, a biological marker of neuronal health, in the basal ganglia of a group of Gulf War veterans and determined that HS2 veterans have lower ratios, and thus less healthy basal ganglia, when compared to healthy veteran controls. A follow-up study on this same Seabees sample (Haley, Fleckenstein, Marshall, McDonal, Kramer, & Petty, 2000) concluded that the decreased NAA/Cr ratios were also associated with altered central dopamine production in the basal ganglia, signifying additional neurotransmitter changes occurring in HS2 veterans. The current study will continue to utilize this same sample of veterans (Seabees) in order to identify the behavioral or functional impairments associated with their basal ganglia pathology.

As demonstrated by Copland et al. in a series of studies (Copland, Chenery, & Murdoch, 2000; Copland D. , 2003) on patients with basal ganglia pathology (non thalamic subcortical stroke and Parkinson's disease), damage to structures of the basal ganglia is associated with impaired performance on verbal executive functions. Specifically, Copland proposed that disruptions to frontal-striatal circuits compromise the controlled attentional based processes of language. As a result, these patients have difficulty restricting their attention to areas of the brain that are important for certain language processes, thereby negatively affecting performance on measures of verbal executive function.

In light of these findings, the current study will explore the verbal executive functions of Gulf War veterans with previously identified pathology of the basal ganglia (aim 1) to determine if group differences in verbal fluency performance exist. Given evidence of basal ganglia pathology in this sample of HS2 veterans, and the close relationship of the basal ganglia and frontal lobes, we would expect the HS2 veterans to perform significantly worse than other veteran groups on measures of verbal executive function. The purpose of aims 2 and 3, detailed below, is to then identify the regions of the brain where activity correlates with verbal fluency performance so that we may explore differences in brain activity between HS2 and healthy veteran controls in these regions. We expect that the HS2 veterans will display activity differences from Healthy Deployed controls in regions where verbal fluency performance and activity are correlated.

CHAPTER 2
METHODS

Participants

Seven veterans with HS1 (mean age 57.5; SD 6.4), fifteen veterans with HS2 (mean age 62.4; SD 6.3), nine veterans with HS3 (mean age 56.0; SD 6.3), and thirteen healthy deployed (HD) veterans (mean age 58.7; SD 4.8) from the Twenty-fourth Reserve Naval Mobile Construction Battalion (Seabees) participated. The Seabees were specifically targeted for study for a number of reasons. First, the Seabees reported with the earliest and most persistent reports of unexplained illness following the Gulf War (Institute of Medicine, Committee to Review the Health Consequences of Service During the Persian Gulf War, 1996). Additionally, the nature of their work exposed them to unique environmental and geographical exposures (Phillips, Matvas, Hansen, Alving, Smith, & Ryan, 2009). All participants were previously enrolled in a study of Gulf War Illness and were recruited for the phase two follow-up study with the same research group at the University of Texas Southwestern Medical Center (UTSW). All veteran participants were right-handed Caucasian males, and there were no group differences in age [$F(3) = 2.52$, $p = .07$]. Of the 47 participants who completed neuropsychological testing and fMRI scanning, 3 were excluded due to excessive movement during the scan. This research was approved by the Institutional Review Board at the University of Texas Southwestern Medical Center and written informed consent was obtained from all participants in accordance with these guidelines.

Experimental Design and Procedure

As part of a week-long battery of testing, participants completed the tasks specific to this study which included three verbal fluency subtests of the Delis-Kaplan Executive

Function System (Delis, Kaplan, & Kramer, 2001) administered outside the scanner, and a separate verbal fluency task performed during the fMRI scan.

Outside the Scanner

Under the direction of trained neuropsychologists, psychometricians at UTSW administered three behavioral measures of verbal fluency from the D-KEFS battery, specifically Letter (phonemic) Fluency, Category (semantic) Fluency, and Category Switching. The Letter Fluency task requires participants to generate words beginning with a specific letter of the alphabet for three consecutive 60 second trials, the Category Fluency task requires participants to generate members of two specific categories for a period of 60 seconds per category, and the Category Switching task requires participants to switch back and forth between generating members of two different categories (e.g. Fruits, Furniture) for 60 seconds. Responses were recorded verbatim and each subtest was scored for the total number of correct responses.

Functional Magnetic Resonance Imaging (fMRI) Task

The fMRI portion of the study was completed using a block word-generation task wherein participants were presented with category cues (e.g. ocean animals) and asked to covertly generate as many members from that category as they could (e.g. whale, shark, dolphin etc.). Periods of word generation alternated with periods of visual fixation wherein the participant was instructed to relax, clear his/her mind, and fixate on a “plus sign.” The task design is shown in Figure 2-1. In total, four fMRI runs were completed for each participant. Each run consisted of eight 15-second blocks of word generation, alternated with pseudo-random visual fixation intervals of 9 sec, 12 sec, or 15 seconds in length. Intervals of visual fixation were varied with the purpose of minimizing the effects of periodic physiological noise and were at least 9 seconds in length to allow the

hemodynamic response to return to baseline levels. The visual presentation was displayed on a custom-built back projection system which the participant viewed while in the scanner.

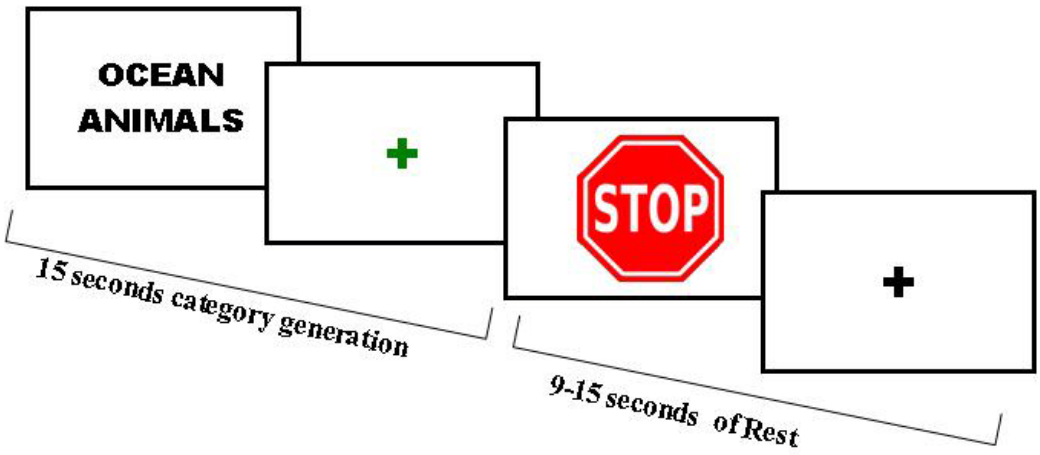

Figure 2-1. Category member generation task

Image acquisition. All scanning was completed on a 3T Siemens Trio with a 12-Channel radiofrequency head coil at UTSW. For each participant, whole-brain high-resolution fMRI data were acquired with an Echo planar imaging (EPI) sequence, Time of repetition (TR)/Time of echo (TE)/Flip Angle = 3000 msec/30msec/90˚. Forty-six 3 mm thick slices were acquired with 1.8 x 1.8 mm resolution. There were 82 measurements in each fMRI scan. Prospective real-time motion correction (Thesen, Heid, Mueller, & Schad, 2000) was employed with all EPI fMRI scans to minimize motion artifacts. A whole-brain 3D T1-weighted MPRAGE sequence (FOV = 230 mm; TR/Time of inversion (TI)/TE/Flip Angle = 2250ms/900ms/3ms/9˚; 0.9 mm x 0.9 mm x 1 mm resolution) was obtained to provide anatomic detail. All the above-mentioned scans were acquired with parallel imaging (GRAPPA; acceleration factor = 2; 24-36 PE

reference lines). Foam padding was utilized to minimize head motion during image acquisition.

Data Analysis

Behavioral Data

In order to test the first aim, whether four groups of Gulf War veterans differ on their performance on three measures of verbal executive function, each behavioral measure of verbal fluency was scored for total correct responses and raw scores for each measure were compared across groups. A one-way ANOVA comparing raw scores across all four groups was conducted for each behavioral measure. Measures with a significant main effect of group were followed up with independent samples t-tests to determine how the groups differed.

Neuroimaging Data

With the purpose of narrowing the focus of continued analyses to the behavioral data that differentiated healthy from ill Gulf War veterans, analyses correlating verbal fluency with brain activity were only conducted on the behavioral measures that exhibited significant group differences in the previous aim. As detailed below, regions of interest (ROIs) were then identified to represent areas of the brain where performance on each behavioral measure correlated with the amount of brain activity in that area. Essentially, the ROIs were created to represent areas of the brain where functional activity may affect performance on the task at hand. A separate map of ROIs was created for each verbal fluency measure that exhibited significant group differences.

Imaging pre-processing. fMRI data were analyzed with the Analysis of Functional Neuroimaging (AFNI) program (Cox, 1996). In order to reduce the effects of head motion during the scanning session, each participant's functional runs were

aligned to the first functional run acquired after the T1-weighted scan using a rigid-body linear transformation. Following motion correction, images were visually inspected for artifact and viewed in cine loop in order to detect uncorrected residual motion. Individuals with significant motion artifacts were removed from further analysis, eliminating three participants from the analyses and leaving the forty four participants described above. Participants with movement greater than 3mm on at least 30% of the acquired functional images were considered motion outliers and excluded. For each voxel, signal intensities across the four runs were concatenated to produce one continuous time-series and the resulting images were deconvolved to produce a hemodynamic response function (HRF) of the fMRI signal. The HRF represented the average percent signal change from baseline for a period of eight TRs. Functional image volumes were spatially smoothed using a 5 mm Gaussian kernel full-width at half-maximum.

Region-of-interest (ROI) analysis. For the second aim, we used area under the curve (AUC) of the deconvolved HRF as the dependent measure to represent overall magnitude of response to the verbal fluency task performed in the scanner. To calculate the AUC statistic, we summed signal intensities at each of the eight TRs comprising the HRF. Anatomic and functional AUC images were non-linearly warped to 2 x 2 x 2 mm MNI space and co-registered using the FMRIB Software Library (FSL) package (Smith, et al., 2004; Woolrich, et al., 2009). To identify the ROIs associated with each behavioral measure, we performed simple linear regressions on a voxel-by-voxel basis using each individual's score on the behavioral measure as the independent variable. Clusters (ROIs) were considered significant if each voxel was significant at $p < .01$ and

the cluster had a volume of at least 624 mm^3. This threshold/volume combination was determined by Monte Carlo simulation in order to protect ROI-wise probability of false positives of at least $p < .05$.

Response Pattern Analysis

The average pattern of activity (averaged HRF) obtained from each ROI was compared across groups in order to detect potential differences in functional response patterns produced between groups during a category fluency task. Only the HS2 and HD groups were included in these analyses because the strongest hypotheses regarding brain pathology involve the HS2 group. The response patterns were evaluated with the purpose of determining whether the most cognitively and functionally impaired group (HS2) displayed an abnormal pattern of activity as compared to healthy veterans (HD). For each participant, averaged HRFs were extracted from each ROI to represent the average functional response in that region across time. The averaged HRFs for each participant and cluster were entered into a 2 (group) x 9 (time/TR) repeated measures ANOVA to investigate differences in the functional response pattern at each ROI.

CHAPTER 3
RESULTS

Behavioral Results

Three separate one-way analyses of variance (ANOVA), with group (HS1, HS2, HS3, HD) as the between subjects factor, were performed examining total correct score of each verbal fluency measure as the dependent variable. As expected, there was a significant main effect of group for the Letter Fluency measure ($F[3,45] = 4.71$, $p = .006$) and Category Fluency measure ($F[3,42] = 3.00$, $p = .041$). There was not, however, a significant main effect of group for the Category Switching measure ($F[3,41] = 1.10$, $p = .362$). Overall, group membership significantly influenced performance on the Letter Fluency and Category Fluency measures only (Table 3-1).

Follow-up independent t-tests were performed to directly compare each of the groups' performance on Letter Fluency and Category Fluency. Due to strong a priori hypotheses that the HD group would outperform the HS2 group specifically, one-tailed t-tests were used to determine significance in the HS2 and HD comparisons. All remaining comparisons were evaluated with two-tailed t-tests. Hence, the HS2 group performed significantly worse than the HD group on both Letter Fluency ($t[28] = -2.98$, $p = .003$) and Category Fluency ($t[25] = -1.98$, $p = .03$), as well as worse than the HS1 group on both Letter Fluency ($t[24] = -3.12$, $p = .005$) and Category Fluency ($t[21] = -2.53$, $p = .02$). Additionally, the HS3 group performed significantly worse than the HS1 group on both Letter Fluency ($t[17] = -2.17$, $p = .04$) and Category Fluency ($t[17] = -2.11$, $p = .05$). The HS3 group, however, did not differ significantly from the HD group on either Letter Fluency ($t[21] = 1.99$, $p = .059$) or Category Fluency ($t[21] = 1.43$, $p = .168$). As expected, these findings indicate that the HS2 group performed worse than

two of the other veteran groups on measures of verbal fluency by generating fewer correct responses.

Table 3-1. Behavioral results – group means

	Letter Fluency			Category Fluency			Category Switch		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
HS1	10	44.60	(11.18)	10	40.40	(6.19)	10	14.20	(3.46)
HS2	16	31.69	(9.71)	13	32.46	(8.27)	12	11.75	(3.67)
HS3	9	33.78	(10.46)	9	34.00	(7.05)	9	12.78	(3.23)
HD	14	43.57	(12.09)	14	38.07	(6.44)	14	12.50	(2.53)

Neuroimaging Results

The ROI results from the correlations between scores on the behavioral measures and amount of functional activity will be considered first. Next, comparisons of the functional response patterns inherent in each ROI between the HS2 and HD groups will be presented in an effort to determine if the HS2 group has an abnormal pattern of functional activity as compared to healthy veterans.

Regions-of-Interest

Using the data from all participants, simple linear regressions were performed on a voxel-by-voxel basis to act as bivariate correlations between scores on the behavioral measures and amount of functional activity produced during a verbal fluency task. Because the Letter Fluency and Category Fluency measures showed significant group differences in aim 1, imaging analyses were conducted for these two measures only. One simple regression was run between the AUC and each individual's score on Letter Fluency, and a second simple regression was run between the AUC and each individual's score on Category Fluency. A ROI was considered significant if the voxel-

wise $p < .01$ and it had a volume greater than or equal to 624 mm^3. Significant ROIs and their associated F-statistics are reported below (Table 3-2) and represent areas of the brain where a strong relationship, either positive or negative, exists between the amount of functional activity produced during a verbal fluency task and performance on a similar task performed outside the scanner.

Eighteen ROIs were identified from the correlations with the Letter Fluency task. Nine ROIs were identified in the left hemisphere of the brain, and nine were identified in the right. Seven ROIs exhibited a positive relationship with AUC, indicating that higher scores on the Letter Fluency task predicted more functional activity in that region of the brain. Conceptually, these can be considered areas of the brain where functional activity may be beneficial to performance on a lexical fluency task. In contrast, eleven ROIs exhibited an inverse relationship with AUC, indicating that lower scores on the Letter Fluency task predicted more functional activity in that region of the brain. Conceptually, these can be considered areas of the brain where functional activity may interfere with performance on a lexical fluency task.

Five ROIs were identified from the correlations with the Category Fluency task. All five were located in the right hemisphere of the brain and exhibited an inverse relationship with AUC, indicating that lower scores on Category Fluency predicted more functional activity in these regions. Conceptually, these can be considered areas of the brain where functional activity may interfere with performance on a semantic fluency task.

Table 3-2. Areas where scores on the behavioral measure significantly correlated with magnitude of functional activity obtained during a verbal fluency task

Anatomical location	Direction of relationship	Volume (mm^3)	Center (x, y, z)	F-statistic from correlations
Letter Fluency				
L Middle temporal gyrus	+	3960	51, 18, -8	29.306
L Fusiform cortex	+	3152	32, 8, -38	19.563
R Angular gyrus	-	2528	-51, 57, 47	21.989
L Orbitofrontal	-	1480	12, -18, -14	18.264
L Angular gyrus	-	1328	46, 64, 46	14.704
R Precentral gyrus	-	1224	-38, 13, 59	13.646
L Basal ganglia	+	1064	18, -2, 10	16.870
R Superior parietal lobule	-	1008	-35, 44, 68	18.644
L Precentral gyrus	-	960	8, 17, 69	13.696
R Superior temporal gyrus	+	920	-51, 29, -1	16.418
R Orbitofrontal	-	824	-24, -18, -21	13.101
L Postcentral gyrus	-	792	16, 50, 52	14.544
L Middle frontal gyrus	+	768	40, -1, 53	13.007
L Hippocampus	+	704	20, 15, -23	20.602
R Precentral gyrus	-	688	-42, -5, 28	13.169
R Middle frontal gyrus	-	680	-37, -10, 54	15.222
R Cerebellum	+	624	-7, 79, -38	19.614
Category Fluency				
R Angular gyrus	-	1416	-48, 55, 48	15.746
R Lateral occipital cortex	-	1224	-32, 67, 54	15.155
R Superior parietal lobule	-	1216	-38, 43, 66	12.772
R Cerebellum	-	1024	-31, 82, -25	14.355
R Precentral gyrus	-	936	-49, 8, 54	15.464

Clusters shown passed a cluster threshold alpha-protection procedure (individual voxel p-value < .01, volume > 624 mm^3; see text for details).

Functional Response Patterns

From each ROI identified in aim 2, an average functional response pattern was extracted and then compared between the HS2 and HD groups. The purpose of these comparisons was to determine if HS2 veterans produced an abnormal pattern of functional activity as compared to healthy veteran controls in areas of the brain that are related to verbal executive functions. Functional response patterns (extracted and

averaged HRFs) were compared between the HS2 and HD groups using a 2 (group) x 9 (time/TR) repeated measures ANOVA for each of the 23 identified ROIs. Contrary to our hypotheses that we would find significant group x time interactions, no significant effects were found from any of the ROIs. Hence, there was no detectable difference in functional response patterns for HS2 versus HD veterans in these regions of the brain.

CHAPTER 3
DISCUSSION

The first objective of the present study was to determine if group differences in verbal executive function (as measured by verbal fluency) exist between three groups of veterans with Gulf War Illness and a Healthy Deployed veteran control group. Three measures of verbal fluency (Letter Fluency, Category Fluency, and Category Switching) were administered and scored for total correct responses. Previous research on patients with Huntington's disease (Monsch, et al., 1994), characterized by basal ganglia pathology, suggested that damage to the basal ganglia primarily affected the initiation and retrieval aspects of fluency thereby negatively influencing performance across all verbal fluency subtests. We expected our sample of HS2 veterans who have previously shown basal ganglia pathology to perform significantly worse than the other veteran groups on all three verbal fluency measures. The second aim of the present study was to identify regions of the brain where activity correlated with verbal fluency performance. The first set of regions were derived from correlations between total correct scores on the Letter Fluency task and the activity produced during a category member generation task. The second set of regions were obtained from correlations between total correct scores on the Category Fluency task and the activity produced during a category member generation task. For the final aim of the present study, averaged functional activity patterns were compared between the HS2 and Healthy Deployed veteran groups. We hypothesized that if behavioral differences in verbal executive functions existed among groups of Gulf War veterans (confirmed in aim 1), and we could identify regions of the brain where activity correlated with performance on these behavioral measures (completed in aim 2), we could determine whether the HS2

veterans' overall pattern of activity within these regions could account for the observed behavioral differences. Essentially, we would expect the HS2 participants to exhibit different patterns of activity than healthy deployed veterans in each extracted region-of-interest identified in aim 2.

Regarding the first aim, significant group differences were found on the Letter Fluency (phonemic fluency) and Category Fluency (semantic fluency) measures only. Group differences were not found for the Category Switching measure perhaps due to the increased difficulty and attentional demands of the task which may have challenged our sample of older adults regardless of syndrome status. More specifically, our results indicated that the HS2 group did perform significantly worse than the HS1 and Healthy Deployed veteran groups on both phonemic and semantic fluency. The HS3 veterans performed similarly to the HS2 veterans on the verbal fluency measures, with significantly worse performance than the HS1 group on both phonemic and semantic fluency. Because few studies exploring the neuropsychological profiles of all three syndrome groups have been published, it is unclear whether these findings are aberrant or accurately reflect the cognitive profile of HS3 veterans. The parallels in behavioral performance of the HS2 and HS3 groups indicate the groups may share some deficits in their cognitive profile. Both the HS2 and HS3 veteran groups have a war-time history of adverse reactions to ingested pyridostigmine bromide tablets. The effects of this drug may have caused comparable chronic neurotoxic syndromes in these two groups, thus affecting their verbal fluency in a similar manner. However, such a conclusion could not be made based off these results alone. Hypotheses regarding the neuropathology of HS2 have been the focus of our research because this group is the most functionally

impaired. Although the previous studies on this sample from 2000 had not identified basal ganglia pathology in these HS3 veterans, future research should examine the breadth of neurological and neuropsychological similarities between HS2 and HS3 veterans.

From our second aim we identified regions of the brain where activity correlated with verbal fluency performance. The first set of identified brain regions resulted from correlations between the Letter Fluency task and the activity obtained during a category member generation task performed in the scanner. Although the Letter Fluency and category member generation tasks are dissimilar in that the former is a test of phonemic fluency and the latter is a test of semantic fluency, their commonalities are what interest us for this study. Recent meta-analytic findings (Henry & Crawford, 2004) have shown that phonemic and semantic fluency measures make comparable demands on frontal structures and processes. As described by Rosen & Engle (1997), successful performance on verbal fluency measures (both phonemic and semantic in nature) require self-monitoring of output to prevent repetition and error, suppression of previously retrieved responses, and generation of cues to access new responses. Under performance of these attention-dependent, verbal executive processes are the suspected causes of the fluency impairments found in our HS2 veterans.

Overall, positive correlations were largely observed in areas of the brain that are important for language and semantics and included the left middle temporal gyrus, the left fusiform gyrus, the left basal ganglia, the left middle frontal gyrus, the left hippocampus, and the right cerebellum. Given that some of these positive correlations occurred in areas of the brain where semantic activation is commonly found, these

findings may suggest that performance on phonemic fluency measures improves when semantic strategies are employed. That performance on both phonemic and semantic fluency depends on the integrity of semantic systems has also been proposed by Henry & Crawford (2004) following their research on verbal fluency and Parkinson's disease. Regarding regions of the brain where an inverse relationship between Letter Fluency and brain activity occurred, these regions were observed in various parietal, orbitofrontal, and motor areas of the brain. That greater activity in these non-language areas is correlated with lower performance on the verbal fluency measure suggests that activity in these areas may be interfering with effective performance on the task. This finding provides support for David Copland's (2003) hypothesis that sub-cortical damage causes impairments in verbal fluency that result from difficulties restricting attentional activitation to areas of the brain that are necessary for carrying out verbal executive functions.

The next series of identified brain regions was derived from correlations with the Category Fluency task. We observed various areas of the brain in the right hemisphere where performance on the Category Fluency task exhibited an inverse relationship with the activity obtained during a category member generation task. Specifically, these are areas where lower Category Fluency scores predict more activity in that region of the brain, or higher Category Fluency scores predict less activity. Again, we observed these regions in various non-language areas of the brain including the precentral gyrus, the angular gyrus, the superior parietal lobule, the occipital cortex, and the cerebellum. This serves as further support for the theory that impaired performance on verbal fluency results from unintentional activity throughout the brain. As compared to the areas

identified using Letter Fluency, fewer areas were identified from these correlations. Further, we did not observe any areas of positive correlation with the Category Fluency task. Such findings may have occurred for a number of reasons, one of which may have resulted from the fact that the Letter Fluency and category member generation task are better matched in terms of difficulty level than the Category Fluency and category member generation task. While the Category Fluency task administered outside the scanner prompts the participant with a broad category such as “Animals,” enabling the participant to utilize a number of semantic categories (e.g. zoo animals, domesticated animals, etc.) the category member generation task administered inside the scanner provides categories that are more particular such as “Ocean Animals” thereby increasing the difficulty of the task. In this way, performance on the semantic fluency task outside the scanner may not correlate as well with the activity necessary to effectively perform the more difficult category member generation task inside the scanner. Still, the presence of multiple areas of inverse correlation seems to suggest that activity in non-language areas of the brain is detrimental to the Category Fluency task.

For the final aim, our results indicated that contrary to our hypotheses, there were no detectable differences in the functional response patterns between the HS2 and Healthy Deployed veteran groups within any of the identified areas of the brain. The relatively small sample size of our groups, in combination with the large number of time-point comparisons inherent in each statistical analysis may have contributed to our lack of significant findings by subsequently reducing our power to detect differences. As such, the small sample size is one potential limitation of the current study. However,

another interpretation of these results could be that no significant differences in functional pattern of activity were observed because HS2 veterans' pattern of activity does not differ from that of healthy veterans. This interpretation is unlikely, however, since we would have at least expected the HS2 veterans' functional activity to differ from the HD veterans in the basal ganglia had we had enough power to detect differences since this same sample showed differential tissue health in this region.

Aside from the small number of participants in our sample, other limitations of the current study include our reliance on correlations made from behavioral data obtained outside the scanner and functional images provided from the scan. An alternative to this approach would involve having the patients perform the category member generation task aloud during the fMRI scan and correcting for any resulting motion artifact during image data processing. An additional limitation of the current study arises from the fact that we are working with an aging population. Thus, it is more difficult to distinguish the effects of age on our behavioral and imaging results from the effects of a potential disease process. However, since our groups are age-matched, group differences should reflect only the differences resulting from the disease process.

In summary, the group differences in verbal fluency that were observed provide support for the notion that HS2 and HS3 veterans demonstrate impairments on verbal executive functions. Further, areas of the brain that exhibited a positive relationship with performance on these measures were largely observed in areas of the brain that are important for language and semantics, whereas areas of the brain that exhibited an inverse relationship with performance on these measures were largely observed in non-language areas. These findings are consistent with the idea that subcortical damage is

associated with a problem restricting attentional activation to areas of the brain that are necessary for verbal executive functions. Although our results did not indicate that the HS2 group produced a unique pattern of activity as compared to healthy veterans in these areas of the brain, future research should not discount the idea that HS2 veterans exhibit significant and verifiable changes in functional activity related to these behavioral findings especially since neuropathological differences in the basal ganglia have already been identified in this sample. Finally, future comparisons to parallel disease models such as Huntington's disease and Parkinson's disease may serve to better elucidate the distinct mechanism behind the cognitive and behavioral sympotomatology of HS2 and the other Gulf War Syndromes.

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BIOGRAPHICAL SKETCH

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