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14. 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 military pesticide applicators classified as higher pesticide-exposed 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 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 and low-level nerve agents 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.

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

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Table of Contents

INTRODUCTION

Questions remain as to whether acetylcholinesterase (AChE) inhibitors including organophosphate (OP) pesticides could have caused lasting neurobehavioral deficits without overt poisoning (subclinical encephalopathy) in veterans of GWI and if so, whether objective biomarkers can be developed to identify at-risk individuals. The goal of the current study is to further elucidate brain-behavior relationships 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). Neuroscience studies using animal models have suggested that multiple neurotoxicant exposures result in lasting effects on the central nervous system (CNS). These findings have led several GWI researchers to hypothesize that the health symptoms of some veterans are related to similar neurotoxicant exposures (Golomb, 2008; Sullivan et al., 2003). The present study will assess brain volumetrics and correlate them with cognitive functioning in GWI veterans exposed to a known group of neurotoxicants, namely organophosphate pesticides. A group of pesticide control personnel who have been well characterized in terms of demographics and pesticide exposure histories by a previous study will be examined (Sullivan et al., 2009). It is hypothesized that increased OP pesticide exposure will be correlated with increased CNS health symptoms and lower brain white matter volumes. 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 & Kleinschmidt-DeMasters, 2001).

These findings prompted researchers from Boston University and the lead toxicologist from the Department of Defense Environmental Exposure Report- pesticides (EER) to begin the recently completed study of cognitive functioning in pest-control personnel from the GWI (DOD grant W81XWH-04-1-0118) called the pesticide cognition study. Results of this study suggest that GWI military pesticide applicators classified as high pesticide exposed reported significantly more health symptoms including muscle pain, weakness, sleep disturbance, gastrointestinal distress, skin rash and confusion and performed less well on cognitive testing in the domains of psychomotor, mean reaction times and visual memory than low-exposed GWI veterans (Sullivan et al., 2009). Investigators from Boston University in collaboration with the lead author from the Environmental Exposure Report - Pesticides (EER) sought to examine this question initially by conducting neuropsychological evaluations with GWI military pesticide control personnel with known pesticide exposures compared with preventive medicine personnel with very little pesticide exposure, known collectively as PCIs (DOD grant W81XWH-04-1-0118). The pesticide cognition study was recently completed and the PCI groups are now well characterized in terms of demographics and pesticide exposure histories and were categorized as high or low pesticide-exposed based on telephone interviews with the DoD and in-person interviews with Boston University investigators. Results of this study suggest that PCI Gulf War veterans classified as high pesticide exposed reported significantly more health symptoms and worse mood functioning than the low exposed PCIs and performed less well on cognitive testing involving psychomotor, mean reaction times and visual memory domains (Sullivan et al., 2009). 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; Bazylewicz-walckzak, 1999). In addition, potential low-level nerve agent exposure (from Khamisiyah weapons arsenal) has been associated with mood complaints and executive system decrements in GW veterans (White et al., 2001) and more recently with motor and visuospatial decrements (Proctor et al., 2006) and with reduced brain white matter volumes (Heaton et al., 2007) when assessed in a dose-dependent manner. These findings continue to support the possibility of subtle, "subclinical" central nervous system (CNS) damage associated with GWI deployment in general and neurotoxicant exposure in particular in GW veterans (White et al, 1992; Baker et al, 1985; Filley et al., 2001).

The specific aims of this project are to identify the relationships between organophosphate pesticide exposure, differences in brain volumetrics including cerebral and subcortical white matter, and health symptoms in pest-control veterans from the GWI. It is hypothesized that PCI veterans categorized as high exposed to OP pesticides will show lower brain white matter volumes, report more health symptoms and perform less well on cognitive testing than low pesticide exposed PCIs. It is also hypothesized that PCIs categorized as high-pesticide exposed and potentially exposed to low-level sarin (Khamisiyah-notified) will shown 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 PCIs 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 make 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 will explore whether OP pesticides alone and/or in combination with presumed exposures to low-dose AChE inhibiting nerve agents (sarin/cyclosarin) could have led to chronic health symptom reports in these PCI veterans.

The specific aims of this project are (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) in specific groups of GWI veterans (if power permits).

BODY

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

STATEMENT OF WORK

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).

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 includes 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 will allow 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, we can obtain structural (brain imaging) and functional (cognitive functioning) relationships between the groups. A three-pronged neurobehavioral pattern including neuroanatomical findings with corresponding neuropsychological test patterns and health symptoms may 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 will be 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 will perform the cognitive and psychodiagnostic interviews during the same time at each MRI site. The entire study protocol (including MRI) is anticipated to take approximately 2.5 hours. Agreements have been finalized with each of the four contract MRI centers included in the table below.

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 have been submitted to the Department of Defense' Human Review Protections Office (HRPO) for approval.

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

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 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 had some over-exposure 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 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 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).In addition, a 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).

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		

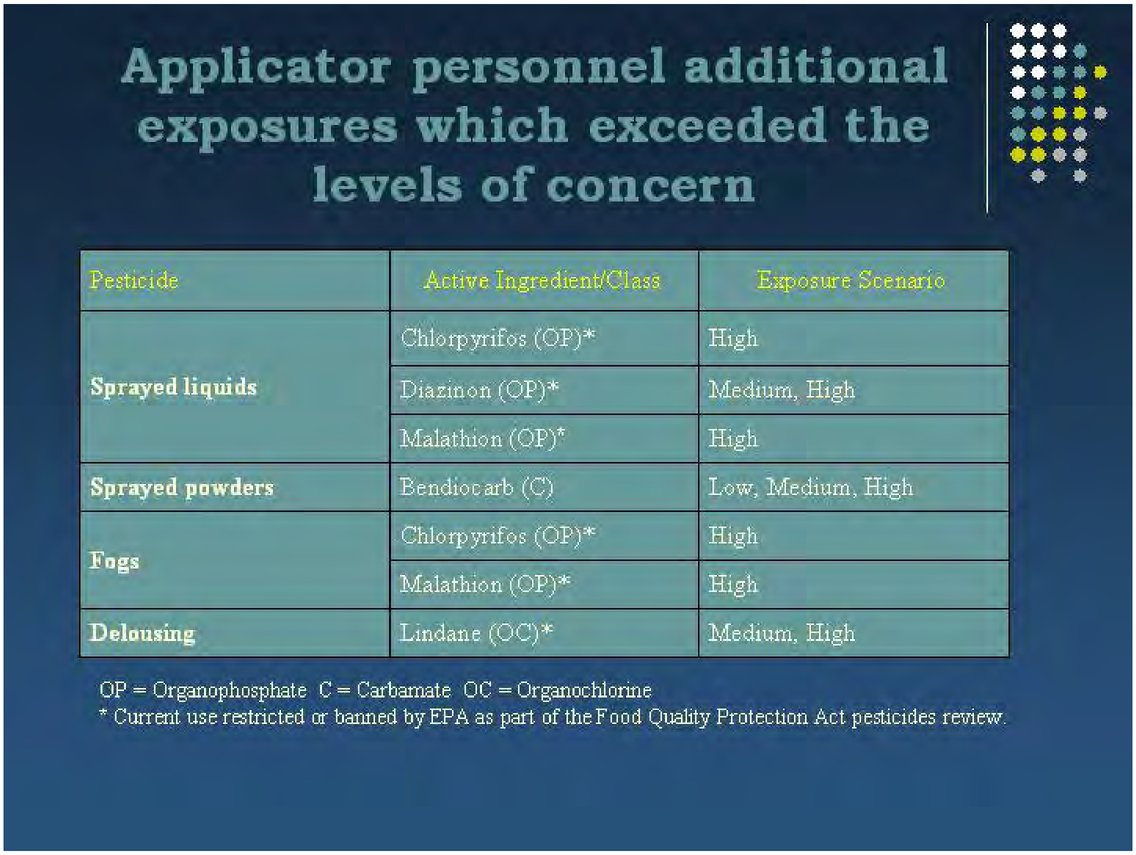
Figure 3. General military exposure levels reaching levels of concern

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.

Figure 4. Applicator exposure levels reaching 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

Study participants will include a subgroup of the 296 PCI veterans who were interviewed by OSAGWI 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 the Pesticide Cognition Study. All PCIs have been categorized as high or low exposed based on the exposure guidelines that were developed by the lead toxicologist, William Bradford of the OSAGWI Environmental Exposures Report-Pesticides (table 4). In addition, BEHC 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 4. 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 (≥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 Boston investigators 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. For the current Pesticide MRI Study, 30 PCIs will be recruited from the original 159 PCIs in the pesticide cognition study described above. The pesticide cognition study cohort is now well-characterized in terms of demographics and exposure histories. Mean age for this cohort is 47.7 years and mean educational attainment is 15.9 years including 13% women. Exposure classification developed during the pesticide cognition study will be used during the proposed pesticide MRI study and includes a dichotomous high/low categorization for pesticide exposure and a yes/no dichotomous variable for Khamisiyah notification (presumed low-level sarin exposed). Fifteen PCIs will be included in the high-pesticide exposed group and 15 PCIs will be included in the low-pesticide exposed group. Each PCI has been categorized as high or low pesticide exposed based on telephone interviews with OSAGWI and in-person interviews with Boston investigators. Through the ongoing pesticide cognition study with Boston investigators, PCIs have 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 have 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, structural MR imaging will be performed with a subgroup of 30 of the previously described PCI veterans. As these PCI veterans currently reside in various states around the country, study participants will be 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 will be able to complete the study based on larger PCI population densities in particular states including Missouri, Texas, Tennessee and Florida. See the table below for a breakdown of potential study participants based on state of residence.

Table 5. 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.

Due to a slow start-up phase and the unanticipated departure of the study research assistant, recruitment efforts were delayed and the first recruitment trips are currently scheduled for late April in Springfield, MO at the Springfield Neurological Institute Imaging Center where 12 study participants are anticipated to be recruited. The second recruitment trip is scheduled for early May at the Apex Imaging Center in Euless, Texas where it is anticipated that an additional 8 study participants will be recruited. Additional recruitment efforts are planned for Hermitage Imaging Center in Nashville, Tennessee where 8 study participants are anticipated in mid-May and at the Arlington Imaging Center in Jacksonville, Florida in late May to complete the recruitment phase of the study. A six month no-cost extension was requested in order to complete this study by the fall with the data cleaning and analysis being performed throughout the summer months and the final report being submitted in October. Study recruitment will be the utmost priority in the coming months in order to complete this project. In order to complete this phase, Dr. Krengel will commit 50% time to this project during the next two months to accomplish this goal.

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

Neuroimaging procedures

Volumetric measures of brain tissues will be obtained from each subject with the use of MRI scanning. Conventional MR images will be 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 will be acquiring 4 scans from each subject in one session lasting approximately 45 minutes. The types of scans we will acquire and the utility they provide are as follows:

1) A three-dimensional scout image. The images from this sequence will allow 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 will provide 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 allows segmentation of the brain into white and gray matter.
4) An axially acquired, fluid attenuated inversion recovery scan (FLAIR). This scan will also be acquired with a 3 mm slice thickness with no gaps between images. This scan will allow us to verify any regions of ischemia in the white matter of the brain.

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

As described above, due a slow start-up phase, the recruitment goals have not been met at this time. However, a recruitment plan has been made and will proceed as planned as top priority for the next two months until the recruitment goal of obtaining MRI images with 30 study participants is complete. In order to complete this phase, Dr. Krengel will increase her time to 50% time during the next two months to accomplish this 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 will be used to assess the relationship between white matter volumes and manual speed, visuospatial function and new learning. Participants will all also complete a questionnaire relating to health symptoms, a mood scale, and a structured interview to document any lasting psychiatric diagnoses. These data will be 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 is blind to the exposure status of the subject will administer 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, 1997). 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 (Wechsler, 1997), and the Boston Naming Test (Kaplan, Goodglass & Weintraub, 1983). Since these tests were already performed in the ongoing pesticide cognition study, and an assessment of native intellectual ability has been ascertained for these individuals, these tests will be omitted from the proposed brief cognitive battery.

Sustained attention is 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 (Letz & Baker, 1988). 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 will be 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 (Mathiowitz et al., 1985). Previous studies of occupational pesticide exposure have documented changes in reaction time and motor speed (NCTB). Therefore, we predict decreased CPT reaction time performance in the high-exposed PCI group and motor slowing on the additional measures will correlate with cerebral and subcortical white matter volumes.

The test battery also includes 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 will be treated as an outcome measure rather than as strictly a potential confounding variable.

In order to assess visuospatial processing, we will administer the Rey-Osterrieth Complex Figure Test (Corwyn & Blysma, 1993) and document total scores for the copying subtest (raw score out of 36). We expect that individuals with increased exposures will 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 will be correlated with volumetric measures of basal ganglia structures (caudate, putamen). In addition, the Stanford Binet copying task will be used in this test battery to document further impairment in visuoconstruction as has been found in our prior research of neurotoxicant-exposed groups (Terman & Merrill, 1973). The total score for copying (out of 16 possible) is expected to be diminished in those who have higher OP pesticide exposures and to be correlated with white matter volumetrics.

Individuals who have documented exposures to neurotoxicants (including OP pesticides) have had difficulty in the areas of acquisition and retrieval. Therefore, we will be examining verbal and nonverbal 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 will also assess the correlation of these test scores with both white matter volumes and subcortical structures. Lastly, a measure of response consistency will be 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) will be computed and we expect 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 current PCI cognition study.

A description of the neuropsychological domains and the complete neuropsychological test battery are presented in the tables below followed by a description of the study instruments and procedures.

Full Neuropsychological Test Battery.		
TEST NAME	**DESCRIPTION**	**OUTCOME MEASURE**
I. Executive System Functioning		
Controlled Oral Word Association Test (FAS letters)	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) Subjects will be administered the Structured Clinical Interview for DSM-IV (Spitzer et al., 1990) and a current Global Assessment of Functioning score will be assessed. This instrument has demonstrated reliable psychometric properties for determining the presence or absence of current or past major Axis I disorders. Dr. Krengel will also administer 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 will fill out a series of self-report, paper and pencil measures designed to confirm and define symptoms of PTSD (PCI) (Keane at al., 1988). 2) Dr. Krengel will also conduct 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 will be asked questions specifically related to recent occupational history (including possible occupational exposure to neurotoxicants), family history of psychiatric disorder, and life stressors. Subjects will complete a symptom checklist consisting of a comprehensive list of frequently reported health and mental health symptoms. A complete description of the study questionnaire is listed in the table below.

As described above, due a slow start-up phase, the recruitment goals have not been met at this time. However, a recruitment plan has been made and will proceed as planned for the next few months until the recruitment goal of obtaining neuropsychological and clinical interviews with the 30 study participants is complete. This will be the utmost priority in order to complete this pilot project and submit the final report by October 14, 2009.

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.

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 will be 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.
- Recruitment trips have been planned to insure the attainment of the recruitment goal of 30 study participants for this study protocol and a plan is in place to complete the data analyses in order to submit the final report in the fall.

REPORTABLE OUTCOMES:

Publications

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, 2009:34.

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

Funding:

1. Drs. Krengel and Sullivan submitted two recent 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 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 recommended for funding.

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.

CONCLUSIONS:

Two recent studies of Gulf War veterans by Boston University investigators have shown lower brain white matter volumes in Gulf War veterans with (1) exposure to the Khamisiyah weapons depot (and potential exposure to low level sarin/cyclosarin) and (2) higher reported health symptoms from shortly after the time of the Gulf War. These recent findings suggest that an objective biomarker for Gulf War illness may be attainable through conventional structural MRI and morphometric analysis of the images. The results of the current study will be able to compare whether brain imaging differences exist between a unique group of Gulf War veterans with known AChE inhibitor exposures through their military occupation as pesticide applicators. Recent reports of OPs and oxidative stress lead support to the theory of mitochondrial dysfunction in Gulf War veterans (Golomb, 2008) which could be a potential mechanism for these findings. This study will be able to assess whether the theory that AChE inhibitors including organophosphate pesticides have contributed to the chronic health effects in Gulf War veterans and potentially lead to viable treatment options.

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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 GWI 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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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