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14. ABSTRACT
Acetylcholinesterase (AChE) inhibitors including organophosphate (OP) pesticides are known to produce chronic neurological symptoms at sufficient exposures. Our previous study of cognitive functioning in military pesticide applicators from GWI, found that veterans classified as higher pesticide-exposed reported significantly more health symptoms and performed less well on cognitive testing than lower-exposed veterans. It was the goal of this follow-up neuroimaging study to identify the relationships between OP pesticides, brain imaging, cognitive functioning and health symptoms in this well-characterized group of pest-control personnel from GWI. It was hypothesized that GWI veterans with higher levels and more exposures to AChE inhibiting pesticides and low-level nerve agents would show lower brain white matter volumes on MRI, report more health symptoms and perform less well on cognitive testing. Results showed that brain white matter volumes were significantly correlated with total health symptoms and with the attention/executive system domain and that cerebral and cerebellar white matter and gray matter volumes were significantly lower in veterans exposed to the OP dichlorvos (pest-strips) and the organochlorine lindane (delouser). Significant interaction effects were also found when comparing DEET and PB pills with hippocampal volumes and visual memory functioning resulting in lower volumes and worse memory function.

15. SUBJECT TERMS
neurotoxicants, MRI, neuropsychological deficits, Gulf War veterans, CNS, pesticides, sarin, DEET, PB

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INTRODUCTION:

Questions remain as to whether acetylcholinesterase (AChE) inhibitors including organophosphate (OP) and carbamate pesticides (without overt poisoning) could have caused lasting neurobehavioral deficits in veterans of Gulf War I (GWI) and if so, whether objective biomarkers can be developed to identify at-risk individuals. The goal of the current study, called the pesticide MRI study, was to elucidate if brain-behavior relationships can be detected in pesticide-exposed GWI veterans by objectively measuring brain volumetrics with structural MRI in GWI veterans with known exposures to organophosphate pesticides as part of their military occupational specialty (MOS). This study specifically compared volumetrics to cognitive functioning and health symptom report.

Previous research by our lab evaluated neuropsychological functions with GWI military pesticide control personnel with known exposures compared with very little pesticide exposure, known collectively as PCIs (DOD grant W81XWH-04-1-0118). This study was called the pesticide cognition study. In fact, the Environmental Exposure Report-Pesticides (EER) (www.gulflink.osd.mil) commissioned by the Force Health Protections and Readiness Program (formerly known as the Office of the Special Assistant for Gulf War Illnesses) reported estimates of exposure for general deployed military and for pesticide applicators from the Gulf War based on interviews with the current study sample of military pesticide applicators and a review of DOD pesticide records. Results of the pesticide cognition study when broken down into the four pesticide x anti-nerve gas pill (PB) exposure groups indicated a significant effect of lowered mean reaction times and increased mood complaints in the high pesticide x high PB exposed group compared with the three other exposure groups. In addition, it appeared that the combined impact of multiple pesticide exposures without exposure to PB, contributed significantly to worse performance on a complex visual memory task (Rey-Osterrieth complex figure). Some individual pesticides also appeared to be the best predictors and thus have more of an independent effect on cognition and mood functioning. Specifically, high dichlorvos exposure from pest strips was significantly associated with mean reaction time performance on the continuous performance test (Sullivan et al., 2009; Krengel et al., 2010). While the fly bait methomyl and the delousing agent lindane were associated with mood functioning on several scales of the Profile of Mood States. These findings are consistent with results of studies of agricultural workers and professional pesticide applicators reporting lasting deficits in neurological and cognitive functioning resulting in peripheral neuropathy, decreased processing speed, visual memory and mood deficits (Stephens et al., 1995; Misra et al., 1994; Steenland et al., 1996; McKenzie-Ross et al., 2010; Kamel et al., 2005). In addition, when comparing PCIs exposed to low-level AChE inhibiting OP nerve agents, sarin and cyclosarin from the Khamisiyah weapons arsenal (as verified by DOD notification), significant results were noted in that those in the Khamisiyah group showed significantly higher musculoskeletal ($p=.03$) and mood and cognition ($p = .03$) subscales of the chronic multisymptom illness (CMI) criteria of Fukuda et al. (1998). While other studies from our group found lower brain white matter volumes in a separate group of GW veterans exposed to the Khamisiyah area for two or more days (Heaton et al., 2007). Collectively, these findings suggested the need for continued assessment of structural (MRI) and functional (cognition) relationships in these groups of veterans with known organophosphate exposures.

Brain white matter has been found to be sensitive to chemical exposures in several studies of neurotoxicant poisonings and has in some cases been linked to development of chronic neurological deficits called toxicant encephalopathy (Filley, 2001). It was also recently found that GW veterans with lower brain white matter volumes were twice as likely to be in the high health symptom reporting group (>10 symptoms) than in the low symptom reporting group in a study conducted by the current investigators of 58 GW veterans from the New England area (Powell, 2009). Correspondingly, glial overactivation (including microglia and astryocytes) has recently been found to be associated with chronic pain syndromes (Fields, 2009) suggesting a potential mechanism for increased health symptom report and altered white matter or glial functioning

(Watkins et al., 2009) in exposed groups. It was therefore hypothesized that in the PCI cohort, increased pesticide exposure would be correlated with increased CNS health symptoms and lower brain white matter volumes in this uniquely knowledgeable group of GW veterans.

The specific aims of this project were to identify the relationships between organophosphate pesticide exposure, differences in brain volumetrics, and health symptoms in pest-control veterans from the GWI. It was hypothesized that PCI veterans categorized as high exposed to OP pesticides would show lower brain white matter volumes, report more health symptoms and perform less well on cognitive testing than low pesticide exposed veterans. It was also hypothesized that veterans categorized as high-pesticide exposed and potentially exposed to low-level sarin (Khamisiyah-notified) would show an additive effect of exposure and show greater white matter volumetric differences on MR imaging, perform less well on cognitive testing and report more health symptoms than the veterans categorized as low-pesticide exposed and with no potential sarin exposure (not Khamisiyah-notified). This group of military pesticide applicators and less-exposed preventative medicine personnel made an ideal group to study for this question given that this unique group of individuals have known exposures to various AChE inhibiting neurotoxicants in the GWI environment (OP pesticides, low-level sarin/cyclosarin), are quite knowledgeable about the types and classes of insecticides used during the GWI and as a group, have not previously undergone neuroimaging for potential long-term CNS effects. This follow-up MRI imaging pilot study explored whether OP pesticides alone and/or in combination with presumed exposures to low-dose AChE inhibiting nerve agents (sarin/cyclosarin) and/or other pesticide classes could have led to chronic health symptom reports in these PCI veterans.

In summary, the specific aims of this project were (1) To determine the neuroanatomical and cognitive effects of AChE inhibiting OP pesticide exposure in specific groups of GWI veterans. (2) To determine the neuroanatomical and cognitive effects of combinations of AChE inhibiting organophosphates including pesticides and low-level nerve agents (Khamisiyah-exposed) and/or other pesticide classes in specific groups of GWI veterans (power permitting).

BODY

The approved statement of work for the entire study period is below:

STATEMENT OF WORK

Table 1. Structural MRI and Cognitive Correlates in Pest-control Personnel from Gulf War I.

Task 1. Finalize Plan for Subject Recruitment for MRI study - Months 1-6:

a. Finalize agreements with MRI centers to obtain brain-imaging scans of GW pest-control interviewees (PCIs) in Missouri, Tennessee, Texas and Florida (month 1-2).

b. Submit human use documents for IRB approvals (months 1-6).

c. Identify pool of potential subjects to recruit for MRI protocol (months 1-2).

Task 2. Perform Subject Recruitment and Data Collection - Months 7-12:

a. Contact potential subjects for recruitment, screen them for exclusion criteria and arrange for travel to MRI centers (months 7-12).

b. Obtain MRI images with 30 study participants (months 7-12).

c. Perform brief neuropsychological evaluations with the 30 study participants including Profile of Mood States (POMS), Trail Making Test (A&B), Continuous Performance Test (CPT), Finger Tap Test (FTT), Controlled Oral Word Association Test (COWAT, FAS test), Multiple Loops and Recurrent Series Writing test, Grooved Pegboard Test, California Verbal Learning Test-II, Rey-Osterreith Complex Figure Test, Hooper Visual Organization Test, Test of Motivation and Memory (TOMM) and a grip strength test using a hand dynamometer. (months 7-12).

d. Obtain information about current health status and any recent changes in medical or psychiatric diagnoses for all study participants by using a self-administered study questionnaire and a brief in-person clinical interview (months 7-12).

Task 3. Data entry and MRI data post-processing - Months 7-16:

a. Segmentation analysis of neuroimaging data and quality control measures will be ongoing (months 7-16).

b.Data entry and cleaning of questionnaires and neuropsychological data will be ongoing (months 7-16).

Task 4. Final Analysis and Report Writing - Months 16-18:

a. Statistical analyses comparing brain MRI volumetrics, cognitive functioning and health symptom report in high and low pesticide-exposed groups (months 16-18)

b. Write final study report (months 16-18).

c. Prepare manuscript for submission (month 18).

Task 1a. Finalize agreements with MRI centers to obtain brain imaging scans of GW pest-control interviewees in Missouri, Tennessee, Texas and Florida.

The planned study protocol included a structural brain MRI, a brief cognitive evaluation, a brief follow-up questionnaire to assess any recent changes in health functioning and a clinical interview to assess current mood and any recent changes in psychiatric diagnoses. These follow-up interviews allowed for an assessment of current health and cognitive functioning in order to assess brain-behavior relationships between MRI volumes and specific cognitive outcomes measures or diagnoses. In this way, structural (brain imaging) and functional (cognitive functioning) relationships between the groups could be obtained. A three-pronged neurobehavioral pattern including neuroanatomical findings with corresponding neuropsychological test patterns and health symptoms could then begin to discern these relationships. Separate study parameters contribute to the general knowledge of GWI veterans' continued illnesses however, studies that can combine findings in multiple modalities (i.e. MRI, cognitive test patterns and corroborating health symptoms) in the same cohort (with extensive knowledge of the neurotoxicants in the GWI theatre) may begin to shed a more clear light on objective biomarker patterns in symptomatic GWI veterans.

The planned procedure for the study protocol was to obtain the MRI scans with study participants by contracting with MRI centers in Missouri, Tennessee, Texas, and Florida. The PI and her study staff performed the cognitive and psychodiagnostic interviews during the same time at each MRI site. The entire study protocol (including MRI) took approximately 2.5 hours. Agreements were finalized with each of the four contract MRI centers included in the table below and were the study sites for this pilot field study.

Table 2. Contracted MRI centers to obtain structural MRIs of GW pest-control personnel

1. Springfield Neurological Institute Imaging 2900 S. National Ave. #A Springfield, MO 65804
2. Hermitage Imaging Center 5045 Old Hickory Blvd. #100 Hermitage, TN 37076
3. Apex Imaging Center 1320 Texas Star Pkwy Euless, TX 76040
4. Arlington Imaging Center 6500 Fort Caroline Rd. #B Jacksonville, FL 32277

Task 1b. Submit human use documents for IRB approvals.

The human use protocol documents were submitted to the local IRB at Boston University and after several revisions were approved in May 2008. During the first continuing review in March 2009, the local IRB requested several minor changes to the wording of the informed consent form (ICF) to reduce redundant language and improve understandability for the study participant. These documents were submitted to the Department of Defense' Human Review Protections Office (HRPO) for approval and were approved in August 2009. A release of medical records form for the environmental exposure questionnaire from the original study was submitted for approval to the HRPO and was also approved in August 2009. A continuing review was submitted to HRPO on April 2, 2010.

Task 1c. Identify pool of potential subjects to recruit for MRI protocol.

A subgroup of pesticide control personnel from the Gulf War who had known exposures to pesticides and had been evaluated previously for cognitive functioning by the current study investigators, were the potential study participants for the current pesticide MRI study. Pesticides were used widely in the Gulf War to protect troops from such pests as sand flies, mosquitoes and fleas that can carry the infectious diseases leishmaniasis, sand fly fever and malaria. Indeed, of the nearly 700,000 US troops deployed to the Gulf region, only 40 cases of infectious diseases were documented (Winkenwerder Jr, W., 2003). US forces used pesticides in areas where they worked, slept, and ate throughout the GW. In fact, on any given day during their deployment, GW veterans could have been exposed to 15 pesticide products with 12 different active ingredients and pesticide applicators were likely exposed to more pesticide products and at higher doses. Troops used pesticides for a number of reasons, including personal use on the skin and uniforms as an insect repellent, as area sprays and fogs to kill flying insects, in pest strips and fly baits to attract and kill flying insects, and as delousing agents applied to enemy prisoners of war.

These widespread, commonly reported uses supported the decision by the former Office of the Special Assistant for Gulf war Illnesses (OSAGWI) to investigate pesticide exposures as a potential contributor to unexplained illnesses in GW veterans. According to the OSAGWI report, the pesticides of potential concern (POPCs) used by US military personnel during the GW can be divided into five major classes or categories: 1) organophosphorus pesticides (OP), such as dichlorvos, malathion, and chlorpyrifos; 2) carbamate pesticides, such as bendiocarb; 3) the organochlorine, lindane; 4) pyrethroid pesticides, such as permethrin; and 5) the insect repellent DEET (see figures 2 through 4). The Environmental Exposure Report – Pesticides (www.GulfLINK.osd.mil) concluded that 42,000 general military personnel could have been over-exposed to pesticides based on the health risk assessment dose-estimates (figure 1) and that the AChE inhibiting pesticides including organophosphates and carbamates could be among the contributing factors to some of the undiagnosed illnesses in GWI veterans.

A recent review of thousands of pesticides as part of the Food Quality Protection Act (FQPA) by the Environmental Protection Agency (EPA) has resulted in the re-evaluation of the safety of some OP pesticides resulting in the restricted use or complete banning of several of the most commonly used chemicals including chlorpyrifos, diazinon, malathion and dichlorvos. As part of this sweeping pesticide review, the EPA also suggested that some OP pesticides may have endocrine disrupting properties at doses much lower than would cause acute cholinergic effects. For example, malathion was reported to affect thyroid functioning and to be associated with thyroid tumors in this report (www.epa.gov/pesticides/cumulative/rra-op). Diazinon was also reported to be associated with delayed bone growth, abnormal bone cysts and with decreased bone mineral density in a separate report (Dahlgren et al., 2004). Another recent report has suggested synergistic interaction effects in salmon exposed to diazinon, malathion and chlorypyrifos such that the AChE inhibition showed higher than simply an additive effect of each of the three OPs individually (Laetz et al., 2009). Other pesticide classes including the insect repellent DEET in combination with the anti-nerve gas pill, (pyridostigmine bromide) has also been shown to cause lower brain volumes in the hippocampus, cingulate cortex, thalamus and hypothalamus (Abdel-Rahman, Shetty & Abou-Donia, 2002) and to independently disrupt immune system functions in animal models (Keil et al., 2009). In addition, the organochlorine lindane has also been severely restricted by EPA because of its persistence in the environment, ability to bioaccumulate, potential as a carcinogen and evidence as an endocrine disruptor (http://www.epa.gov/oppsrrd1/reregistration/REDs/lindane_red_addendum.pdf).

Figure 1. Pesticide use and Application Overview.

Pesticide Use and Application Overview

Use	Designation	Purpose	POPCs, Active Ingredient	Application Method	User or Applicator
General Use Pesticides	Repellents	Repel flies and mosquitoes	DEET 33% cream/stick	By hand to skin	Individuals
			DEET 75% Liquid	By hand to skin, uniforms or netting	
			Permethrin 0.5% (P) Spray	Sprayed on uniforms	
	Area Spray	Knock down spray, kill files and mosquitoes	d-Phenothrin 0.2% (P) Aerosol	Sprayed in area	
	Fly Baits	Attract and kill flies	Methomyl 1% (C) Crystals	Placed in pans outside of latrines, sleeping tents	Individuals, Field Sanitation Teams, Certified Applicators
			Azamethiphos 1% (OP) Crystals		
	Pest Strip	Attract and kill mosquitoes	Dichlorvos 20% (OP) Pest Strip	Hung in sleeping tents, working areas, dumpsters	
Field Use Pesticides	Sprayed Liquids (emulsifiable concentrates, ECs)	Kill flies, mosquitoes, crawling insects	Chlorpyrifos 45% (OP) Liquid	Sprayed in corners, cracks, crevices	Field Sanitation Teams or Certified Applicators
			Diazinon 48% (OP) Liquid	Sprayed in corners, cracks, crevices	Certified Applicators
			Malathion 57% (OP) Liquid		
			Propoxur 14.7% (C) Liquid		
	Sprayed Powder (wettable powder, WP)	Kill flies, mosquitoes, crawling insects	Bendiocarb 76% (C) Solid		
	Fogs (Ultra-Low Volume Fogs, ULVs)	Kill flies, mosquitoes	Chlorpyrifos 19% (OP) Liquid	Large area fogging	Certified Applicators
			Malathion 91% (OP) Liquid		
Delousing Pesticide	Delousing Pesticide	Kill lice	Lindane 1% (OC) Powder	Dusted on EPWs, also available for personal use	Certified Applicators, Military Police, Medical Personnel

Figure 2. Active ingredients in pesticides of potential concern.

Active ingredients contained in pesticides of potential concern

Repellents	Pyrethroids	Organophosphates	Carbamates	Organochlorines
DEET	Permethrin	Azamethiphos	Methomyl	Lindane
	D-Phenothrin	Chlorpyrifos	Propoxur	
		Diazinon	Bendiocarb	
		Dichlorvos		
		Malathion		

Figure 3. General military exposure levels reaching levels of concern

General Military population exposures which exceeded the levels of concern

Pesticide Type	Affected Group	Active Ingredient/Class	Exposure Scenario
Fly baits	Only individuals who handled (applied) fly baits	Azamethiphos (OP) *	Medium, High
		Methomyl (C)	High
Pest strips	General military population	Dichlorvos (OP)*	Low, Medium, High
Sprayed Liquids	General military population	Chlorpyrifos (OP) *	High
		Diazinon (OP)*	High
		Malathion (OP)*	High
Sprayed Powders	General military population	Bendiocarb (C) *	Medium, High

OP = Organophosphate C = Carbamate
•Current use restricted or banned by EPA as part of the Food Quality Protection Act pesticides review.
Source: Environmental Exposure Report – pesticides

Figure 4. Applicator exposure levels reaching levels of concern

Applicator personnel additional exposures which exceeded the levels of concern

Pesticide	Active Ingredient/Class	Exposure Scenario
Sprayed liquids	Chlorpyrifos (OP)*	High
	Diazinon (OP)*	Medium, High
	Malathion (OP)*	High
Sprayed powders	Bendiocarb (C)*	Low, Medium, High
Fogs	Chlorpyrifos (OP)*	High
	Malathion (OP)*	High
Delousing	Lindane (OC)*	Medium, High

OP = Organophosphate C = Carbamate OC = Organochlorine
•Current use restricted or banned by EPA as part of the Food Quality Protection Act pesticides review.
Source: Environmental Exposure Report - pesticides

Study participants included a subgroup of the 296 PCI veterans who were interviewed by the Department of Defense in 1997-2000 to perform a health risk assessment of pesticide exposure in GWI veterans. PCIs include veterans who were involved in pest control activities in various capacities during the GWI. PCI's include entomologists, physicians, environmental science officers, preventive medicine specialists, field sanitation team members, military police and other pest controllers. One hundred fifty nine PCIs participated in a previous study by our lab, the Pesticide Cognition Study. All PCIs had previously been categorized as high or low pesticide and PB exposed based on the exposure guidelines that were developed by the lead toxicologist, William Bradford of the DOD Environmental Exposures Report-Pesticides (table 3)(high PB exposure was determined if 180 mg or more active ingredient PB ingestion was reported). In addition, study investigators obtained Khamisiyah notification (yes/no) information for each PCI from DOD in order to compare the impact of potential low-level sarin exposure in combination with the pesticides of potential concern.

Table 3. Guidelines for Pesticide Exposure Classification

Guidelines for Pesticides

Low exposure

An individual will be assigned to the low-exposure category for pesticides if he or she does not fit the guidelines for high exposure, as described below. For example, an individual exposed to pyrethroids other than via fogs, but no other pesticides, would be assigned to a low pesticide exposure group.

High exposure

An individual will be assigned to the high-exposure category for pesticides if any of the following apply:

1) PCI reported experiencing acute signs and/or symptoms of pesticide overexposure, other than minor skin irritation, at least once. A general statement, such as "became ill" will qualify.

2) PCI probably applied pesticides from any of the following groups on two or more occasions: organophosphate (OP) emulsifiable concentrate (EC) or ultra low volume (ULV) products, carbamate ECs or powders, lindane used for enemy prisoners of war (EPWs), fly baits ($\geq$2 pounds handled), and/or fogs. PCI may or may not have worn adequate personal protective equipment (PPE).

3) PCI was probably present during applications of OP ECs/ULVs, carbamate ECs/powders, DDT, and/or fogs on two or more occasions.

4) PCI probably spent at least 1 week living/working in structures treated inside with OP and/or carbamate ECs, ULVs, powders, DDT, and/or pest strips, and likely experienced substantial post-application exposure.

5) PCI probably applied DEET to self at least 30 times. PCI must provide enough information to conclude that usage was equivalent to or above this level. DEET application 30 times per month is the 25th percentile value determined by the RAND (2000) survey for ground forces who used DEET (50% reported no use).

Of the 159 PCI subjects initially interviewed by our lab for the pesticide cognition study, 98 PCIs were categorized as high pesticide exposed and 62 PCIs were categorized as low-pesticide exposed. In addition, 59 of these PCIs were potentially exposed to low-level sarin from the Khamisiyah weapons detonations. The pesticide cognition study cohort is now well-characterized in terms of demographics and exposure histories. Mean age for this cohort was 47.7 years and mean educational attainment was 15.9 years including 13% women. Exposure classification developed during the pesticide cognition study was used during the current pesticide MRI study and included a dichotomous high/low categorization for pesticide and PB exposures and a yes/no dichotomous variable for Khamisiyah notification (presumed low-level sarin exposed). Each PCI was categorized as high or low pesticide exposed based on telephone interviews with DOD and in-person interviews with Boston investigators and previously completed a 2-hour neuropsychological screening battery that includes paper and pencil measures of cognition, as well as computer-assisted measures of reaction time. They also completed a health symptom questionnaire and an assessment of environmental stressors tracking environmental and occupational exposures since the time of the GWI.

For the current Pesticide MRI Study, 30 PCIs were targeted for recruitment from the original 159 PCIs in the pesticide cognition study described above. The study plan was to include fifteen PCIs in the high-pesticide exposed group and 15 PCIs in the low-pesticide exposed group. As these PCI veterans currently reside in various states around the country, study participants were asked to report to one of 4 MRI centers convenient to their current residence for the neuroimaging protocol. In this way, the most study participants would be able to complete the study based on larger PCI population densities in particular states including Missouri, Texas, Tennessee and Florida. Table 4 presents a breakdown of potential study participants based on state of residence.

Table 4. PCI current residence by most populated States

State	total PCIs
Missouri	**17**
Texas	**15**
Tennessee	**13**
Florida	**10**

Task 2a. Contact potential subjects for recruitment, screen them for exclusion criteria and arrange for travel to MRI centers.

Four study recruitment trips were conducted and resulted in 24 study participants recruited and fully participating in the study protocol. This resulted in an 80% completed recruitment rate for the projected 30 study participants. There was one additional study participant who was recruited but withdrew due to feeling claustrophobic as soon as he entered the MRI machine. He reported no further feelings of discomfort after being removed from the MRI and was withdrawn from the study due to an incomplete study. There were also three other potential study participants that had to cancel their appointments due to unanticipated work demands or ill family members. Two previous study participants from the pesticide cognition study were reported deceased during recruitment efforts for the current study. Several other potential study participants had since moved to a different state and the travel distance was too far for them to participate in the current study. Subject demographics are presented in the table below and included an overall mean age of 53.5 years, a mean education attainment of 15.5 years and 13% women. These demographics are representative of the larger study sample that they were derived from as reported above (mean education of 15.5 years, 13% women and 47.7 years mean age at the prior assessment).

Table 5. Subject Demographics		
Mean age	**Mean education**	**% women**
53.5	**15.5**	**13**

Task 2b. Obtain MRI images with 30 study participants.

Neuroimaging procedures

Volumetric measures of brain tissues were obtained from each subject with the use of structural MRI scanning. Conventional MR images were acquired using 1.5 Tesla GE whole body imagers for the practical reason that the GE scanner is currently the most readily available type of scanner in MRI centers around the country. For this study, we acquired 4 scans from each subject in one session lasting approximately 45 minutes. The types of scans we acquired and the utility they provided are as follows:

1) A three-dimensional scout image. The images from this sequence allowed us to align the imaging planes in the scanner and set up the remaining scans in an optimal fashion.
2) A high resolution T1 weighted SPGR scan acquired in the sagittal plane with a flip angle of 30 provided the platform for conducting volumetric procedures with the brain.
3) A double turbo spin echo scan acquired in the axial plane with a 3 mm slice thickness and no gaps between images allowed segmentation of the brain into white and gray matter.
4) An axially acquired, fluid attenuated inversion recovery scan (FLAIR). This scan was acquired with a 3 mm slice thickness with no gaps between images. This scan allowed us to verify any regions of ischemia in the white matter of the brain.

As previously stated, a recruitment goal of 30 study participants for this pilot study was largely met with a total recruitment attainment of 80% of the projected goal. Specific recruitment attainment for each recruitment field trip is listed in Table 6 below.

Table 6. Total Recruitment Summary

State	Total subjects Recruited	Percent
Springfield, MO	**9**	**37.5%**
Arlington, TX	**4**	**17.0%**
Nashville, TN	**8**	**33.0%**
Jacksonville, FL	**3**	**12.5%**
Total	**24**	**80% recruitment goal**

Task 2c. Perform brief neuropsychological evaluations with the 30 study participants including Profile of Mood States (POMS), Trail Making Test (A&B), Continuous Performance Test (CPT), Finger Tap Test (FTT), Controlled Oral Word Association Test (COWAT, FAS test), Multiple Loops and Recurrent Series Writing test, Grooved Pegboard Test, California Verbal Learning Test-II, Rey-Osterreith Complex Figure Test, Hooper Visual Organization Test, Test of Motivation and Memory (TOMM) and a grip strength test using a hand dynamometer.

Neuropsychological and Interview Instruments: In addition to analyses from structural imaging, study participants' scores on a brief battery of neuropsychological test variables were used to assess the relationship between white matter volumes and manual speed, visuospatial function and new learning. Participants all also completed a questionnaire relating to health symptoms, a mood scale, and a structured interview to document any lasting psychiatric diagnoses. These data were collected in order to evaluate the relationship between cortical, subcortical and white matter volumes and health symptom complaints and scores on neuropsychological testing and OP pesticide exposure status.

A tester who was blind to the exposure status of the subject administered the neuropsychological test battery. The neuropsychological test battery to be used assesses the functional domains of attention and executive abilities, psychomotor function, visuospatial skills, memory, and mood, as defined in Sullivan et al., (2003). The battery includes tests shown to have high specificity and sensitivity for detecting changes in neuropsychological functions that have in past studies demonstrated utility in the assessment of toxicant-induced brain damage, and psychiatric disorders (White & Proctor, 1992). The domains included in this category are attention and executive function, motor skills, mood and memory (see Sullivan et al, 2003). Also typically included in cognitive test batteries are tests designed to tap relatively stable native intellectual abilities including the Information subtest from the WAIS-III (Weschler, 1997), and the Boston Naming Test (Kaplan et al, 1983). Since these tests were already performed in the pesticide cognition study, and an assessment of native intellectual ability has been ascertained for these individuals, these tests were omitted from this brief cognitive battery.

Sustained attention was measured by number of errors on a test of continuous performance (CPT), a computer-assisted test from the Neurobehavioral Evaluation System (NES3 (Letz & Baker, 1988), an instrument widely used in the field of occupational health, that represent adaptations of traditional neuropsychological instruments for computerized stimulus presentation and recording of responses. The NES instruments have reliable psychometric properties and have demonstrated validity in epidemiological and laboratory studies of exposure to a wide variety of neurotoxicants. Also used as measures of executive functioning, are measures of cognitive flexibility (MNs, multiple loops) and alternation of set (Trail making test, part B) (Reitan & Wolfson, 1985). Psychomotor functioning is also measured by a computerized version of the finger tap test (NES3), the time to completion on the grooved pegboard test and reaction time on the CPT test. Additionally, grip strength was measured by a hand dynamometer in order to assess PCI health symptom complaints of weakness. This measure has been shown to have good inter-rater reliability (Mathiowetz et al., 1984). Previous studies of occupational pesticide exposure have documented changes in reaction time and motor speed (NCTB). Therefore, we predicted decreased CPT reaction time performance in the high-exposed PCI group and motor slowing on the additional measures to correlate with cerebral and subcortical white matter volumes.

The test battery also included the Profile of Mood states as a self-report assessment of current mood. The indicators of importance are current fatigue, confusion, tension and depression. Mood has been shown to be associated with changes in subcortical-limbic system and neurotransmitters as a result of toxicant exposures (McNair et al., 1971) and as such, mood was treated as an outcome measure rather than as strictly a potential confounding variable.

In order to assess visuospatial processing, we administered the Rey-Osterrieth Complex Figure Test (Corwin & Blysma, 1993) and documented total scores for the copying subtest (raw score out of 36). We expect that individuals with increased exposures would have difficulty maintaining the overall configuration, tremulous writing and segmentation as a result of basal ganglia dysfunction commonly seen in individuals with these deficits. Their performance was correlated with volumetric measures of basal ganglia structures (caudate, putamen). Individuals who have documented exposures to neurotoxicants (including OP pesticides) have had difficulty in the areas of acquisition and retrieval. Therefore, we examined verbal and visual memory with the use of the Rey-Osterrieth Complex Figure Immediate and Delayed recall and the California Verbal Learning Test-II –alternate version (Delis et al., 2000) measures of total recall trials 1 to 5 (raw score) and Long-delay free recall (raw score). We also assessed the correlation of these test scores with both white matter volumes and subcortical structures (hippocampus). Lastly, a measure of response consistency was used to document the possibility of diminishment in motivation (Tombaugh, 1996) (i.e. purposeful failure of tasks or minimal exertion of effort). Raw scores (out of a possible score of 50) were computed and we expected that only a few individuals will fall below a score of 45 (indicating decreased motivation). Expected exclusion rate based on this test is <5% based on the previous PCI cognition study.

A description of the neuropsychological domains and the complete neuropsychological test battery are presented in the table 7 below followed by a description of the study instruments and procedures. All 24 study participants completed the relatively brief neuropsychological battery without reporting any fatigue or needing breaks.

Table 7. Full Neuropsychological Test Battery.

TEST NAME	DESCRIPTION	OUTCOME MEASURE
I. Executive System Functioning		
Controlled Oral Word Association Test (FAS letters) (COWAT)	Often used as a language measure but can be used to assess executive system functioning in error types.	Total score for each letter Types of errors
II. Tests of Attention, Vigilance and tracking		
Trail-making Test (Reitan &Wolfson, 1985)	Timed connect-a-dot task to assess attention and motor control requiring sequencing (A) and alternating sequences (B)	Completion
Computerized Continuous Performance Test (CPT; Letz & Baker, 1988)	Target letter embedded in series of distractors; to assess sustained attention and reaction time	Reaction Time Total Errors
Multiple Loops and Recurrent Series Writing		Impaired or unimpaired measures
III. Tests of Motor Function		
Finger Tapping Test (FTT; Letz and Baker, 1988)	Speed of tapping with index finger of each hand; assesses simple motor speed	Mean Taps
Grooved Pegboard Test (Klove, 1963)	Speed of inserting pegs into slots using each hand separately; assesses motor coordination and speed	Raw Score
Grip Strength Test		Raw Score on both hands
IV. Tests of Visuospatial Function		
Hooper Visual Organization Test (HVOT; Hooper, 1958)	Identifying objects from line drawings of disassembled parts; assesses ability to synthesize visual stimuli	Raw Score
Rey-Osterreith Complex Figure (ROCFT; Corwin & Blysma, 1993)	Copying a complex geometric design; assess ability to organize and construct	Raw Score

TEST NAME	DESCRIPTION	OUTCOME MEASURE
V. Tests of Memory		
California Verbal Learning Test (CVLT II; Delis et al., 1987)	List of 16 nouns from 4 categories presented over multiple learning trials with recall after interference; assesses memory and learning strategies	Total Trials 1-5 Long Delay
ROCFT-Immediate and 20 minute recall	Immediate and Delayed recall of a Complex figure	Raw Score
VI. Tests of Personality and Mood		
Profile of Mood States (POMS; McNair et al., 1971)	65 single-word descriptors of affective symptoms endorsed for degree of severity and summed on six mood scales	T-Scores
VII. Tests of Motivation		
Test of Motivation and Malingering (TOMM; Tombaugh, 1996)	Immediate forced choice recognition of line drawings of 50 common objects; assesses motivation and malingering	Raw Score

Task 2d. Obtain information about current health status and any recent changes in medical or psychiatric diagnoses for all study participants by using a self-administered study questionnaire and a brief in-person clinical interview.

Clinical interview: 1) Study participants were administered the Structured Clinical Interview for DSM-IV (Spitzer et al., 1990) and a current Global Assessment of Functioning score was assessed. This instrument has demonstrated reliable psychometric properties for determining the presence or absence of current or past major Axis I disorders. Dr. Krengel also administered the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1990), a state-of-the-art instrument for confirming the diagnosis of current or past PTSD and for evaluating the intensity, frequency, and severity of the disorder and its individual symptom criteria. Extensive research now indicates that this instrument has highly acceptable psychometric properties (Weathers et al., 2001). Subjects also filled out a series of self-report, paper and pencil measures designed to confirm and define symptoms of PTSD (PCI) (Keane et al, 1998). 2) Dr. Krengel also conducted a semi-structured clinical interview eliciting information pertaining to recent past and current mood disorders, substance use, neurological and medical illness, traumatic brain injury, and history of other traumatic events. Subjects were asked questions specifically related to recent occupational history (including possible occupational exposure to neurotoxicants), family history of psychiatric disorder, and life stressors. Subjects completed a health symptom checklist (HSC) consisting of a comprehensive list of frequently reported health and mental health symptoms. A complete description of the study questionnaire is listed in table 9 below.

As described above, 24 study participants completed the entire study battery including the neuropsychological battery, questionnaires and clinical interviews. In total, 2 individuals met criteria for current Post-traumatic stress disorder (PTSD) and 3 individuals met criteria for current major depression. No study participants were in acute distress during the interview session and all individuals with current psychiatric diagnoses were currently under medical supervision. These rates of psychiatric diagnoses are similar to those reported previously during studies conducted by our lab (Sullivan et al., 2003; Krengel and Sullivan, 2008).

Table 8. Total Psychiatric Diagnoses

Diagnosis	N	Percent
PTSD	**2**	**8**
MDD	**3**	**12.5**

Table 9. Study Questionnaire Descriptions

Name	**Description**
Demographics	Subjects report information on age, education, gender, ethnicity, marital status and current occupation.
Health Symptom Checklist (HSC)	A comprehensive list of 34 frequently reported health and mental health symptoms. The HSC determines how often in the past 30 days the health symptoms were experienced. Symptoms from nine body systems are assessed (cardiac, pulmonary, dermatological, gastrointestinal, genitourinary, musculoskeletal, neurological, and psychological).
Medical Conditions	Included in this checklist is a list of 21 medical conditions that the subject is asked to rate if they have ever had the condition, how it was diagnosed (self or doctor) and when it was diagnosed.
Brief Symptom Inventory (BSI)	The Global Severity index of the BSI is a summary index that represents the most sensitive single inventory indicator of a subjects' psychological distress level by combining information on a number of psychological symptoms and their intensity.
PTSD checklist (PCL)	A 17-item checklist following DSMIII-R or DSM-IV guidelines and is a structured interview for clinical diagnosis of PTSD.
Structural Neurotoxicant Assessment Checklist (SNAC)	The SNAC assesses the degree of past exposure to neurotoxicants during civilian and military occupations and includes questions pertaining to recent occupational and environmental exposures. One page related to recent exposures from hobbies will be administered only.
Telephone Recruitment form	This telephone recruitment form is used by study staff to recruit and track responses for potential study participants. Questions include current medical diagnoses, medication use, screens for metal in the body and for possible pregnancy.

Task 3a. Segmentation analysis of neuroimaging data and quality control measures will be completed. The full series of images from each scanning session were coded and hand carried to Linux workstations at Boston University School of Medicine where they were reconstructed for morphometric analyses by the study imaging expert, Dr. Killiany. All the images were transferred to workstations for processing with Freesurfer and 3D-Slicer software. Cortical and subcortical segmentation and parcellation procedures were applied to subdivide the brain into approximately 35 cortical and subcortical regions of interest. Of particular interest for this study was the overall measure of gray matter, white matter (cerebral and cerebellar) and regions of white matter abnormalities as well as cortical and subcortical volumes. These regions were expressed as volumes on the basis of the number of voxels they occupy and expressed as a percent of the intracranial volume to adjust for head size. The regions of interest generated using these steps were reviewed for accuracy using 3D-slicer.

Task 3b. Data entry and cleaning of questionnaires and neuropsychological data will be completed.

Questionnaire and neuropsychological data were cleaned and entered for all 24 study participants. Study questionnaire descriptions are listed in Table 9. From the health symptom checklist, study participants were classified as meeting criteria for chronic multi-symptom illness (CMI) criteria of Fukuda (1998) as well as documenting the total number of health symptoms endorsed on the health symptom checklist (HSC) as originally adapted by Proctor et al., (1998). Rates of CMI and mean health symptom report are listed in Table 10 below. These self-reports allowed for analyses of health symptoms and brain volumetrics as well as neuropsychological functioning comparisons. Of particular interest, the mean number of health symptoms reported and percentage of veterans meeting CMI criteria were very similar to a previous study of health symptoms and structural MRI in a completely separate group of GW veterans from the Boston area (Powell, 2009).

Table 10. Health Symptom and Chronic Multisymptom Illness (CMI) rates

Health Symptoms		Chronic Multisymptom Illness	
Mean	**Standard deviation**	**N**	**Percentage**
10. 7	**9.1**	**16**	**67%**

Task 4. Final Analysis and Report Writing:

Task 4a. Statistical analyses comparing brain MRI volumetrics, cognitive functioning and health symptom report in high and low pesticide-exposed groups.

The goal of this study was to recruit 15 high pesticide exposed and 15 low pesticide exposed Gulf War veterans and to compare brain volumetrics, cognitive functioning and health symptom report between the groups. The strategy was designed to more fully compare both structural (brain volumetrics) and functional (cognitive performance) relationships between higher symptom and lower symptom reporting Gulf War veterans. The actual recruitment attainment breakdown included 24 total study participants including 17 high-exposed and 7 low-exposed individuals. In addition, Khamisiyah exposure rates included 10 exposed veterans and 14 non-exposed (see table 11 below).

Table 11. Exposure Group Breakdown

	AChE Pesticides			
Khamisiyah	**High**	**Low**	**Total**	
Yes	5	5	10	
No	12	2	14	
Total	17	7	24	

MRI data and Exposure groups.

White matter volumes were hypothesized to show a negative correlation with the high AChE inhibitor pesticide exposed group. Study results found that there were no mean differences between the high exposed and low exposed groups with respect to acetylcholinesterase inhibitors (32.8 vs. 32.5) nor were there significant differences when the groups were compared with respect to white matter hypointensities although there was a mean difference between the groups (.13 vs. .15). There was a mean difference of two percentage points found between the exposed and non-exposed groups (32.8 vs. 30.9) with respect to total percent gray matter volume but students t-tests or univariate ANOVA analyses controlling for age did not show a significant difference between groups (see table below). These results likely reflected the small sample sizes and uneven groups.

However, when individual pesticide exposures that had shown significant independent differences in the pesticide cognition study were compared with respect to white matter volumes, there were a significant between groups difference for the interaction effect of dichlorvos (pest-strips) and lindane exposures ($p = .03$). When gray matter volumes were compared between individual pesticide exposures, there were significantly lower volumes between high and low exposed dichlorvos groups ($p = .01$). In addition, there was a significant interaction effect found for the high lindane (delouser) and dichlorvos (pest-strips) exposed group ($p=.008$). Further analyses comparing cerebellar white matter volumes between high and low AChE inhibitor pesticide groups were non-significant. However, when individual exposure groups were compared, lindane (delouser) and dichlorvos (pest-strips) showed a significantly lower interaction effect with regard to cerebellar white matter volumes ($p =.03$) (Table 12). Although significant, these comparisons represent small sample sizes and should be further replicated in larger study samples.

Table 12. Brain Volume Comparisons by Pesticide Exposure Groups

AChEi Pesticides	N	% White Matter Mean / SD	% Gray Matter Mean / SD	% White Matter hypointensities	% Cerebellum white matter Mean / SD
Low	7	32.8 (4.5)	32.9 (2.2)	.13 (.04)	1.9 (.18)
High	17	32.5 (2.8)	30.9 (4.1)	.15 (.03)	1.9 (.23)
Dichlorvos	**N**	**% White Matter Mean / SD**	**% Gray Matter Mean / SD**	**% White Matter hypointensities**	**% Cerebellum white matter Mean / SD**
Low	12	33 (3.8)	33 (3.0)	.13 (.04)	1.9 (.21)
High	12	33 (2.1)	29 (3.5)*	.15 (.03)	1.9 (.23)
Lindane	**N**	**% White Matter Mean / SD**	**% Gray Matter Mean / SD**	**% White Matter hypointensities**	**% Cerebellum white matter**
Low	13	33 (3.4)	32 (3.1)	.14 (.04)	2.0 (.22)
High	11	32 (2.5)	30 (4.1)	.14 (.04)	1.9 (.20)

* Significant at $p = .01$

Table 13. Brain volumetric Comparisons by lindane and dichlorvos Exposure groups

Brain Volume	Non-exposed group Mean	Dichlorvos x Lindane group Mean	p-value
% White matter	34	33	.03
% Gray matter	33	27	.008
% Cerebellum White matter	1.9	1.75	.03

*mean white matter, gray matter and cerebellar volumes adjusted for age and presented as % intracranial volume.

Table 14. Exposure Group Breakdown				
		Dichlorvos		
Lindane	**High**	**Low**	**Total**	
High	6	5	11	
Low	6	7	13	
Total	12	12	24	

Due to recent reports of neuronal cell death particularly in the hippocampus but also in the cingulate cortex, thalamus and hypothalamus in animals exposed to combinations of DEET, PB and/or other neurotoxicants (malathion or permethrin) (Abdel-Raman et al., 2002; Abdel-Raman et al., 2004), initial ANOVA comparisons were performed comparing malathion and DEET exposure on hippocampal volumes. Results showed no significant interaction effects in mean hippocampal volumes between DEET and malathion exposed groups (F=.022, p=.88). Additional ANOVA analyses were performed comparing individual and combined hippocampal volumes with DEET, PB and interaction effects controlling for age and gender. All models showed significant interaction effects in the DEET x PB exposed group showing lower hippocampal volumes when compared with the non-exposed or individually exposed groups and when adjusted as a percentage of total intracranial volume (Table 16). These results were significant when adjusting for age (p = .003) or age and gender (p = .004). Correspondingly, animal research has found that neuronal stem cells in the dentate gyrus of the hippocampus are highly vulnerable to these particular combined exposures and show much less proliferation than non-exposed animals when sacrificed days after exposure and also when sacrificed three months after exposure suggesting potential lasting effects from these combined exposures (A. Shetty, personal communication). Sample sizes for the current comparisons were small and were not adjusted for multiple comparisons however, they do suggest the need for further study of these combined exposures in larger groups to further validate this finding.

Table 15. Exposure Group Breakdown				
		PB		
DEET	**High**	**Low**	**Total**	
High	7	4	11	
Low	5	8	13	
Total	12	12	24	

Table 16. Hippocampal volumetric comparisons by Exposure group

Brain Volume	**DEET Mean**	**DEET p-value**	**PB Mean**	**PB p-value**	**DEET x PB Mean**	**DEET x PB p-value**
R-hippocampus	**.30**	**.59**	**.31**	**.99**	**.25**	**.004**
L-hippocampus	**.30**	**.91**	**.30**	**.85**	**.25**	**.005**
Total hippocampus	**.60**	**.72**	**.61**	**.93**	**.50**	**.004**

*mean hippocampal volumes adjusted for age and gender and presented as % intracranial volume.

<u>Neuropsychological outcomes and Exposure Groups.</u>

Neuropsychological performance between the high and low acetylcholinesterase inhibitor pesticide groups was first compared by performing multivariate analysis controlling for age and education by cognitive domain and then by individual tests within the domains. Results are presented in tables 17 and 18 for the cognitive domain comparisons. Although virtually all of the domains were in the more impaired direction (slower for motor domains and less proficient for memory and visuospatial testing etc.) in the high pesticide exposed group, the comparisons lacked sufficient statistical power to show a significant between groups difference in this small sample. However, combined interaction effect analyses of AChE inhibitors and the insect repellent DEET showed a trend for significance for the CPT mean reaction times ($F = 3.4$, $p=.07$).

Table 17. Neuropsychological domains by Exposure Category

Domain	Mean low Pesticide N=7	Mean high Pesticide N=17	P-value
Mood	218	210	.25
Memory	107	95	.34
Motor	713	741	.43
Visuospatial	58	56	.58
Attention/executive	165	158	.13

Table 18. Neuropsychological outcomes in high and low Pesticide Exposed groups

Cognitive Domain	low Pesticide Group Mean N = 7	high Pesticide Group Mean n = 17	Significance P-value
Attention/Executive			
Trails A – time to completion	28	32	Ns
Trails B – time to completion	63	69	Ns
COWAT – Total letters	31	33	Ns
COWAT – Total animals	19	23	ns
CPT – # false positives	1.7	1.6	Ns
CPT - # no responses	.57	.12	Ns
Multiple loops – Total errors	3.2	2.2	ns
Recurrent series writing – total errors	2.6	2.9	ns
Psychomotor			
Finger Tap test - # taps preferred hand	55.4	55.7	Ns
Finger Tap test - # taps non-preferred hand	50.7	50.5	Ns
Grooved Pegboard - time preferred hand	68.4	77.4	Ns
Grooved Pegboard – time non-preferred hand	77.1	80.4	Ns
CPT – mean response time	396	400	ns
Grip Strength Test – dom hand total pressure	35	39	ns
Grip Strength Test –non-dom hand total pressure	36	38	ns
Visuospatial			
Hooper – total correct	27.2	27.1	Ns
Rey-Osterrieth figure copy – total correct	31.1	28.7	Ns
Memory			
CVLT – # correct trials 1-5	50.7	44.9	Ns
CVLT – short delay # correct	10.1	10.3	Ns
CVLT – long delay # correct	12.0	10.7	Ns
Rey- Osterrieth - immediate recall, # correct	22.7	19.7	Ns
Rey-Osterrieth - delayed recall, # correct	21.2	19.2	Ns
Motivation			
TOMM	48.6	48.8	Ns

Additional analyses were conducted to compare combinations of high and low DEET separately and with the OP malathion or the anti-nerve gas pill pyridostigmine bromide (PB) exposed individuals with memory functioning outcomes. For these comparisons, the memory domain was divided into visual memory and verbal memory categories. ANOVA analyses performed comparing the verbal memory with DEET and PB combination groups found no significant differences between the groups (p=.92). However, when visual memory domain was compared for DEET x PB interaction effects, a significant interaction effect was found between the groups (p=.02) with the DEET x PB group performing significantly worse than the separately exposed or non-exposed groups (see table below). When the specific tests within the visual memory domain were then compared (Rey-Osterreith immediate and delayed copy) they all showed significant interaction effects with the DEET x PB group showing the lowest scores overall (see Table 19 below). In addition, comparisons with the visuospatial memory domain and DEET x PB interactions showed significantly lower scores in the exposed group. Within the visuospatial domain, the Rey-Osterrieth copy condition was significantly lower in the DEET x PB group as well (p=.04).

Table 19. Cognitive Outcomes by Exposure groups

Cognitive Outcome	PB Mean	DEET Mean	DEET x PB Mean	DEET x PB p-value
Verbal Memory	84	78	81	.92
Visual memory	49	44	35	.02
Rey-O immed. recall	24.3	23.8	17.7	.01
Rey-O Delay Recall	24.9	20.1	17.4	.04
Visuospatial domain	61.2	57.2	54.6	.03
Rey-O Copy	32.5	30.9	27.5	.04

MRI data and Neuropsychological domains.

Correlation analyses were performed to assess the relationship between white matter volumes and cognitive functioning. It was hypothesized that white matter volumes would be correlated with psychomotor, mood and attention/executive system domains. Results suggested that percent white matter volumes were significantly negatively associated with the attentional/executive system domain ($r=0.57$, $p=.001$) but were not significantly associated with the psychomotor and mood domains. Percent white matter hypointensity was also compared by cognitive domain and was found to be positively correlated with the attention/executive domain ($r=.60$, $p=.002$) and with mood ($r=.47$, $p=.02$). These correlations remained significant and were of similar magnitude when controlling for age through partial correlation. Additional analyses comparing visuospatial functioning with the Rey-Osterrieth complex figure copy condition and basal ganglia structures showed a significant correlation with left pallidum ($r= -.52$, $p=.02$). Memory domain functioning was analyzed by comparing hippocampal volumes and memory domain tests. Univariate analyses of variance showed a significant relationship between hippocampal volumes and the memory domain ($F = 7.7$, $p=.01$). Within this domain, significant differences were found between right hippocampal volume and the visual memory domain ($F = 26.8$, $p<.001$). The attention/executive system domain was significantly associated with white matter brain volume ($F = 5.5$, $p=.03$). The mood domain was significantly associated with the right hemisphere caudal anterior cingulate cortex volume ($F = 5.0$, $p = .04$).

Exposures and health symptoms.

Health symptoms and AChE inhibitor pesticides did not show a significant relationship ($t = -.21$, $p=.83$) when compared by student's t-tests. Chronic multisymptom illness (CMI) and AChE pesticides were not significantly different when compared by Chi-square analyses (value = .40 $p=.52$). When Khamisiyah exposed groups were compared, they also did not show a significant relationship with total health symptoms or with CMI criteria. Individual pesticides of concern also did not show significant health symptom report differences between groups. These results were found to be significantly different in the larger study sample and may reflect a lack of sufficient power to detect these differences in this small pilot study sample.

MRI data and health symptoms.

Additional study hypotheses were that brain volumetric measures would be associated with health symptom report. Specific hypotheses were that white matter volumes would be correlated with cognitive functioning and with health symptom functioning. White matter correlation analyses by total number of health symptoms reported showed a significant negative relationship (correlation coefficient -.51, $p=.01$) (see table 20 below). These findings correspond to results from a recently completed study from the current investigators that found that GW veterans with lower white matter volumes were twice as likely to be in the high symptom reporting group which included reporting 10 or more health symptoms from the health symptom checklist (Powell, 2009).

Table 20. White matter and health Symptom Correlations

		whitematter	Healthsymptom
Whitematter	Pearson Correlation	1	-.505*
	Sig. (2-tailed)		.012
	N	24	24
Healthsymptom	Pearson Correlation	-.505*	1
	Sig. (2-tailed)	.012	
	N	24	24

4b-c. Write final study report and prepare manuscript for submission.

This report is the final study report for this pilot study of structural MRI and cognitive functioning in pesticide exposed Gulf War veterans. A manuscript is being prepared to submit for publication from this report.

KEY RESEARCH ACCOMPLISHMENTS

- A pool of potential study participants was identified from a group of previously studied pest control personnel deployed to the Gulf War.
- MRI centers were finalized where brain imaging was conducted.
- Potential study participants were categorized based on current residence and identified for recruitment if residing in the most populous states of Missouri, Texas, Tennessee and Florida.
- IRB approvals were obtained and human use was approved for this study protocol.
- Four recruitment trips were planned and conducted resulting in attaining 80% of the recruitment goal of 30 study participants for this study protocol.
- Data cleaning and analyses have been performed.
- Results suggest white matter volumes are significantly correlated with health symptom reports. These results correspond to results from a previous study conducted by our study group of a separate group of GW veterans.
- Results suggest that white matter volumes significantly correlated with attention/executive domain functioning.
- Results showed that cerebral white matter volumes were not significantly associated with OP pesticide exposures when combined together as a group however, cerebral and cerebellar white matter and gray matter volumes showed a significant interaction effect and lower volumes in the lindane (delouser) and dichlorvos (pest-strips) exposure group, suggesting further follow-up of these particular exposures.
- Results showed that gray matter volumes were not significantly lower in the combined OP pesticide group but were significantly lower in the dichlorvos (pest-strips) exposed vs. non-exposed groups.

- Results suggest that DEET and PB exposures showed significantly lower hippocampal volumes (structural) and lower performance on visual memory testing (functional) that appeared to correlate with animal modeling studies.
- Preliminary results have been submitted for presentation at conferences.

REPORTABLE OUTCOMES:

<u>Publications</u>

1. Cognitive functioning in Gulf War I veterans exposed to Pesticides, Pyridostigmine Bromide and Khamisiyah Weapons Depot (Abstract). Sullivan, K., Krengel, M., Thompson, T., Comtois, C., & White, RF. International Neuropsychological Society, 35th Annual Meeting Program and Abstract Book, 2007: 210.
2. Qualitative Findings in Complex Figure Drawing in Military Pesticide Applicators from the Gulf War. (Abstract). Sullivan, K., Janulewicz, P., Krengel, M., Comtois, C., & White, R. International Neuropsychological Society, 35th Annual Meeting Program and Abstract Book, 2007: 209.
3. Comtois, C., Sullivan, K., Krengel, M. & White, R.F. (Abstract). Health Symptom Correlates among Military Pesticide Applicators from GWI. Massachusetts Neuropsychological Society Annual Meeting, May 2007.
4. Pinto, L., Sullivan, K., Krengel, M., Powell, F., Killiany, R. & White, R.F. (Abstract). Structural MRI Findings Correlate with High Symptom Status Among Gulf War Veterans. Massachusetts Neuropsychological Society Annual Meeting, May 2007.
5. Krengel, M, Comtois, C, Sullivan, K & White RF. (Abstract). The Cognitive Correlates of Chronic Multisymptom Illness in GWI Military Pesticide Applicators. International Neuropsychological Society, 36th Annual Meeting Program and Abstract Book, 2008: 103.

6. Sullivan, K., Krengel, M. Comtois, C., White, RF. (Abstract) Neuropsychological Functioning in Military Pesticide Applicators from Gulf War I. International Neuropsychological Society, 37th Annual Meeting Program and Abstract Book, February 2009.
7. Krengel, M. & Sullivan, K. Independent neuropsychological effects of pesticide exposures in military pesticide applicators from Gulf War I. International Neuropsychological Society, 38th Annual Meeting Abstracts, Journal of the International Neuropsychological Society, Supplement 1, February 2010: 34.
8. Sullivan, K. Krengel, M. Killiany, R., Heeren, T. & White, RF. Structural MRI and cognitive correlates in Military Pesticide Applicators from Gulf War I. Submitted for Massachusetts Neuropsychological Society meeting, June 8, 2010.

Invited Presentation

1. Krengel, M, Sullivan, K & White, R.F. Neuropsychological Functioning and Health Symptom Report in Pesticide and Pyridostigmine Bromide Exposed Gulf War Veterans. Stanford Research Institute, Palo Alto, CA, February 12, 2007.
2. Krengel, M., Sullivan, K., Grande, L. Neuropsychological Patterns of Blast and non-blast related Traumatic Brain Injury in OIF/OEF veterans. International Neuropsychological Society symposium, Hawaii, February 8, 2008.
3. White, R.F., Heaton, K, Krengel, M, Ringe, W, Vasterling, J. Neuropsychiatric Aspects of Combat Exposures (Blast Injuries, TBI and PTSD), International Neuropsychological Society symposium, Hawaii, February 8, 2008.
4. Sullivan, K., Krengel, M. The Pesticide Cognition Study. Research Advisory Committee on Gulf War Veterans Illnesses meeting, Washington, DC, November 17, 2008.
5. Krengel, M., Sullivan, K. Working on a Mystery: Application of Environmental Health Sciences Technology, Boston University School of Public Health, December 10, 2008.

6. Sullivan, K. Theories of Gulf War Illness and potential treatments. Boston University School of Public Health, April 8, 2009.

7. Sullivan, K. The chronology of Gulf War research at Boston University. Collaborative for Health and the Environment, April 6, 2009.

8. Sullivan, K., Krengel, M. Structural MRI and cognitive correlates in military pesticide applicators from Gulf War I. Military Health Research Forum 2009, Kansas City, August 2009.

9. Krengel, M., Sullivan, K. The pesticide cognition study. Military Health Research Forum 2009, Kansas City, August 2009.

Manuscripts in preparation: (from previous DOD funding sources)

1. Krengel, M., Sullivan, K., White, RF et al., Cognitive Functioning in military pesticide applicators from the Gulf War.
2. Sullivan, Krengel, White, RF et al., Health Symptom Report in pesticide applicators from the Gulf War.
3. White, Sullivan, Krengel, Killiany et al., Lower white matter volumes predict higher health symptoms in Gulf War veterans.

Planned Manuscripts from current funding

1. Sullivan, K., Krengel, M., Killiany, R., Heeren, T. & White, RF. Structural MRI and Cognitive Correlates in Military Pest-Control Personnel from the Gulf War.

Funding:

1. In December 2009, Dr. Krengel and colleagues submitted a VA Merit Review grant to study the trajectory of health symptom report and to devise a more sensitive algorithm for case criteria for Gulf War illness by comparing multiple test and health

symptom reports from a large longitudinally followed population-based sample of GW veterans (n=2300) from Fort Devens, Massachusetts. Unfortunately, this grant was not reviewed as it was determined that Dr. Krengel did not meet the clinical criteria as a 5/8ths VA clinician for this funding mechanism after initially being encouraged to apply for this funding source.

2. In April 2008, the Congressionally Directed Research Advisory Committee on Gulf War Veterans Illnesses (RAC-GWVI) scientific staff office was relocated to the Boston University School of Public Health with Dr. Roberta White as the new Scientific Director and Dr. Kimberly Sullivan as the new Scientific Coordinator for the Committee.

3. Drs. Krengel and Sullivan submitted two grants (Sept. / Oct. 2007) to the congressionally directed medical research program (CDMRP) to study the residual effects of blast-related traumatic brain injury (TBI) in Iraq (OIF) and Afghanistan (OEF) returnees. The first grant was aimed at treating veterans living in rural areas and included a cognitive behavioral treatment (CBT) administered through televideo equipment in the veterans homes. This grant was listed as an alternate for funding but was ultimately not funded. The second grant included establishing a database of blast and non-blast related sequelae in TBI diagnosed returnees through a collaboration of five polytrauma network site (PNS) clinics around the country. This grant was not ultimately recommended for funding.

CONCLUSIONS:

Two recent studies of Gulf War veterans by our larger group of investigators have shown lower brain white matter volumes in Gulf War veterans with (1) exposure to the Khamisiyah weapons depot for 2 or more days (and potential exposure to low level sarin) and (2) higher reported health symptoms from shortly after the time of the Gulf War (Heaton et al., 2007; Powell, 2009). These recent findings suggest that an objective biomarker for Gulf War illness may be attainable through conventional structural MRI and morphometric analysis of resultant images in appropriately selected groups. The results of the current study found lower brain white matter volumes in highly symptomatic compared with less symptomatic Gulf War veterans with known environmental exposures to pesticides as part of their military occupation as pesticide applicators, but not in the Khamisiyah exposed group. This finding validates the previous finding of lower white matter volumes in high symptom reporters in a separate group of GW veterans (Powell, 2009) and may also reflect the lack of sensitivity of dichotomous (yes/no) classification of Khamisiyah exposed groups without respect to duration of exposure. Although the current study appeared to lack sufficient power to detect significant differences in the overall combined AChE inhibitor exposure group by brain volumetric or symptomatic groups, there were significant differences noted in the pesticides shown to have independent effects from the prior pesticide cognition study. The specific pesticide exposures that showed significant differences with regard to brain volumetric correlations and with cognitive functioning were the organophosphate dichlorvos (pest-strips) and the organochlorine lindane (delouser). These particular exposures showed interaction effects when combined resulting in significantly lower cerebral and cerebellar white matter and gray matter volumes in this cohort.

Additional study results suggested a significant interaction effect and lower hippocampal volumes with combined high DEET and PB exposure. A significant interaction effect resulting in lower scores for the visual memory domain were also found for combined DEET and PB exposure suggesting both a structural and functional relationship between these exposures. These findings were shown in a small study sample and need to be further validated in larger samples however, they do correspond with animal studies showing lower hippocampal volumes in similarly combined exposures (Abdel-Raman et al, 2002) and should be further clarified. This could be particularly important as the RAND report (Fricker et al., 2000) estimates that 25 percent of GW veterans would be classified as having high exposure to the insect repellant DEET during their deployment.

The results of this pilot study should be replicated due to the small sample sizes however, the findings related to the organochlorine lindane remains of concern because of its persistence in the environment, ability to bioaccumulate, potential as a carcinogen and evidence as an endocrine disruptor (United States Environmental Protection Agency, 2006). The findings related to dichlorvos exposure are also of continued concern given the conclusions of the DOD Environmental Exposure Report- Pesticides (Winkenwerder, 2003) which suggested that up to 30,000 Gulf War veterans could have been overexposed to dichlorvos from pest-strips improperly hanging in enclosed areas during their deployment. In addition, the fact that these pesticides included pest strips (dichlorvos), delousers (lindane), insect repellents (DEET) and anti-nerve gas pills (PB) suggests that these findings could be applicable to the larger cohort of Gulf War veterans because these pesticides were used by general military personnel in addition to certified pesticide applicators.

Future study results may be further clarified by the inclusion of paraoaxanase (PON1) study profiles as an additional susceptibility biomarker. PON1 is the enzyme that detoxifies OP pesticides from the body and some genotypes are more effective in clearing organophosphates than others (Furlong et al., 2010). PON1 status is a combined genotype and circulating PON1 blood level measurement. Therefore, some individuals with PON1 status may be more vulnerable to OP exposures than others and future studies may benefit from blood analyses to determine both paraoxonase genotype and circulating levels to calculate PON1 status in exposed individuals (Furlong et al., 2010; Furlong et al., 2007). Together, structural MRI volumetric measurements and PON1 status measurements may get closer to identifying objective indicators of pathology that distinguish ill from healthy veterans and may help to identify potential avenues for treatment.

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K. SULLIVAN, M. KRENGEL, C. COMTOIS & R.F. WHITE. Neuropsychological Functioning in Military Pesticide Applicators from Gulf War I.

Objective: Gulf War veterans (GW) continue to report persistent cognitive and health symptom complaints many years following their deployment. Exposure to acetylcholinesterase (AchE) inhibiting pesticides and anti-nerve gas pills (PB) has been a suspected cause for these persistent complaints. The goal of this study was to evaluate the role of combinations of AchE inhibitors (pesticides and PB) on current cognitive functioning and health symptom status of GW veterans with known AchE exposures.

Participants and Methods: Participants included a unique group of 159 preventative medicine personnel (PM) including military pesticide applicators (high exposed) and PM personnel with very little pesticide exposure (low exposed). The groups were further categorized into high or low exposure to anti-nerve gas pills (PB), thus creating four exposure groups for comparison. It was hypothesized that the group with high pesticide and high PB exposure (group 4) would perform significantly worse on cognitive measures and report significantly more health complaints than CWI veterans with very little pesticide or PB exposure (group 1).

Results: Multiple regression analyses showed that group 4 performed significantly worse on CPT mean reaction times and reported increased mood complaints and health symptoms when compared with group 1. Significantly worse visual memory performance on the Rey-Osterrieth Complex Figure was found in group 2 (high pest, low PB) suggesting a different exposure vulnerability for this domain.

Conclusions: These findings support the hypothesis that exposure to multiple AchE inhibiting pesticides during their deployment contributed to the persistent cognitive and health symptom complaints in some Gulf War veterans.

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Memory Functions

J.W. ALBERTS. The Role Of A Dual Activation-Inhibition Process In Both False And Accurate Retrieval Of Information From Memory.

Objective: Memory retrieval involves the activation of relevant information while inhibiting competing, irrelevant information. Since false memories can be viewed as impaired retrieval selection, children who demonstrate difficulty with cognitive inhibitory control in a selective-attention task may show a greater propensity to produce false memories. Three experiments were conducted to assess whether children designated as less efficient or more efficient inhibitors on the basis of Stroop interference, also produce higher rates of false memories.

Participants and Methods: 200 Children aged 8- and 10-years participated in this study.

Inhibitory control was measured as the degree of interference occurring on a Stroop task. Those demonstrating greater Stroop interference were assigned as less efficient inhibitors, those demonstrating less Stroop interference were assigned as more efficient inhibitors. The relationship between inhibitory control and observable behaviour was assessed using the Parent form of the Connor's Behaviour Rating Scale. False memories were measured by the number of falsely remembered critical lure words in a DRM memory task.

Results: ANOVA analysis indicated children designated as less efficient inhibitors produced significantly higher rates of false memories. No significant differences were found in regards to correct and incorrect recall. T-score analysis revealed a higher proportion of children assigned as less efficient inhibitors were rated as having difficulty relating to cognitive problems.

Conclusions: Results are discussed in terms of a dual process of activation/inhibition in relation to false memories. This study provides converging evidence supporting the role of a dual process of activation-inhibition in both false and accurate retrieval of information from memory.

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J.W. ALBERTS. Does Age-related Susceptibility To False Memories Account For Developmental Differences In Rates of False Memories?

Objective: Contemporary researchers suggest children are more susceptible to false memories than adults. Therefore, the aim of this study was to examine the role of development in susceptibility to false memories. The hypotheses tested was whether age or cognitive processes such as inhibitory control, accounts for higher rates of false memories, and whether retrieval practice reduces rates of false memories.

Participants and Methods: 149 children aged 8 and 10 and 137 Adults participated in this study.

Children and Adults were designated as less or more efficient inhibitors on the basis of Stroop interference. False memories were assessed on the basis of the intrusion of critical lure-words on a DRM memory test. Immediately following the presentation of study lists, participants completed a retrieval practice task; completing word-fragments of study words.

Results: ANOVA analysis revealed regardless of age, individuals assigned as less efficient inhibitors produced significantly higher rates of false memories. Also, while retrieval practice significantly increased accurate recall, no significant decrease in false memories was observed.

Conclusions: These results provide further evidential support for the hypothesis that inhibitory control plays an important role in identifying individuals more susceptible to false memories from those that are less susceptible to false memories. Furthermore, age alone does not appear to account for increased susceptibility to false memories.

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C.K. BLOCK & S.W. SAUTTER. Perception of Memory Complaints and Effort on Memory Performance.

Objective: Examination of perception of memory complaints and effort on memory performance in a clinical sample.

Participants and Methods: There were 160 consecutive outpatients referred for memory complaints, with a mean age of 53 years (range 19 to 91 years), a mean of 14 years education (range 8 to 21 years), 51% female, and 77% Caucasian. Inclusion criteria required completion of the RBANS and Green's MCI and MSVT.

Results: No one best predictor of memory performance (percent retained on RBANS) emerged in a multiple regression of the MCI, $F(9, 150) = .73$, $p = .685$. Using a Chi Square analysis, a relationship was observed between perceived memory difficulties (MCI) and effort (MSVT) such that individuals with a high perception of memory difficulties had poor effort, $\chi^2(1) = 6.11$, $p < .01$. When perception of memory and effort were examined against RBANS percent retained, no main effect of perception on memory performance was found, $F(1, 99) = .13$, $p = .72$, $\eta^2 = .001$. A main effect was found for effort on memory performance, $F(1, 99) = 17.96$, $p < .001$, $\eta^2 = .16$. An interaction effect was observed between perception of memory and effort on memory performance, $F(1, 99) = 4.93$, $p < .05$, $\eta^2 = .05$. Individuals with high perception and poor effort had the lowest percent retained.

Conclusions: Effort, rather than perception, was found to influence subsequent memory performance. This finding may inform the differential diagnoses of memory complaints and subsequent selection of appropriate treatment strategies.

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Participants and Methods: Sixty one adequately dialyzed patients with ESRD and 30 demographically matched controls (NC) were the participants for this study. To assess their general cognitive status as well as affective symptoms, the Mini-Mental State Examination and the Hospital Anxiety and Depression Scale were used. Acquisition and recall of verbal material were assessed with the Rey Auditory Verbal Learning Test, whereas visual learning was assessed with the Brief Visual Memory Test-Revised.
Results: In comparison to NCs, individuals with ESRD obtained significantly lower memory scores. Further, the pattern of their performance was suggestive of retrieval deficits. However, mild to severe memory impairment was observed only in half of ESRDs. Regression analyses revealed that age, years of education, depression symptoms, blood urea nitrogen (BUN) and a history of coronary artery bypass grafting (CABG) were significant predictors of memory performance of dialyzed patients.
Conclusions: Memory performance of dialyzed patients is often below that of NCs, although severe mnemonic deficits seem to be rarely observed in this population. Lower memory scores of subjects with ESRD are associated with older age, fewer years of education, more depressive symptoms, higher BUN and the history of CABG. Moreover, memory profile of dialyzed individuals is similar to that seen in subjects with subcortical cerebrovascular disease.
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M. KRENGEL & K. SULLIVAN. Independent neuropsychological effects of pesticide exposures in military pesticide applicators from Gulf War I.
Objective: Gulf War (GW) veterans continue to report cognitive complaints many years following their deployment. Exposure to acetylcholinesterase (AChE) inhibiting pesticides has been a suspected cause for these complaints. The goal of this study was to evaluate the role of specific pesticides on current cognitive functioning in GW veterans with known exposures.
Participants and Methods: Participants included a unique group of 159 preventive medicine personnel (PM) including military pesticide applicators (high exposed) and PM personnel with little pesticide exposure (low exposed). In a prior analysis, veterans were characterized as being high or low exposed to 12 different pesticides of potential concern (POPC). Our prior work showed significant cognitive differences from combinations of pesticide exposures with those individuals in the high exposed group performing worse in the areas of memory and reaction times than those in the low exposed group. In the current analysis, we questioned whether specific pesticides would be independent predictors of neuropsychological performance. In order to address this question, stepwise regression analyses were performed.
Results: Results suggested that dichlorvos (pest-strips) was the best predictor for performance in the psychomotor domain ($p=.01$), methomyl (fly bait crystals) and lindane (delousing powder) were the best predictors for the mood domain ($p<.001$ and $p<.005$) and diazinon (sprayed liquid) was the best predictor for performance in the visuospatial domain ($p=.03$). Specific cognitive tests within each domain were significantly different and drove the overall results.
Conclusions: Findings suggest that although combinations of pesticides have contributed to persistent cognitive and mood differences in GW veterans, individual pesticides also had independent contributions.
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L. KRIVITZKY, J. STRANG & S. EVANS. Neuropsychological functioning in two adolescents with leukoencephalopathy from "chasing the dragon"
Objective: "Chasing the dragon" refers to the phenomenon of inhaling heroin vapor leading to toxic leukoencephalopathy. There appears to be little information in the literature on long term outcome in these cases. This study aims to characterize neuropsychological and rehabilitation outcomes in two adolescents with heroin induced leukoencephalopathy.
Participants and Methods: Two subjects are included (Subject 1: 17 year old male; Subject 2: 15 year old female). Both were found unconscious and brought to the ED with an initial GCS score of 3. MRI scans from both indicated diffuse white matter (wm) abnormalities (Subject 1: subcortical and periventricular wm, posterior cerebellum; Subject 2: centrum semiovale, occipital lobes, basal ganglia, periaqueductal wm, and bilateral cerebellum). Neither was known to be a chronic drug user, although both had been experimenting in the year preceding the injury. Subject 1 underwent neuropsychological evaluation (1 month post). Subject 2 was unable to complete comprehensive testing (3 months post), but underwent screening.
Results: Subject 1 demonstrated strengths in intellectual and basic academic functioning. Weaknesses were noted in speed of processing and executive functioning. Physically, he made significant improvements, with only mild right-sided weakness remaining. Subject 2 has demonstrated slowly improving cognition and strengths in language and basic academic skills. Physically, she has profound dysautonomia and significant problems with tone and thus is dependant for mobility.
Conclusions: Although the two subjects had different severity and courses of recovery, their presentations both suggest impact on aspects of motor and executive functioning. These outcomes are consistent with MRI findings of diffuse wm pathology. Further evaluation of the medical factors (e.g., anoxia, extent/location of wm damage) may help elucidate the reasons for their different recovery trajectories.
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H.A. NEILSON, C.C. BARONE, F. VILA-RODRIGUEZ, G.W. MACEWAN, A.M. BARR, R.M. PROCYSHYN, D.J. LANG, A.E. THORNTON & W.G. HONER. Stimulant-Specific Effects on Decision Making in Polysubstance Users.
Objective: Using stimulants and other illicit substances despite clear health risks represents poor decision making. Substance users may have pre-existing poor decision making skills, but these skills may be further impaired by the acute or neurotoxic effects of stimulant drugs. This study investigates whether more frequent use of cocaine (including crack cocaine) and methamphetamine is associated with poorer decision making.
Participants and Methods: Fifty-eight residents (45 M, 13 F, age 27-60) of single-room occupancy hotels completed the Iowa Gambling Task (IGT), a measure of decision making in which choosing low reward, low risk options yields the highest average gains. Self-reported substance use was recorded over several months with a timeline follow-back method, and urine drug screening was completed concurrently with the IGT. Seventy percent of the participants tested positive on the urine drug screen for two or more illicit substances. Regression analysis was used to evaluate potential associations between patterns of substance use and decision making performance on the IGT.
Results: After taking into account acute substance effects (based on urine drug screen results), demographic factors, and frequency of cannabis and heroin use, higher frequency (days per month) of cocaine use predicted poorer decision making on the IGT ($p < .05$). In contrast, frequency of methamphetamine use was not significantly associated with decision making.
Conclusions: More frequent use of cocaine is associated with poorer decision making in currently using polysubstance users. The same relationship was not detected for methamphetamine use, suggesting that any effects of methamphetamine use on decision making may not be dose dependent.
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A.G. VALDERRAMA, O. INOZEMTSEVA, E. MATUTE & J. JÚAREZ. Cognitive flexibility differences between cocaine and methamphetamine abusers.
Objective: The aim of this study was to demonstrate the presence of cognitive flexibility differences between cocaine (CO) and metham-

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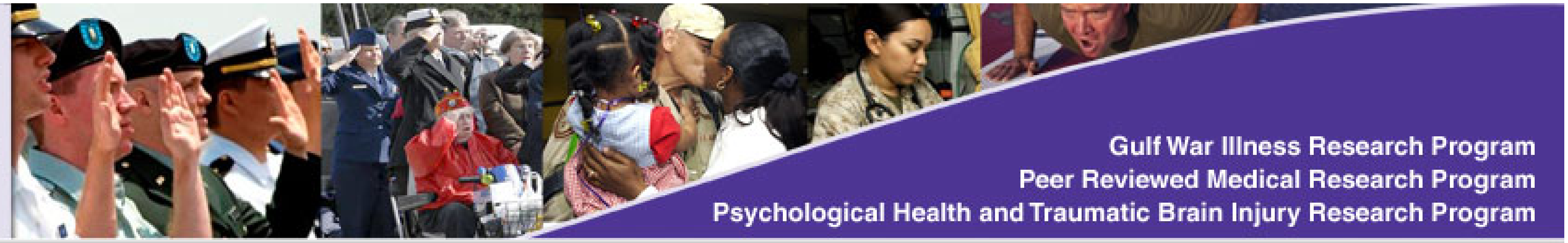

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#1708 Summary

Abstract

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Title and Abstract

Abstract Title: Structural MRI and cognitive correlates in military pesticide applicators from Gulf War I.

Abstract: Acetylcholinesterase (AChE) inhibitors including organophosphate (OP) pesticides are known to produce chronic neurological symptoms at sufficient exposure levels. Our previous study of cognitive functioning in pest-control personnel from the GWI, found that higher exposed military pesticide applicators reported significantly more health symptoms and performed less well on objective cognitive testing than the lower-exposed veterans. It is the goal of this follow-up neuroimaging study to identify the relationships between OP pesticides, brain imaging, cognitive functioning and health symptoms in a subgroup of this well-characterized group of pest-control personnel from GWI. It is hypothesized that GWI veterans with higher levels and more exposures to AChE inhibiting pesticides will show lower brain white matter volumes on MRI, report more health symptoms and perform less well on cognitive testing than less exposed veterans. Each participant will undergo a structural brain MRI, a brief neuropsychological screening battery and a clinical interview. They will also complete a current health symptom questionnaire. This follow-up neuroimaging study will evaluate the combination of exposures to AChE inhibitors as factors in the expression of GWI veterans′ continued health symptoms. Knowledge of these relationships will be useful in identifying objective indicators of pathology that distinguish ill from healthy veterans and may help identify potential avenues for treatment.

Supporting Agencies

Agencies: Department of Defense