Research Advisory Committee on Gulf War Veterans' Illnesses

June 18-19 2012, Committee Meeting Minutes

Department of Veterans' Affairs
Washington, DC

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Attendance Record

Members of the Committee

James Binns, Chairman
Roberta White, Scientific Director
Beatrice Golomb
Anthony Hardie
Marguerite Knox
William Meggs
James O'Callaghan
Lea Steele

Committee Staff

Kimberly Sullivan, Associate Scientific Director
Arpita Husain

Designated Federal Officer

Victor Kalasinsky

Guest Speakers

Dane Cook
Robert Haley
Apostolos Georgopoulos
Alvin Terry
Diane Rohlman
Christopher Brady
Rodney Johnson
Lisa Conboy
Britta Holzel
Chenchen Wang

VA Office of Research and Development
Robert Jaeger
Victor Kalasinsky

Abbreviations

ACTH - Adrenocorticotropic Hormone

AChE – Acetylcholinesterase

ALS - Amyotrophic Lateral Sclerosis

CBT – Cognitive Behavioral Therapy

CFS – Chronic Fatigue Syndrome

CMP – Chronic Muscle Pain

DLPFC - Dorsolateral Prefrontal Cortex

DoD – Department of Defense

DTI – Diffusion Tensor Imaging

FA - Fractional Anisotropy

fMRI – Functional Magnetic Resonance Imaging

GW – Gulf War

GWI – Gulf War Illness

HPA – Hypothalamic-Pituitary-Adrenal

IOM – Institute of Medicine

MAVERIC – Massachusetts Veterans Epidemiology Research and Information Center

MD - Mean Diffusivity

MEG - magnetoencephalography

MRI – Magnetic Resonance Imaging

OEF/OIF – Operation Enduring Freedom/Operation Iraqi Freedom

ORD – Veterans Affairs Office of Research and Development

PAG - Periaqueductal Grey

PB – Pyridostigmine Bromide

PPI - PsychoPhysiological Interaction

PTSD – Post-Traumatic Stress Disorder

RAC – Research Advisory Committee on Gulf War Veterans' Illnesses

RAS - Reticular Activating System

RFA – Request for Application

TCM – Traditional Chinese Medicine

VA - Veterans Affairs

VHA – Veterans Health Administration

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
June 18-19, 2012
Boston University Medical Campus, 80 East Concord Street, Room 109, Boston, MA

Agenda
Monday, June 18, 2012

8:00 – 8:30	**Informal gathering, coffee**	
8:30 – 8:35	**Welcome, introductory remarks**	**Mr. Jim Binns, Chairman** **Res Adv Cmte Gulf War Illnesses**
8:35 – 9:15	**Diffusion Tensor Imaging (DTI) in Gulf War Veterans with Chronic Pain**	**Dr. Dane Cook** **William S. Middleton Mem Veterans Hospital**
9:15 – 10:15	**fMRI reveals abnormal central processing of sensory and pain stimuli in ill Gulf War**	**Dr. Robert Haley** **University of Texas Southwestern Veterans**
10:15 – 10:30	**Break**	
10:30 – 11:15	**MEG imaging Patterns in Gulf War Illness**	**Dr. Apostolos Georgopoulos** **Minneapolis VA Medical Center**
11:15 -12:15	**Functional consequences of repeated organophosphate exposure: potential non-cholinergic mechanisms**	**Dr. Alvin Terry** **Georgia Health Sciences University**
12:15 – 1:15	**Lunch**	
1:15 – 2:00	**Meta-analysis of Cognitive effects from Organophosphate exposures**	**Dr. Diane Rohlman** **Oregon Health Sciences University**
2:00 – 2:45	**Gulf War Brain Bank Update**	**Dr. Christopher (Kit) Brady** **VA Boston Healthcare System**
2:45 – 3:00	**Break**	
3:00 – 5:00	**VA Gulf War Research Program: Update and Discussion**	**Mr. Jim Binns, Chairman** **Res Adv Cmte Gulf War Illnesses**
	ORD: strategic plan, FY2013 budget, RFA's, other initiatives	**Dr. Victor Kalasinksy** **Dr. Robert Jaeger** **VA Office of Research and Development**
	OPH: An Overview of OPH's Gulf War Activities	
5:00 – 5:30	**Public comment**	

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
June 19, 2012

Boston University Medical Campus, 80 East Concord Street, L109, Boston, MA

Agenda

Tuesday, June 19, 2012

8:00 – 8:30	**Informal gathering, coffee**	
8:30 – 9:15	**From inflammation to sickness and Cognitive dysfunction: when the Immune system subjugates the brain**	**Dr. Rodney Johnson University of Illinois, Urbana**
9:15 – 10:00	**The effectiveness of acupuncture in the Treatment of Gulf War Illness**	**Dr. Lisa Conboy The New England School of Acupuncture**
10:00 –10:45	**The effects of mindfulness practice on the neurobiology of pain processing and emotion regulation**	**Dr. Britta Holzel Massachusetts General Hospital Harvard Medical School**
10:45 –11:30	**A randomized trial of Tai-Chi For fibromyalgia treatment**	**Dr. Chenchen Wang Tufts University School of Medicine**
11:30 – 11:45	**Break**	
11:45 – 12:15	**Structural MRI in Military Pesticide Personnel from the Gulf War**	**Dr. Kimberly Sullivan Dr. Maxine Krengel Boston University School of Public Health**
12:15 – 1:00	**Committee discussion**	**Mr. Jim Binns, Chairman Dr. Kimberly Sullivan Res. Advisory Cmte Gulf War Illnesses**
1:00 – 1:30	**Public Comment**	
1:30pm	**Adjourn**	

DAY 1

The June 18th, 2012 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (hereinafter referred to as the Committee) was held in Room 109A/B at the Boston University Medical Building, 80 East Concord Street, Boston, MA.

Welcome, Introductions & Opening Remarks

Mr. James Binns, Committee Chair

Chairman James Binns called the meeting to order at 8:30 AM. He thanked the speakers, the Committee members and the public for coming and Boston University for holding the meeting. Dr. Kimberly Sullivan, Associate Scientific Director of the Committee, then introduced the first speaker Dr. Dane Cook.

Diffusion Sensor Imaging (DTI) in Gulf War Veterans with Chronic Pain

Dr. Dane Cook, William S. Middleton Memorial Veterans Hospital

Dr. Cook said that the focus of his research was to analyze the influence of physical activity and exercise on brain mechanisms of pain, fatigue sensitivity and regulation in health and disease. He indicated that chronic muscle pain (CMP) was considered one of the major factors of GWI and follow-up data illustrated that these symptoms had not been resolved in many veterans (See Appendix A- Presentation 1). Dr. Cook stated that the main question in his research was whether central nervous system dysregulation explained the persistent health symptoms experienced by veterans with GWI. He stated that his previous data showed that GW veterans with CMP were more sensitive to heat pain than healthy GW veterans and they became more sensitive following acute exercise**.** Dr. Cook also showed fMRI data that demonstrated augmented brain responses to mild, moderate and strong heat pain stimuli in GW veterans with CMP. The results showed that brain responses to mild, moderate and strong pain stimuli for a representative healthy veteran showed a dose-response relationship within the insula and motor regions of the brain. Brain responses to mild, moderate and strong pain stimuli for a GW veteran with CMP showed that there was no such dose-response relationship.

Dr. Cook also discussed new data from his studies with fibromyalgia (FM) patients that showed relationships between physical activity and sedentary behaviors and pain processing. The results showed that greater physical activity behaviors were positively associated with brain responses in regions involved in pain inhibition during pain modulation in FM. His results also showed that sustained sedentary behaviors were negatively associated with brain responses during pain modulation. The greater the sedentary behaviors, the less activity that was noted in pain modulatory brain region during a pain modulation task. Dr. Cook remarked that for those veterans who were very sick, that decreasing sedentary behavior would be a good step towards changing nervous system processing of pain.

Dr. Meggs asked Dr. Cook how he measured pain modulation. Dr. Cook said that while the patients were lying in the magnet, he delivered painful stimuli either alone or while they tried to do a cognitive task at the same time. Their instructions were to pay attention to the cognitive task and to work as efficiently and accurately as possible. He gave them a painful stimuli and the cognitive task would distract the patient from the painful stimulus as they paid attention to the cognitive task.

Dr. Cook stated that psychophysiological interaction (PPI) analyses were conducted which looked at the interaction between the psychological task, in this case brain responses to pain stimuli, and activity in a seed region on fMRI. The results showed negative relationships for controls between the periaqueductal grey (PAG) and sensory brain regions and a positive relationship between the insula (sensory integration region) and the dorsolateral prefrontal cortex (DLPFC); a region heavily involved in descending pain control. He remarked that these relationships were absent in FM patients. Dr. Cook said that patients with CMP were more sensitive to pain and were less efficient at regulating pain which could have been caused by poor communication between brain regions involved in descending pain control.

He remarked that the next step in research was to use DTI to measure the integrity or damage of the neuronal connections between brain regions. He explained that DTI was an imaging modality that provided information about the diffusion of water in biological tissues. He explained that this allowed researchers to use DTI to measure the integrity of brain white matter, following the logic that reduced anisotropy (greater random motion of water molecules) reflected less axonal integrity. White matter integrity was generally indexed by fractional anisotropy (FA) which measured the extent to which water diffuses in a non-isotropic manner and the inverse of this was mean diffusivity (MD), which measured the total diffusion within each voxel. When one had high FA values in healthy white matter, it was suggestive of dense axonal packaging, high myelination, and large axonal diameter which were all indicative of healthy information processing. If one had low FA values, it was suggestive of axonal degeneration and demyelination. Low MD values were suggestive of dense axonal packaging and high myelination. High MD values were suggestive of axonal degeneration and high myelination.

Dr. Cook's preliminary DTI data demonstrated decreased FA and increased mean diffusivity in GW veterans with CMP which was suggestive of poor white matter integrity. Healthy controls had healthier white matter in the cingulate gyrus and portions of the posterior corona radiata, postcentral gyrus and superior parietal lobule. GW veterans with CMP showed greater MD values compared to the healthy values which were suggestive of less white matter integrity along the corona radiata and near the middle frontal gyrus. Dr. Sullivan asked if the patients met the criteria for GWI or just chronic pain. Dr. Cook responded that they all met the criteria for CMP, and some of them met the criteria for GWI.

Dr. Cook's results concluded that GW veterans with CMP show decreased white matter integrity in several brain regions and white matter density was associated with fatigue and pain processing. For MD values there appeared to be opposite relationships in GW veterans with CMP and healthy GW veterans, which suggested altered communication along spinal tracts that were involved in pain processing and modulation. He indicated that a critical next step would be to determine whether potentially efficacious treatments of GWI influenced brain structure and function and whether these changes predicted illness improvement.

Dr. White asked if there were any relationships that he knew of with DTI and lupus. Dr. Cook indicated that he did not know of any relationships between the two, but he believed that there was at least one study reporting DTI results with lupus patients. Dr. Sullivan asked if he looked at inflammatory markers in his study and Dr. Cook responded that he had not collected these markers in this study. He remarked that he was collecting blood markers in another study and said that he definitely needed to bring in more peripheral markers into his studies as well. Mr. Hardie asked Dr. Cook what he thought the most important take-home message was from his results. Dr. Cook said that it seemed that there was a problem regulating pain centrally from patients with CMP. He said new data looking at the structure of the brain suggested that the reason for the dysregulation could be that the communication between regions involved in modulation was broken and the critical step was to determine what method would improve the health of GW veterans. Dr. Golomb asked if Dr. Cook's work was actually addressing the mechanisms for GWI. Dr. Cook responded that he was not sure if the results would be specific to only GWI but he thought it would be applicable to chronic widespread pain.

Dr. Sullivan asked Dr. Cook if he had looked at white matter differences across the brain and he confirmed that he had done a whole brain analysis. Dr. Meggs asked if Dr. Cook had used other painful stimuli in addition to heat. Dr. Cook replied that he had used pressure pain in the past but had not seen many differences between groups when he did that. Mr. Hardie asked if he was aware that heat sensitivity was an issue with MS patients, and what his thoughts were in relation to that mechanism. Dr. Cook responded that this could be related to demyelination, but he was not sure if that dealt directly with GWI or not.

Chairman Binns asked if Dr. Cook had any other thoughts on potentially useful treatments for GWI. Dr. Cook responded that he thought that anything that could reset the dysregulated system would be beneficial and that brain stimulation methods could be efficacious. He said the problem with drug therapies was that they really targeted just one or two systems, but he found that behavioral therapies affected multiple systems and seemed to be a more balanced approach.

Chairman Binns thanked Dr. Cook for his presentation and Dr. Sullivan then introduced Dr. Robert Haley.

fMRI reveals abnormal central processing of sensory and pain stimuli in ill Gulf War Veterans

Dr. Robert Haley University of Texas Southwestern

Dr. Haley first presented on his study regarding fMRI and Quantitative Sensory Testing (QST) with GW veterans (See Appendix A – Presentation 2). The QST protocol included a heat thermode strapped to the inner right forearm which delivered a warm sensation and heat pain sensation to the participant. The participant was put in the fMRI scanner and three runs of innocuous warm sensation were performed followed by three runs of heat pain sensation. The temperature of when the veteran first felt pain was taken, and then the temperature at which the veteran first felt warm was taken and then the point halfway between the two was also taken. The pain thermode setting was the temperature at which the veteran felt pain. Ten thermal stimuli were conducted at each run. The results showed that with sick veterans and healthy controls, there was no difference in the warm and heat pain detection thresholds.

Analyzing fMRI activation to innocuous warm stimulation in the clinical groups showed that patients with Haley GWI Syndrome 3 were no different than the controls while patients with Syndrome 1 and 2 showed generalized hypoactivation compared with prior studies of normal subjects. Dr. Haley concluded that GW veterans with Syndrome 1 and Syndrome 2 differed significantly from controls in different brain regions. Analyzing fMRI activation to noxious heat pain stimulation in the clinical groups showed that patients with Syndrome 1 and 2 had generalized hyperactivation compared with prior studies of normal subjects. Patients with Syndrome 1 and 2 showed significantly higher activation than controls in several brain areas. Dr. Haley then reported his fMRI findings in FM and PTSD patients.

Mr. Hardie asked what definition Dr. Haley had used for fibromyalgia. Dr. Haley replied that he used the survey definition which included pain on the left and right side above and below the diaphragm and in the axial skeleton.

Dr. Haley then discussed a study that analyzed event-related potential patterns associated with hyperarousal in GWI subgroups. This protocol included an electroencephalography (EEG) procedure. The results of this experiment suggested abnormal functioning of cholinergic inhibition in the Reticular Activating System (RAS) of the brainstem. Dr. Haley concluded that this finding was important because several of his prior studies had found abnormalities of cholinergic brain function in the brainstem of GW veterans.

Dr. Haley then discussed a recent paper that he had published regarding the validation of a research case definition of GWI. He described selecting a representative sample of Gulf War-era veterans with the final study sample consisting of 8,020 veterans. A Goodness-of-Fit statistical procedure was used and demonstrated a good fit to the national sample data, which Dr. Haley suggested led to a more validated case definition of GWI. In this analysis, GWI was four times more prevalent in the deployed than the non-deployed population. Dr. Haley then discussed

another research paper that was currently in revision. Results of this study showed that neurologic processing of sensory stimuli was abnormal in ill Gulf War veterans and the nature of this abnormality varied across the three Haley syndromes. He remarked that chronic pain in GWI may be due to damage to the RAS of the brainstem.

Dr. Steele asked Dr. Haley his views on Syndrome 2. He said he was unsure what caused it, but he did not think it was a problem with neurotransmitters and he thought that white matter may be at the main root of the problem in Syndrome 2.

Dr. Meggs asked how much overlap in symptoms Dr. Haley saw between the three syndromes in his patients. Dr. Haley responded that there were symptoms that overlapped but then there were groups that were very unique.

Dr. Golomb said that there could be cellular damage and dysregulation causing the differences in symptoms and that there could be differences in severity and stage of symptoms. Dr. Haley said that he believed that Syndrome 2 and 3 were related, and were maybe two stages of the same syndrome but he thought that Syndrome 1 was a different disease.

Dr. Sullivan asked if he looked at his DTI results in relation to where the FA differences were located within the brain. Dr. Haley responded that it was hard to comment on because locating white matter was difficult. The analysis was not straightforward, but a statistical group was inventing new statistical techniques to analyze the data. She then asked if he tried to correlate the data with health symptoms. He replied that he had not yet done that, since his laboratory still had not agreed on how to analyze the DTI findings.

Dr. Meggs commented that it was hard to analyze the white matter in the living brain, but he said that maybe he could map networks with the brains in the brain bank.

Chairman Binns asked Dr. Haley what he suspected would be the most useful therapeutic treatments. Dr. Haley responded that he did not know what the appropriate treatments would be since they needed to learn the mechanism of the disease better because he hoped to find a treatment through empirical experimentation. He thought a quick cost-effective diagnostic test needed to be developed first. Dr. Steele agreed that it would be a good idea to have an appropriate diagnostic test. Dr. Golomb also agreed, but she believed an appropriate diagnostic test should not have chemical introductions. Chairman Binns thanked Dr. Haley for his presentation and Dr. Sullivan introduced the next speaker.

MEG imaging Patterns in Gulf War Illness

Dr. Apostolos Georgopoulos Minneapolis VA Medical Center

Dr. Georgopoulos explained that a key advantage to using magnetoencephalography (MEG) was

that it directly measured neural activity of integrated synaptic activity, was very sensitive, and had high temporal resolution (See Appendix A – Presentation 2). Dr. Georgopoulos gave a brief overview about neural communications and said that neural communications were accomplished by ongoing, dynamic interactions among multiple neuronal connections.

Dr. Georgopoulos explained that the MEG instrument that he used in his studies measured magnetic signals in the brain. The MEG instrument reflected integrated synaptic activity of neuronal populations which provided a direct neural measure. It was not distorted and not delayed passing through tissues and therefore the results provided instantaneous information about brain events.

He discussed the Synchronous Neural Interactions (SNI) test which was a test that assessed dynamic brain function by evaluating neural interactions at high temporal resolution using MEG. The test itself was advantageous because it was simple, noninvasive, safe and reproducible. It was also sensitive to changes in brain function. He discussed the first application of the test, which was on a chronic alcoholic patient and he remarked that the SNI test had the prospect of becoming the first routine test for assessing dynamic brain function, aiding in differential diagnosis, monitoring disease progression, and evaluating the effects of treatment intervention.

For his current studies, Dr. Georgopoulos focused on subjects with GWI and PTSD. His research suggested that PTSD was a temporal lobe syndrome and that electrical stimulation of the temporal cortex in awake human subjects could elicit the re-enactment and reliving of past experiences. He hypothesized that PTSD reflected an involuntarily persistent activation of interacting neural networks involved in experiential consolidation. PTSD involved abnormal dynamic communication of brain areas mostly in the right hemisphere and that this miscommunication was graded with PTSD severity, primarily in relation to the flashback components.

His GWI study was designed to apply the SNI test to evaluate potential abnormalities in neural communication in GWI, when compared to control GW veterans. The results of his pilot study suggested that GWI was a distinctly separate entity but the current study needed to be extended to larger numbers.

Dr. White asked if he had a slide with the brain mapping of GWI. He responded that he did not yet but he would have it soon, and could send it to the Committee. Dr. Sullivan followed up saying that the Committee would be interested in seeing that pattern graphed. Dr. Steele further asked what the brain mapping for GWI looked like after the scan. He indicated that he did not run the scan yet, but when he did he would provide the data to the Committee.

Dr. O'Callaghan asked if he had a signature of aging in his studies. Dr. Georgopoulos responded that unfortunately no one really wanted to study normal aging, but this measure did not vary much with age.

Chairman Binns asked if he was in touch with the individuals who built the pieces of the MEG equipment to build more if this was determined to be a good biomarker for GWI. Dr. Georgopoulos said that he was in touch with the manufacturers and the cost was substantial, about a half million dollars per scanner to build new ones. Chairman Binns thanked him for his presentation, and Dr. Sullivan introduced the next speaker.

Functional consequences of repeated organophosphate exposure: potential non-cholinergic mechanisms

Dr. Alvin Terry Georgia Health Sciences University

Dr. Terry started his presentation with an overview of the basal forebrain cholinergic system and reviewed organophosphate (OP) pesticides before discussing his animal studies (Appendix A – Presentation 3). He stated that the focus of his lab was to determine the consequences of repeated, subthreshold exposures to representative organophosphates on cognitive function in animal models and to determine the consequences of repeated, low-level exposures to representative OPs on neurobiological substrates of cognitive function.

In his previous studies, he found that exposure to chlorpyrifos caused impairments in spatial learning, decreased expression of cholinergic marker proteins in the brain, decreased expression of neurotrophin-related proteins in the brain and impairments of anterograde and retrograde axonal transport.

Dr. Terry studied whether deficits in attention could be shown prospectively in OP exposure models. He discussed several behavioral tasks the rats completed for these studies. He summarized that repeated exposures to subthreshold levels of chlorpyrifos lead to protracted impairments of sustained attention and an increase in impulsive behaviors in rats. He studied primary cortical neurons by using specialized MitoTracker imaging measurements. He found a concentration-dependent decrease in the transport of mitochondria in axons, an increase in mitochondrial length, and a decrease in mitochondrial number which was indicative of increased fusion versus fission events. Importantly, he found that the neuronal changes occurred at OP concentrations that did not inhibit acetylcholinesterase (AChE) activity, was not blocked by cholinergic antagonists, and did not appear to be associated with directly toxic effects on mitochondria. The results suggested that an underlying mechanism of OP-based alterations in neurological function might involve alterations in mitochondrial dynamics and/or their transport in axons.

Dr. Sullivan asked if he looked at inflammatory cytokines in relation to the mitochondrial effects. He replied that his lab had not yet done that.

He then discussed his paper regarding behavioral data on the OP sarin surrogate (DFP) and the insecticide chlorpyrifos (CPF). He showed results of the effects of repeated exposures to CPF or

DFP on cholinesterase activity in the plasma and brain at various time points during a 45 day OP-free washout period. Results showed that repeated, subthreshold exposures to CPF and DFP lead to chronic deficits in spatial learning and memory and that insecticide and nerve agent OPs had differential effects depending on the cognitive domain evaluated.

Dr. Terry then discussed plans for his current and future studies. He explained that he would be using manganese-enhanced magnetic resonance imaging (MEMRI) studies to evaluate axonal transport with OP exposures. He said that manganese was a good contrast agent for MRI and it was known to be axonally transported. With this study, he hoped to determine the consequences of repeated subthreshold exposures to representative OPs on axonal transport in the living rat brain and to determine the consequences of repeated subthreshold exposures to representative OPs on myelin in the living rat brain. His preliminary data showed that repeated, subthreshold exposures to both insecticide and nerve agent OPs lead to protracted impairments of attention and memory-related behavioral tasks in animals. He also said that insecticide and nerve agent OPs may have differential effects on specific domains of cognition.

Dr. Terry concluded his presentation by listing some potential therapeutic strategies for GWI. He suggested that potential treatments could be cholinergic-based compounds, glutamate receptor antagonists, mitochondrial-targeted antioxidants, drugs that increase axonal transport, drugs that improve neurotrophin function and cytokine-based treatments.

Dr. Sullivan thanked Dr. Terry for his presentation, and said that his work was instrumental in showing that there could be chronic cognitive effects from chronic low level OP exposures. Dr. Sullivan said that she thought it was important that he was looking at the myelin effects in the hippocampus in his current study and she asked if he thought the OP exposure was affecting the myelin directly, or if it was affecting the axon, and then the axon caused effects on the myelin. He responded that he was not sure if he could comment on anything meaningful at this point in his study but there were a few papers that suggested that the axon needed to be properly myelinated for transport and he did not know whether OP's targeted oligodendrocytes or not yet. He said that he knew a lot about rat changes, but he needed to delve into the mechanisms to find out more. Dr. Sullivan responded that if he could target this question in his current study it would be very helpful in understanding the long-term effects of OP exposures.

Mr. Hardie commented that he got the sense that some of the folks involved in GWI research did not have a real clear picture of the level of pesticide exposure that GW veterans were exposed to and he said that some people believed that the extent was that a pesticide truck drove by once in a while. He said that it was much more than that and that some pesticides were not intended on the skin, and troops were spraying them onto their skin as well. Dr. Haley added that it was important to know the real level of pesticide exposure from the GW deployment, which was not easy to find out. Dr. Golomb said that there was also a lot of inhalation exposure during the war

as well.

Dr. Steele said that epidemiological studies showed that chronic low-level exposure was a risk factor for GWI. Dr. Steele then asked if the rats in Dr. Terry's studies were exposed to one and/or two exposures, or if they were exposed to a low level of exposure over a specific time period. Dr. Terry responded that in the early studies with chlorpyrifos, it was a certain dosage over a week but he had not looked at low doses chronically.

Chairman Binns mentioned that there had been theories that metabolites from the original exposures may still be sequestered in the fat of individuals and that might explain ongoing symptoms in some individuals. Dr. Terry responded that he thought that theory was possible. He said that he had done some work with an analytical chemist but it was only with certain metabolites. He said that they have not done the studies that Chairman Binns was asking about over a long period of time but the EPA was interested in those studies. Chairman Binns thanked Dr. Terry for his presentation and then called a lunch break.

Meta-analysis of cognitive effects from organophosphate exposures

Dr. Diane Rohlman Oregon Health Sciences University

Dr. Rohlman started her presentation with a review of the literature on low-dose OP exposures in humans. Most of these studies focused on occupational groups including agricultural workers (Appendix A – Presentation 4). She stated that the majority of studies reported neurobehavioral differences in exposed occupational groups, and were predominantly focused on adults. Although most studies reported at least one cognitive decrement on psychometric testing, many studies reported several cognitive decrements in these exposed groups. However, some studies reported no cognitive differences between exposed and unexposed groups.

Dr. Rohlman explained that the variations in study results could be caused by a lack of standardization across studies. For example, even within the same test, different parameters and administrations could have been used that caused different end results (i.e. computer vs. pencil and paper administration). Populations with low education or with limited computer literacy, or cultural differences also could cause discrepant findings among studies. She added that most of the studies were cross-sectional designs and cross sectional designs may also not provide information about previous chronic exposures.

Dr. Rohlman stated that despite the differences, her meta-analytic review of 24 studies indicated deficits in exposed vs. control subjects in several functional domains. She organized measures used in the studies into functional domains including motor speed/coordination, information processing speed, complex visual motor/executive function, and memory. Nineteen of the twenty-four studies that she reviewed showed that occupational exposures to OPs were associated with neurobehavioral deficits. However, a relationship between OP dose and

behavioral deficits had not been defined in humans. Only two of twenty-four studies had demonstrated a link between neurobehavioral performance and current biomarkers of OP exposure: blood cholinesterase (ChE) activity and urinary levels of OP metabolites.

Dr. Rohlman stated that there were potential reasons for the lack of correlation between biomarkers of OP exposure and neurobehavioral deficits. She said that the lack of correlations could be caused by incomplete information on pesticide formulations, or lack of detailed data on workers' exposure history. She remarked that there could have been genetic differences in the expression and/or activity of enzymes that metabolize OPs or that proteins that scavenge OPs differentially influence peripheral versus central outcomes.

She hypothesized that OP-induced neurobehavioral deficits were dose-related and that biomarkers based on alternative, non-cholinergic mechanisms would be better predictors of OP neurotoxicity. The two biomarkers she chose to focus on were oxidative stress and inflammation.

She then discussed her study of agricultural workers involved in CPF application on cotton fields located in Menoufia, Egypt. She remarked that this population was unique because they followed the same pesticide application series for many years and they had a standardized application regimen. The cohort consisted of applicators, technicians and engineers. Applicators applied CPF using a backpack sprayer. Technicians walked with an applicator to direct the path of the applicator and point out heavy insect infestation. Engineers periodically walked the fields but more often directed application from the edge of the fields.

Human exposure was quantified by collecting participant blood and urine as biomarkers and then comparing neurobehavioral deficits to assess if they were associated with the biomarkers. Novel biomarkers in the rat model were analyzed for the behavioral effects assessed in humans with the novel biomarkers of oxidative stress and inflammatory markers.

She stated that CPFs and pyrethrin were applied to the cotton that was planted in the summer months. In June prior to the application, Dr. Rohlman's team performed neurobehavioral testing, and collected blood and urine from applicators to assess biomarker levels. She repeated this testing in June and July, twice in August, and again in September. Session 1 was the pre-application season, Session 2-4 was during the season and session 5 was post-season. Applicators differed from technicians and engineers in sessions 1-4 but the technicians did not differ from engineers in sessions 1-4. There were no differences at session 5 collected in September, over 1 month after the season ended. Looking at plasma cholinesterase, mean values of AChE activity ranged from 94-99% of baseline, and samples from controls were 100% at baseline. Applicators had more cholinesterase inhibition at sessions 2 and 3 than the technicians and engineers but they did see recovery at session 5.

Dr. Golomb then asked if applicators often went on to become technicians. Dr. Rohlman responded the applicators and technicians sometimes changed positions but the engineers did

not.

Dr. Rohlman gave a brief overview of the neurobehavioral test battery that she conducted with the applicators. The cohort performed the Trail Making Test (TMT); an attention task involving complex visual scanning with a timed motor component. Data analysis included regression models that compared performance for time points of sessions two through five. Controls performed the TMT faster than applicators at all time points assessed. The controls performed faster than technicians and engineers at Session 2 only. The engineers and technicians performed the TMT faster than applicators. The engineers and technicians did not differ from each other on this task.

Dr. Jaeger asked if the cotton workers used any personal protective equipment. Dr. Rohlman responded that no personal protective equipment was used because of the hot weather and it was expensive. She said that previous studies show that the workers had mostly dermal exposures, so respirators were also not provided. Dr. Golomb added that even though it was mostly dermal exposure, there could be respiratory concerns as well.

Dr. Rohlman concluded that neurobehavioral deficits in cotton workers exposed occupationally to CPF were dose-related and that ChE inhibition and urinary metabolite levels were associated with exposure but do not correlate well with neurobehavioral deficits. She added that inflammatory biomarkers were not likely to be effective biomarkers of OP-induced neurotoxicity and that she felt that biomarkers of oxidative stress showed potential as biomarkers of OP-induced neurotoxicity.

Dr. White thanked Dr. Rohlman for the presentation. She pointed out that Dr. Rohlman used the word deficit in her presentation and she said that when GW veterans are tested, they may or may not have what is clinically considered a deficit, and they generally show a decrement of function across domains. She then asked Dr. Rohlman if she saw a deficit or a decrement in the Egyptian pesticide applicators. Dr. Rohlman replied that that there was a deficit in her cohort and she said that Dr. White was right that the definition of deficit needed to be more precise. Dr. White suggested that she could define the degree of deficit by comparing it to the controls.

Dr. Steele asked if the two markers for oxidative stress were in the brain and Dr. Rohlman responded that they were brain markers. Dr. Sullivan asked how long after the exposures that the study of these biomarkers were assessed. Dr. Rohlman said that she looked at this immediately after the study was over. Dr. Sullivan suggested that perhaps oxidative stress markers were early markers and it could be possible that inflammatory markers would show at later time points.

Dr. Meggs said that it was curious that pre-season urinary metabolites were higher than post-season, and he asked her if there was an explanation for that. She said that this data was from 2009, and that there was an unusual infestation, so people were applying before the actual season. Going into the

season, applicators had elevated urinary metabolite levels. They replicated this study in the following year and saw lower levels in the pre-season. Dr. Sullivan asked how long the urinary metabolites levels lasted in the body. Dr. Rohlman responded that they lasted roughly 48 hours.

Dr. Steele asked if there were similar studies for people who hadn't been exposed for a while but had a history of persistent exposure, and if these people still retained the cognitive decrement. Dr. Rohlman confirmed that this was the case and that there had been a number of studies that had looked at people who had been poisoned and they did have lasting deficits as well as people who had been chronically exposed over time and also showed deficits when they had been tested. She said that in another study she conducted with adolescent applicators, they were followed for ten months and she did see clear elevations of urinary metabolites in that group.

Dr. Steele asked Dr. Rohlman based on what she had seen in those adolescents, if the effects were more marked in the younger brains. Dr. Rohlman said that she has not looked at that, but it was a good hypothesis. She said that studies with children that had assessed prenatal exposure saw a correlation with the biomarker. Post-natal exposures and exposures with adults were not associated with the biomarkers. She said that you could also argue that the brain is more robust in the developed brain and it may be more protective, which was one of the questions they were trying to look at in her current studies. Dr. Golomb responded that with older age, there could be more mitochondrial dysfunction and more free radicals. She said that there were some studies in GW veterans in which those that are older were more affected with symptoms.

Chairman Binns thanked Dr. Rohlman and Dr. Sullivan then introduced the next speaker, Dr. Christopher Brady.

Gulf War Brain Bank Update

Dr. Christopher (Kit) Brady VA Boston Healthcare System
Dr. Neil Kowall VA Boston Healthcare System

Dr. Brady said that The VA National Registry of Veterans with ALS and VA Biorepository Brain Bank (VABBB) was developed by VA in response to findings that linked ALS to deployment to the Persian Gulf and military service in general (Appendix A – Presentation 5). The Brain Bank was coordinated at the Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC) at the VA Boston Healthcare System (VABHS). He explained that the veterans or next-of-kin received regular follow-up from VABBB staff and that the tissue was analyzed, processed and stored at the Southern Arizona Core Tissue Laboratory (SACTL) at the Southern Arizona VA Healthcare System (SAVAHCS) in Tucson, AZ. The diagnostic neuropathological analyses were conducted at the VA's in Bedford and Boston. He said that tissue and data was regularly being released to research investigators who requested it. Dr. Sullivan asked Dr. Brady how much tissue had been released to researchers to date. Dr. Brady said that the VABBB had released tissue to about four investigators. Dr. Steele asked how many

brains were in the bank. Dr. Brady responded that 88 brains were in the ALS brain bank. Dr. Sullivan asked if he knew how many brains were from GW veterans. He said that he believed there were four or five enrolled in the bank. He added that the VABBB had developed a National Tissue Recovery Network. This network consisted of VA and non-VA pathology departments in 47 states.

He then reported that there was a 55% success rate in consenting referrals, a 100% success rate in tissue recovery when they were contacted by next-of-kin and an 88% success of recovered tissue of high quality for research. He stated that this model was adapted to develop the Gulf War Veterans' Illnesses Biorepository (GWVIB) 2-year pilot study (CSP501B).

Dr. Brady said that new challenges for the development of the GWVIB was for GWVIB to be open to all 1990-1991 Gulf War veterans regardless of whether they receive care at the VA or not. Another issue was that the GWVIB was not sure of the research tissue needs of investigators and they needed to locate where the greatest numbers of GW were located as well. Dr. Brady used VISN level data to find out where the greatest numbers of sick GW veterans were located to ensure that contractors were located in those areas for tissue recovery. Data showed that many sick GW veterans were concentrated in the southeastern US. Dr. Brady reported that the VABBB network was well developed in this region and throughout the US. Dr. Brady then addressed the question of the tissue needs of investigators. He stated that the value of postmortem CNS tissue had already been established via feedback from the RAC-GWVI and from the literature. The literature suggested that accurate diagnoses of neurodegenerative diseases could only be obtained through post-mortem pathology and tissues were necessary for clinico-pathological correlation. Dr. Brady mentioned that the need for non-CNS tissue had not been established and that collecting non-CNS tissue presented considerable logistical hurdles. There were issues with packaging, shipping and processing the tissues. He mentioned that non-CNS tissue collection could be considered in the future if the need arose but for now the biorepository would focus on CNS tissue primarily.

Dr. Brady announced that the website was going live on July 9, 2012 for veterans to sign up to donate their postmortem brain tissue and he provided website and contact information for veterans interested in getting more information about tissue donation. Dr. Brady also planned to post this information on GW veteran web sites and newsletters, and to provide outreach to veteran organizations.

Dr. Brady then discussed the tissue processing and storage procedures. After the tissue specimen was prepared, gross analysis and brain sectioning was performed and frozen. A neuropathology report was generated and then distributed for each tissue sample. Tissue Matrix data storage was used to track data to the slide level and included information including where the tissue came from, cause of death and tissue quality. Distribution of tissue and data to the investigators interested in the tissue is then performed.

He concluded by explaining the details of the review committee that determines who will receive the tissue donations for research purposes. Monthly meetings were held to review submissions and notify investigators if they would receive the requested tissue. Dr. Steele asked if VA and non-VA investigators could request tissues. Dr. Brady responded that any researcher could request the donated tissue.

Dr. Sullivan asked if the biorepository only had funding for two years. Dr. Brady confirmed that was the case. He said that even if somehow they did not receive any brains over the first two years of funding, they would still have a lot of useful data from the enrollees. Dr. Golomb said an issue was that if she were a veteran, the idea that it might only last for two years and that their contribution might end up not being that meaningful could be an inhibiting factor.

Chairman Binns then asked if Dr. Brady could report back to the Committee on the number of GW veteran brains that were currently in the brain bank. Dr. Sullivan then asked if the brain bank had back-up power for the freezers. Dr. Brady indicated that there was back up power and alarms for the freezers. Dr. Golomb said that they had alarms in San Diego and when she had been away for a trip that the power had gone out and the back-up generators were on but they still lost about $5 million dollars' worth of research tissue. She suggested that adequate procedures be devised ahead of time so that this would not happen with the VA brain bank.

Dr. Steele asked about the follow-up measures with enrolled GW veterans. She noted that with people with ALS, a check-up every 6 months to a year was fine since it was a neurodegenerative disease and they would pass away fairly soon compared to those with GWI. She said that if GWI veterans were dying slowly from GWI and it may be a slow time frame of mortality that could involve 10 to 20 years, that her concern was that a two year funding period would not capture many of these potential postmortem tissue samples. Dr. Brady said that he tried to recruit very sick folks and prioritize enrollment, but they would obviously take anyone that would be interested in enrolling to donate tissue.

Mr. Hardie said for those who have suffered from GWI, many have remained service oriented and if their participation in this effort could make a difference for future generations of veterans, he thought that this was something that he and other veterans would be strongly in favor of.

Chairman Binns thanked Mr. Hardie for his comments and Dr. Brady for his presentation and then announced a short break.

VA Gulf War Research Program: Update and Discussion & ORD: strategic plan, FY2013 budget,RFA's, other initiatives

Chairman Binns started the afternoon discussion session by thanking the representatives from the Office of Public Health (OPH) and Office of Research Development (ORD) for being able to

attend the meeting. Before hearing their presentations, he wished to provide an overview of the various issues that had come up in the past five months, since the Committee's last meeting, regarding the Department of Veterans Affairs and Gulf War Illness Research.

He first reviewed the VA budget for Gulf War illness research. On February 13th, the Department of Veterans Affairs and other departments of the US government released their budgets of Fiscal Year 2013. The VA budget showed that the GWI budget for 2012 was $15 million and the budget request for 2013 was $4.86 million.

Regarding the VA Gulf War Research strategic plan, Chairman Binns said that the purpose of the plan was to set a new course for VA Gulf War illness research. This plan was discussed in detail at the last meeting of the Committee. However, VA ORD has now given the Committee a new version of the plan to which many changes have been made. For example, an important change to the plan was the deletion of the following language:

"The IOM report concluded with a call for 'a renewed research effort with substantial commitment to well-organized efforts to better identify and treat multisymptom illness in Gulf War veterans . . . to alleviate their suffering as rapidly and completely as possible.'

In the preface to the IOM report, the chairman of the IOM committee, Dr. Stephen Hauser, a former president of the American Neurological Association, emphasized the need 'to speed the development of effective treatments, cures, and, it is hoped, preventions.' He stressed that the committee regarded this goal as achievable: 'We believe that, through a concerted national effort and rigorous scientific input, answers can likely be found.' "

In place of this language, Chairman Binns noted that ORD had added the following language:

"VA is committed to studying and treating chronic multisymptom illness and any other conditions affecting Gulf War Veterans. No Veteran should feel that his/her particular ailment is less important to VA than any other"

Chairman Binns indicated that with this statement, the budget request of $4.86 million for fiscal year 2013 would not have to be spent on GWI research at all. Rather than a focused program to implement the recommendation of the IOM, the plan had become a license for ORD to spend "Gulf War" research money on any illness found in Gulf War veterans, even where Gulf War veterans represent a small fraction of the veterans with the illness. This represented a continuation of ORD's past practice of overstating the amount of Gulf War research in reports to the Committee, the Secretary and Congress.

Chairman Binns then stated that, following legislation passed by Congress in 2010, VA's Office of Public Health had contracted with the IOM to do a new study of treatments for chronic multisymptom illness in Gulf War veterans. He reminded the Committee that the 2010 IOM

report confirmed that GWI was not a psychiatric illness, and that since the issuance of the Committee's first report in 2004, Department of Veterans Affairs' policy was to fund no research based on premise that the underlying cause of GWI was psychiatric. However, at a public meeting of the new IOM committee in February 2012, five of the eight speakers selected to speak made presentations that implied that chronic multisymptom illness in Gulf War veterans is psychiatric. This agenda was very troubling, in view of the fact the IOM's own recent report had concluded otherwise. It was not conceivable that IOM staff would plan such an agenda on its own. Chairman Binns reviewed representative slides from the psychiatric-oriented speakers. He noted that many of the speakers' names were familiar to the Committee as spokesmen for the now-discredited view that Gulf War illness is psychiatric, observing that "we've seen this movie before."

Committee members expressed shock and concern at the content of the presentations. Dr. Jaeger asked if the transcription for this discussion session could be ready earlier than the rest of the meeting minutes so that he could convey the Committee's concerns back to his leadership in ORD.

Speaking from the audience, MAJ Denise Nichols said that she had listened on the telephone to the IOM meeting that Chairman Binns was describing, and that she was very angry at the content of the meeting as well. To hear the old psychiatric theory being revived was not what veterans deserved. She, Mr. Hardie and fellow veteran Paul Sullivan have worked very hard to try to hold onto their fellow veterans and to keep them from being suicidal in some cases. If the VA took care of this problem 21 years ago, and the truth had been told to GW veterans, then there would be less money spent and veterans would be receiving proper treatment now. She had hoped that there would be improvement in the VA with the addition of Dr. Jaeger and Dr. Kalasinsky, but it was hard for her to give hope to the veterans that are out there that things will change for the better.

Dr. Jaeger said that he understood GW veterans' frustrations and that he and Dr. Kalasinsky would convey those concerns to his leadership when he returned to Washington. He also said that he understood that the Committee submitted their official recommendations to the Secretary and he urged the Committee to continue doing so. He addressed the Committee's concerns about organizing and better categorizing the research portfolio so that it could be seen what the VA and what the Committee regarded as Gulf War Illness research. He also stated that VA was working to put up its funded Gulf War research on the NIH reporter website where it could be viewed by others. Dr. Jaeger said that ORD was trying to strengthen its collaboration with other offices of VA, particularly with OPH, and he stated that he and Dr. Kalasinsky are in touch with someone from the OPH monthly to talk about projects that are ongoing. He also stated that he and Dr. Kalasinsky had spoken to VA personnel in regards to the VA electronic health record to see if a flag could be put in the veteran's medical record.

Dr. Jaeger mentioned that in the last RAC meeting there was discussion about educating VA clinicians on GWI, and he said that the relationship between the Office of Academic Affiliations was strengthening, which was beneficial because they were the office that helped with training physicians on GWI. He also stated that VA was also trying to strengthen their collaboration with DoD and that he and Dr. Kalasinsky had started attending the DoD Deployment Health meetings and meetings at Fort Detrick. He also said that there had been joint program reviews in terms of coordinating VA and DoD CDMRP funding. He also addressed the concern expressed at the last RAC meeting regarding making better use of existing Gulf War databases. Dr. Jaeger said that there was an agreement to put VA, ORD and OPH researchers on site in San Diego to work with the database on the Millennium Cohort study. He finished by saying that he and Dr. Kalasinsky were definitely trying to improve problem areas. He then introduced Dr. Kalasinsky to speak about the VA research Gulf War portfolio and the VA Gulf War strategic plan.

Dr. Kalasinsky said that there had been a concern raised at the last meeting with respect to the research portfolio regarding the $3.1 million listed for funding for GW research in the DoD portfolio for fiscal year 2010 and that this was inaccurate when he looked into it. He explained that the cause of the error was the time it took to get the data after the report was submitted. He showed that the revised number for funding trends for GW research in DoD was in fact $10.2 million for fiscal year 2010 and the number for fiscal year 2011 would be about $8 million more. He also stated that the VA had spent about $6 million in funding for GW research in this fiscal year. He indicated that on Chairman Binns' slides, there was a VA budget estimate for $15 million for FY12 for GWI research, and a current estimate of $4.9 million, but that the actual number was now projected to be $6.8 million. Dr. Kalasinsky emphasized that the $15 million was what the VA leadership had been willing to spend, but that there were not enough proposals that they could fund to meet this amount. He indicated that there were eleven proposals in the previous cycle, of which one proposal was funded. In the most recent grant review cycle, there were sixteen proposals reviewed and two had been recommended for funding. He indicated that VA was willing to fund good proposals, but there needed to be more proposals to review.

Dr. Sullivan commented that they had seen and heard about several very promising projects from presenters at this meeting that could be funded as larger projects through the VA. Dr. Kalasinsky agreed that could be possible if the proposals were submitted for review.

Dr. Golomb then asked whether the two proposals that would be funded would actually be related to GWI. Dr. Kalasinsky responded that they were related to GWI. She emphasized that the projects should not be related to stress, post-traumatic stress disorder (PTSD), amyotrophic lateral sclerosis (ALS), or multiple sclerosis. Dr. Golomb also made a comment on the quote that was added to the strategic plan which stated that conditions that Gulf War veterans suffer from will be considered equally and that no veteran should feel that his/her condition is less important than any other. She found that this statement was completely inappropriate for several

reasons. One reason was that illnesses like MS and ALS have other research funding mechanisms. The other issue was that, while these conditions were found in GW veterans, they did not affect a fourth to one-third of deployed Gulf War veterans.

Dr. Kalasinsky responded by saying that the two studies that would be funded in the latest review cycle were not related to stress. He clarified that the quote that Dr. Golomb mentioned in the revised strategic plan did not directly say that all illnesses of GW veterans should be treated equally. A few committee members replied that that was how the quote read to them. Dr. Steele read the quote verbatim which said "No Veteran should feel that his/her particular ailment is less important to VA than any other." Mr. Hardie added that it would be more appropriate to use the term "more important" in lieu of less important, to which Dr. Golomb agreed. Dr. Kalasinsky indicated that the terminology could be changed in this section of the strategic plan.

Dr. Steele said that although VA indicated that there had not been sufficient proposals submitted that were related to GWI, that there were a number of VA investigators who presented their Gulf War research at the last RAC meeting that were funded by DOD. She added that those projects had been specifically funded by the CDMRP Gulf War Illness research program. She asked why these VA investigators who were funded through CDMRP weren't also being funded by VA to do this research.

Dr. Kalasinsky responded that the process at the VA involved review panels and then the panel made decisions on which proposals should be funded. Dr. Steele indicated that that the same process was done at for the CDMRP proposals. Mr. Hardie added that at the most recent CDMRP panel, there were more than $30 million worth of proposals that were all worthy of funding and of that, DoD could only fund $6 million. He added that many of those researchers were VA researchers and many were unable to be funded. Mr. Hardie stated that he did not understand why they would not be funded by VA.

Dr. Jaeger added that Dr. Kalasinsky had gone out and redoubled his efforts to recruit additional pools of reviewers to serve on the VA Gulf War panels and to broaden the expertise of the panel related to GWI research. Dr. Jaeger added that although the numbers are not as impressive as the Committee wished it would be, the indicators were going in the right direction in terms of total number of proposals submitted.

Dr. Sullivan responded that she believed that there should be more than two proposals getting funded. She asked Dr. Kalasinsky how the process was determined on which proposals actually get funded. Dr. Kalasinsky responded that VA looked at the scores of the review panel. Dr. Golomb added that if there was a low funding rate, researchers may not want to even submit proposals out of concern that their chances weren't good for getting funded. Dr. Kalasinsky responded that he did not believe that the pool of reviewers was biased by a particular subject. Dr. Golomb responded that she did not believe the panel members were biased towards a

particular subject matter, but their attitude towards GWI could be different because of the historical training at the VA and attitude of the VA which had emphasized stress and psychological factors as the source of illness in GW veterans.

Dr. Kalasinsky indicated that the review panel contained a variety of different people, and not just VA researchers. Dr. Steele pointed out that in the early years of the RAC, it was a major problem that panel reviewers knew nothing of GWI and many proposals were rejected because of the reviewers' lack of understanding of the subject area. She stated that ORD had worked with the Committee to establish a GWI dedicated ad-hoc study section, which included GWI experts. She added that during 2004-2006, there was a lot of funding for GWI research and that the creation of the dedicated study section was a very successful effort.

Dr. Kalasinsky added that within the last round of grant reviews, he had spoken with the investigators that weren't funded and encouraged them to resubmit their revised proposals. With respect to the CDMRP, he had asked VA researchers why they chose to submit to CDMRP as opposed to submitting to the VA. He said that the feedback that he received was that there were fewer restrictions on the CDMRP money and that VA had more legal restrictions on funds. Mr. Hardie recommended that the law should be changed then to make it easier to fund good researchers, and Dr. Golomb agreed with this suggestion. Dr. Kalasinsky responded that it would be a Congressional matter and not the Secretary's choice to make those kinds of changes. Mr. Hardie responded that VA did have an Office of Congressional Affairs, and most federal agencies are fairly effective in getting laws changed if they feel it is necessary.

Dr. Jaeger added a comment on why researchers applied to different agencies outside of the VA. He said that the researcher's strategy was generally to maximize interactions with every federal agency that could give money for their research. He said researchers strived to have a balance of funded proposals from as many different agencies as they could over time.

Dr. Steele responded that in that case, it would make more sense for researchers to also apply to VA instead of just CDMRP. Dr. Jaeger responded that VA was working on bringing the numbers back up and that Dr. Kalasinsky had encouraged researchers to resubmit proposals that had been turned down for funding in the last funding cycles.

Mr. Hardie said that he had a message directed to VA ORD. He stated that he had received a VA publication that was sent to all veterans entitled the "State of VA Research 2012: Improving Veteran's Lives." He found it unacceptable that this publication characterized Gulf War Illnesses research as investigating whether service in the Gulf War was linked to illnesses that Gulf War veterans had experienced, while for all other diseases the research was expressed in terms of providing service and treatment. He added that ORD was broken, and remained broken under the current leadership.

Dr. Kalasinsky then moved on to discussing the VA Gulf War research portfolio and the projected research expenditures for 2012. He said that the VA was willing to spend $15 million or more than $15 million if necessary to fund GW-related research, and that his goal was that they received more fundable proposals to be able to spend $15 million. He finished his presentation by showing a slide that included the currently funded Gulf War studies through VA ORD, which totaled $6.8 million in FY2012.

Dr. White added that she is the current chair for the integration panel for CDMRP, and that Dr. Steele was the chair before her, and they both worked very hard with DOD to get researchers interested in the RFP's and to target appropriate researchers to apply for this available funding. When RFP's came out, Dr. White had lists of researchers that she had CDMRP contact to advertise the funding availability. Some of the contacts were not VA researchers but had VA alliances, and she was unsure if VA currently had that kind of a system set up. She suggested that members of the Committee could contribute to identifying who ORD could contact when their RFAs were released to get more and better proposals submitted. She added that the combination of the way the CDMRP RFA's are written and the outreach efforts are why CDMRP gets so many proposals for their GWI research program. Dr. Kalasinsky said that Dr. White's suggestion was a good one and as a first measure he would be setting up a meeting with VA researchers to encourage them to be more involved in submitting Gulf War research proposals.

Dr. Golomb then asked if VA has considered a veteran advisory group to assist in the review process. Dr. Kalasinsky said that the VA had not considered that but he did not think that it fit very well with the current review process procedures.

Dr. Jaeger asked Dr. Golomb if she meant that a second level of review should be done with veteran input. Dr. Golomb responded that she recommended a second level of review and/or the incorporation of veterans into the primary review committee. Dr. Jaeger responded that in terms of serving on the review committee, if they had veterans who had the credentials to do the scientific review then that could be possible. Dr. Golomb responded that they could serve other roles, such as a relevance review as opposed to a scientific review. Dr. Jaeger responded that he did not believe that he or Dr. Kalasinsky could speak on behalf of how the review panel was organized with respect to the inclusion that Dr. Golomb was asking about. Dr. Golomb added that she wondered if the review panel could be modified because she believed that the veterans deserved a voice in the review process.

Mr. Hardie agreed that it would be beneficial if veterans could be involved at a certain level of the review process. Dr. White asked if there were rules regarding individuals outside the VA being able to participate in the grant review discussions. Dr. White said that if there were very knowledgeable non-VA Gulf War research investigators involved in the review panels, then it might make it more interesting for more researchers to submit proposals for the GWI research program.

Dr. Kalasinsky responded that he was unsure if there were rules regarding outside reviewers, but that he would have a meeting with VA investigators to encourage them to submit proposals. Dr. Jaeger added that the purpose of the future meeting with VA researchers was to make sure that they did not get discouraged with VA GW research, and to encourage other researchers to become involved. He also thought this would keep researchers informed on what other researchers are doing on their GWI research studies.

Mr. Hardie encouraged Dr. Kalasinsky to call the CDMRP staff because he thought they may have the authority to release the names of VA researchers who did not receive funding from CDMRP and could apply to VA for their proposed studies.

Dr. Kalasinsky then discussed the CDMRP call for consortium proposals. He stated that the VA was planning on issuing a special RFA for VA researchers who may be interested in working with whatever consortium would be funded through the CDMRP.

Dr. Golomb asked if she could go back to the issue of modifying the training for VA clinicians and she provided an anecdote from a GW veteran patient at the VA whom she saw recently. She said that this patient went to the VA because his outside physicians were not familiar with GWI. When he was referred to a neurologist at the VA, the neurologist said that VA did not believe in GWI. She said that this brought her patient to tears. She said that this patient now flies down to San Diego to get care from Dr. Golomb. She expressed that this was not how GW veterans should be treated at the VA and that the VA clinicians need to be more knowledgeable on this topic. Dr. Kalasinsky agreed, and said that a concerted effort was needed to make sure that cases like that do not happen.

LTC Marguerite Knox, a member of the Committee and a Gulf War veteran, then expressed her anger and disappointment at what she was hearing at the meeting and what she considered levity for a serious situation. She expressed her anger that it seemed to her that the comments from the Committee were being taken lightly and in jest by ORD staff. Dr. Jaeger indicated that he did not take the comments lightly or in jest and Dr. Kalasinsky agreed. LTC Knox indicated that as veterans, they had been trying to be positive for twenty-one years and the lack of change at VA for GW veterans regarding understanding their health problems was very discouraging and disappointing. She felt that VA did not understand what the veterans have been going through during this time at all.

Dr. Steele then stated that a big issue in the recent changes to the VA Gulf War research strategic plan was the lack of urgency in the new version and she added that when looking at the projects included in the Gulf War research portfolio, that she was concerned there were so many studies that were irrelevant to GW veterans or GWI. She noticed that some of the projects the Committee felt were unrelated to GWI had been removed from the VA Gulf War research

portfolio years before, but now she saw them back in the current Gulf War research portfolio. She asked Dr. Kalasinsky why they were added back in to the funding portfolio.

Dr. Kalasinsky replied that those studies were included in the previous GW research portfolio documents before he was a part of the VA ORD staff and that was why they were included back in. Dr. Steele responded that those projects should not have been in the research portfolio to begin with and should not be added back in now. Dr. Sullivan agreed with Dr. Steele and said that she believed that GWI research efforts were increasing at ORD, but the previous projects were inappropriate to include in the GW research portfolio. Dr. Kalasinsky said that VA ORD will make changes to future portfolio funding documents, but that he could not report on those projects separately because they were included as part of prior reports to Congress. Dr. Steele then said that those projects should not have been reported to Congress as GW research projects at VA to begin with, because they were unrelated to GWI research, which she felt was deceptive and misleading to Congress. Mr. Hardie said that this was another example of how VA ORD remained broken. Dr. Steele added that the science is getting better and stronger in understanding the mechanisms of GWI, but the VA was not appropriating funding to this evolving science.

Dr. Golomb stated that she felt that Dr. Kalasinsky and Dr. Jaeger cared about this issue, but that the Committee needed to find out who was making the decisions above their level to change the strategic plan to this unacceptable version. She felt that those individuals needed to be out of the decision-making chain of command for GWI research in the future. Dr. Meggs agreed with Dr. Golomb's statement.

Dr. Jaeger responded to Dr. Golomb by stating that following the last Committee meeting in January where the strategic plan was discussed at length, the strategic plan was then reviewed by the National Research Advisory Council (NRAC), and then it was reviewed by other offices in the VA, and then the four service chiefs at VA. He stated that in this lengthy process, a lot of individuals had suggested changes to the strategic plan, but it was hard to determine who suggested which changes. He was however able to provide the old and new drafts of the strategic plan, with the changes highlighted. He added that he and Dr. Kalasinsky were doing what they could do to present the gravity of the situation and the Committee's unhappiness with the latest version of the strategic plan to his chain of command.

Dr. White then said that she was shocked when she saw that the communication and coordination section of the strategic plan was changed so much in the new draft of the plan. Dr. Kalasinsky responded that the Gulf War Steering Committee just could not do some of the tasks that the working groups suggested for them to do, and that was pointed out to VA ORD by other offices when they reviewed the plan and that he did not know that these items weren't possible when it was discussed in January. Dr. White indicated that this was really disappointing to her, because other sections of the strategic plan also got changed in a way that made the strategic plan an ineffective plan now.

Dr. Steele added that the working groups were charged by Dr. Buja to put in timelines and milestones in their sections of the strategic plan to make the plans move forward. She said that, looking through the document now, everything related to urgency, timelines and milestones seemed to be completely gone. Mr. Hardie voiced his disappointment with the editing of the document as well and added that the focus on GWI in the plan had almost entirely been deleted from the document. He also felt that the VA had not been doing a good job with dealing with GWI, considering that there were still many VA clinicians that did not believe that GWI exists and tell their patients that. He strongly urged the Committee to vote against this new version of the strategic plan until it could be fixed or made more similar to the version that was agreed upon by the RAC and the NRAC representatives the January meeting. Dr. Golomb also added that she believed that it should be possible to determine who in VA made these unilateral changes to the strategic plan if the older copies of the strategic plan drafts were reviewed after they were sent to ORD for editing by the other VA offices. She felt that it was important to look through those drafts and to identify who made the objectionable changes and to remove those people from involvement in this issue going forward.

Mr. Hardie made a note that at the last Committee meeting, the title of the plan was different as well. It was formerly called the Gulf War Illness Strategic Plan, and this time it was called the Gulf War Strategic Plan. Dr. Kalasinsky said that was an oversight, and Dr. Steele said that she did not believe that it was an oversight because the word illness had been dropped throughout the whole document.

Chairman Binns suggested that since there was little time left for this discussion that perhaps Dr. Kalasinsky could make a closing statement for his presentation. Dr. Kalasinsky made a closing statement that he would disagree that there was nothing substantial left in the edited version of the strategic plan. He felt that it laid out a number of things that could be done for GW-related research that were important. He indicated that the problems were that there were certain things that VA ORD could and that they could not do, and he indicated that the sections that were gone were things that VA ORD could not do after they looked into their feasibility.

Dr. Steele asked specifically what VA ORD could not do in the strategic plan. She believed the strategic plan could express urgency, and that the word illness should not have been dropped from the document. Chairman Binns indicated that they needed to move on to introduce the speakers from the VA Office of Public Health (OPH). Dr. Kalasinsky finished by saying that the strategic plan that was agreed to in January would not be able to get final approval because there were certain things that VA could not do. He stated that this time, a plan was created that could be approved. Chairman Binns indicated that they could talk about this matter the next day, because they needed to move on to introduce the OPH representatives.

OPH: An Overview of OPH's Gulf War Activities

Dr. Sullivan introduced Dr. Victoria Davey and Dr. Wendi Dick from OPH to discuss the recent Gulf War activities in their office. Chairman Binns thanked Dr. Davey for making the trip to Boston to attend this RAC meeting and to address the Committees questions regarding OPH Gulf War studies. He noted that Dr. Davey held the corresponding leadership position at OPH to the position Dr. Kupersmith holds at ORD.

Dr. Davey started her presentation by discussing the resurvey of the National Cohort of Gulf War Era veterans. The national survey began in 1995 and is now on its third cycle. She said that OPH had designed the survey, submitted it to OMB for approval, and she acknowledged that in the process it did not get to the RAC for review or comment before it was sent out for public comment by OMB. She stated that she did appreciate the comments on the survey that the RAC provided during the public comments to OMB and to her staff. She stated that she realized that there was still some unhappiness with the survey from the Committee.

Dr. Davey said that the survey was a comprehensive assessment of health and wellness of GW veterans and it had four domains: social, physical, mental and functional. She stated that the survey was designed to provide an overall population health assessment of GW veterans. The mailing of the survey began on May 21st, and went out to 500 pilot veterans. OPH anticipated that the last mailing of the survey would go out in December of this year with all the data be collected by the Spring of 2013. She stated that the majority of the questions in the survey were about physical symptoms. The other questions dealt with self-reported mental health and medical diagnoses. Dr. Davey indicated that she knew one of the concerns about the survey was that there were too many questions that focused on stress. She then distributed copies of the survey to the Committee members for review.

Dr. Steele stressed that the largest problem that she saw with the survey was that this survey did not allow for the assessment of Gulf War Illness in these veterans because the survey did not ask about chronic symptoms necessary to a diagnosis of GWI. She added that there was no way to get a determination of GWI without those questions being included.

Dr. Davey said that she understood Dr. Steele's point, and she said that the survey gave a good snapshot of the health of veterans now. Dr. Steele disagreed and said that it would not provide a good snapshot because the main health problems of GW veterans were not being asked in this survey. Dr. Steele said that by adding a few questions on the survey, it could capture more relevant information. Dr. Davey said that they would look for ways to get information that the Committee wanted in the next survey. Dr. Meggs said that it seemed that the recommendations that the Committee had provided to OPH had been edited out of the survey. Dr. Golomb asked what questions OPH thought were more important in this population, since the questions to determine GWI were excluded for other questions. Dr. Davey said that the gastrointestinal,

emotional and social health questions were important to OPH. Mr. Hardie added that there were five pages on stress in the survey, and there were only brief questions on chronic multi-symptom illness, which were worded in a way that veterans with GWI may answer inappropriately. He said that many veterans, including himself, do not think of their illness as "unexplained," since it has been well-explained in the 2008 report of the Committee and by their own experience.

Mr. Hardie said that it is a wonderful idea to resurvey GW veterans every five years, but he found the current content of this survey to be irrelevant to GW veterans. He stated that it is very important for OPH to work with the Committee to make the content of the survey more informative to achieve the goal of improving veterans' lives. Dr. Davey agreed and she hoped that OPH and the Committee could craft new ways of working together to get the questions that they all want answered, and to get veterans treated appropriately. Dr. Golomb added that the current survey was a damaging expenditure of funds because the main focus on psychiatric questions would push healthcare and research for GW veterans in a direction that was not in their best interest.

Chairman Binns said that the Committee had a positive experience with OPH on the 2002/2003 survey. Dr. Han Kang agreed to add a few questions that the Committee had recommended despite the delay and cost of these additions. Chairman Binns felt that at the beginning of the Committee, VA offices took seriously the Congressional mandate to consult with the Committee for large studies and surveys before they went out to the veterans. He said that for the recent survey, the Committee found out about the new survey after it was drafted and on its way to OMB for public comments. He stated that the Committee made recommendations at that time and at one point, someone from OPH contacted Dr. Steele and asked if she would be willing to help out with the survey. She indicated yes, but the contact was never followed up on. The Committee made two sets of recommendations regarding this survey in the Fall of 2010 and in the Spring of 2011. Chairman Binns then said that in early 2012, the Committee was quite surprised to hear Dr. Schneiderman of OPH say that the Committee could not see the finalized survey and that there could be no further changes to it. Chairman Binns expressed his belief that this survey did not advance research on GWI.

Dr. Davey said that she appreciated Chairman Binns' concerns and she hoped to rectify the relationship between OPH and the Committee.

LTC Knox asked that if OPH had the authority to do it, then why the situation was not already rectified before the survey went out. Dr. Davey said that OPH had good researchers, and it was in the best interest to let this survey happen. Several Committee members then stated that they did not believe that it was in the best interest to let this version of the survey go out. LTC Knox stated that so much time and money had been wasted by inappropriate GW research over the years, and veterans' voices were not being heard. She stated that she felt that this survey was not in the veterans' best interest to send out without the suggested revisions. Dr. Davey responded

that there was a different group of outside experts that were consulted who felt that this survey answered questions that needed to be answered for GW veterans. LTC Knox stated that she did not believe that Dr. Davey truly knew the situation that many GW veterans have been dealing with for 21 years. LTC Knox then said that she was so disappointed by VA's disrespect of GW veterans that she had spent her last hour on the committee. LTC Knox left the room.

Chairman Binns noted that LTC Knox's action reflected the fact that VA staff had collectively pushed these issues over the edge of tolerance for many Committee members, and that staff did not have credibility with the Committee any longer. Chairman Binns said that VA staff needed to show change through actions and not words. Dr. Davey said that from her view, and what she heard from Dr. Kalasinsky and Dr. Jaeger was that OPH and VA were all willing to work with the Committee in a different way, if the Committee was willing to work with them in a different way. She was happy to open that door again, and she hoped that the relationship would be stronger than it has been in the past.

Dr. Sullivan said that people on the Committee and in the audience were expressing the emotion that they were feeling because they were not being heard year after year and meeting after meeting. She expressed that in regards to the survey, in the last meeting the Committee was told that the survey was going out because there was not enough time for changes before it had to go out, but the Committee had suggested changes long before the last meeting in January. She said that to this Committee, it felt like they had not been heard at all when they had requested that constructive changes be considered to the survey.

Mr. Hardie then said that the GW veterans in the room are a small body who carry a lot of weight on their shoulders. They tried to represent the voices of all GW veterans, and for those collective voices to not be heard was very frustrating. He reminded everyone that this committee was not a VA, or ORD committee, but a Congressionally-chartered committee. Mr. Hardie told Dr. Davey that if this were his office, Dr. Schneiderman would be fired on the spot because of his inappropriate behavior at the prior meeting when discussing the planned survey. He stated that he appreciated that Dr. Davey was listening to his thoughts and views on this subject. Dr. Davey said that the staff at OPH care about the health of the veterans, and do nothing but work for the sake of the veterans. She understood that OPH needed to regain the Committee's trust, and she hoped that they could do that in the future.

Dr. Davey then discussed the new IOM treatment study for GWI. The OPH charged the IOM in December to perform a review of treatments for GWI. Dr. Davey stated that after the charge that OPH did not intervene with the IOM Committee. She also said that the IOM was going to do a review of the literature and point out to researchers the gaps and the holes in treatments for GWI. Mr. Hardie asked if OPH had read the Congressional language directed at the creation of the IOM assignment, because it stated that they should not be doing a literature review. He stated

that the IOM should be consulting with practitioners in the field and not performing a literature review as the IOM typically does.

Mr. Hardie then requested that OPH provide the Chairman with a copy of the contract that was given to the IOM by OPH for this new committee. Mr. Hardie said that he had seen the charges in the legislation, and the charge was very different than a literature review. The charge was directed at practitioners who were successful in treating veterans. Dr. Davey said she would be happy to try and get the documents for Mr. Hardie. Dr. Steele added that there was not much literature on treatment for GWI, so there was no need for the IOM to review that topic.

Dr. Davey indicated that the final request from the Committee was to update the Committee on the study of multiple sclerosis that was mandated by congress in Public Law 110-389. This law stated that VA would contract with the IOM to conduct a comprehensive epidemiological study to identify any increased risk of developing multiple sclerosis in GW veterans. Dr. Davey stated that one study performed by Shannon Barth and Dr. Han Kang and another study by Dr. Mitchell Wallin at OPH showed no increased incidence in MS in GW veterans. Dr. Steele said that neither of the studies that Dr. Davey mentioned addressed if MS was elevated in GW veterans compared to non-deployed veterans. Dr. Steele also said that she did not understand why there was not more familiarity with GW research at OPH and why there were not directed efforts to ease the health problems of GW veterans.

Mr. Hardie stated that the VA had not followed the law in this case. He had contacted the IOM to see if a study had been commissioned as mandated by Congress and he said that he had clearly documented evidence that VA had not contracted with the IOM as the law directed. Dr. Sullivan then noted that there were issues with the two epidemiological studies as well, since the Barth paper was a mortality study that only identified GW veterans with MS who had died from the disease, and the paper by Dr. Wallin had no information about incidence rates on MS, which was a surprise that the first paper from that study did not even address incidence rates in GW veterans at all.

Chairman Binns said that at this point, the scientific case for asking these questions, and spending money on them was overwhelming to the point that the only reason people would not want to do this work was because perhaps they did not want the answers. He stated that he was still here on the Committee because the IOM said that treatment answers can still be found for GWI. He suggested to Dr. Davey that she and others in leadership roles at VA needed to find out who those people are and remove them from positions of authority. Dr. Davey said that OPH worked with the needs of the patient using population health based programs. She said that OPH needed to collaborate with DoD and she hoped that OPH and the Committee can work better together.

Public Comments

Chairman Binns then asked for public comments. Veteran Venus Hammock was the first public commenter. She stated that she had been lobbying for GWI since 1993. She said that veterans feel that their voice has not been heard and that GW clinics and referral clinics no longer exist. She said Gulf War specialty clinics at the WRIISC are difficult to get to, as there are only three clinics. She was grateful that the RAC still existed but furious, and many are furious, and disappointed on the task force existence. She also said that there are not outreach numbers for Gulf War veterans to call. She said that her practitioners are not well versed in GWI, even though they are supposed to have received training on it through the VA. She also found it difficult for herself and other veterans to call into VA advisory board meetings since 1997. She said that less than 50% of what she has heard was audible. She will continue lobbying and she thanked everyone for their time.

MAJ Denise Nichols was next to comment. She reminded everyone that veterans travel to Committee meetings without getting paid. They have their health and family health issues to deal with little VA help. She also commented on the research seminar that VA had held in Washington, DC and there was very little on Gulf War health issues. She concluded that she was tired of empty words from VA without action.

Chairman Binns adjourned the meeting until the following day at 8:30 AM.

DAY 2

The June 19th, 2012 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (hereinafter referred to as the Committee) was held in Room 109A/B at the Boston University Medical Building, 80 East Concord Street, Boston, MA.

Welcome, Introductions & Opening Remarks

Mr. James Binns, Committee Chair

Chairman James Binns called the meeting to order at 8:30 AM. He thanked the participation of so many interested parties at this meeting. Dr. Sullivan then introduced the first speaker Dr. Rodney Johnson.

From inflammation to sickness and Cognitive dysfunction: when the Immune system subjugates the brain

Dr. Rodney Johnson, University of Illinois Urbana

Dr. Johnson thanked everyone for inviting him to speak about his research. He gave a brief

overview about the immune system and in particular the microglial cells in the brain. He said that the brain was not responsible for detecting peripheral infections, and that was the role of the microglial cells of the immune system. These cells were responsive to signals emerging from the peripheral immune system and accounted for about 15% of the cells in the brain. He said that when the microglial cells received stimulus from the peripheral immune system, they responded and produced their own inflammatory cytokines which played a major role in controlling the behavior of sickness symptoms.

He then discussed a study related to microglial cells and aging. The principal finding from the study was that Interleukin-6 (IL-6) production was affected in normal aging. There were age-dependent increases in serum IL-6 and splenocyte IL-6 production with aging. The important finding was that splenocytes from old mice spontaneously secreted more IL-6 than splenocytes from young mice. Thus, the IL-6 gene was dysregulated in splenocytes from old but otherwise healthy mice. He showed results from a microarray analysis where he looked at the expression of a number of genes in the brain of old animals compared to young adult animals. There were a number of genes that were differentially expressed. When the genes were broken into different functional categories, about half the genes were upregulated and the other half were down regulated. He said that the old animals were developing a gene expression profile suggesting increased inflammation.

His lab had been able to develop procedures that isolated the microglial cells from the brain from young adult and aged animals using specific markers that allowed the researchers to distinguish them from infiltrating monocytes. He said that the lab could take those microglial cells and stain them further for major histocompatibility class (MHC) class II which is often used as a marker for activated microglial cells. When he looked at this marker of activation, he saw in the adult animal that usually 2-3 % of the microglial cells were MHC class II positive. In the brains of old healthy mice, this number went down to about 25%. The basic premise was that neurodegeneration could prime microglial cells. During aging, these cells became primed and those primed microglial cells expressed markers that allowed one to distinguish the resting versus the primed cells. He explained that in a study that used laser capture microdissection, neuronal cell layers were separated from the hippocampal tissue using a laser. The results showed that the aged animal had higher baseline level expression of the proinflammatory cytokine interleukin 1 beta. When the cells were stimulated with LPS from e-coli to mimic a peripheral infection, the baseline level expression of cytokines increased in the young and aged animals. Dr. Johnson's data suggested that this also resulted in functional outcomes since the data showed that LPS disrupted spatial-working memory in the old but not the young mice. In the young adult animals given LPS, there was no effect on neuron morphology, but in the aged animals given the same treatment, atrophy of the dendritic branches of the hippocampal neurons were seen (which seemed to be related to the increased inflammation).

Dr. Johnson stated that one study showed that mild stress impaired spatial learning and memory in aged mice. His studies showed that mild stress did not induce IL-1Beta in the young animals, but it did in the old animals. He also showed that these increased proinflammatory cytokines induced by mild restraint stress resulted in increased cytokine signaling in the hippocampus as well.

Dr. Meggs asked if IL-6 crossed the blood brain barrier. Dr. Johnson responded that there was data that IL-6 was actively transported through the blood brain barrier. He said that the other major pathway is the neural pathway that could activate communication in the brain and in a process that he did not fully understand, activated microglial cells.

He then discussed a recent study about influenza where there was anecdotal reports suggesting that influenza infection was associated with long lasting cognitive deficits. A mouse adapted strain of human influenza was inoculated in test mice then the mice were tested with a learning memory test. Both mice with and without the flu learned their task quite well. For more complex memory tests, the control animals performed the task quite well but those with influenza infection performed poorly. He remarked that influenza was upregulating the activity of microglial cells resulting in increased cytokine production. Mice that were given the flu had far less branching at the ends of the dendrites so there was a loss of dendritic complexity. He concluded that if one had this primed microglial cell and if one had an infection, there would be an excessive production of cytokines which leads to cognitive impairment.

Dr. Johnson stated that flavonoids could be a method to slow the progression of disease. He said that all neurodegenerative diseases contained at least three components: activated microglia, reactive oxygen species and inflammatory cytokines. He hypothesized that perhaps flavonoids could regulate microglial cell activity in the aging brain. He then gave a brief background of flavonoids and their health benefits and then described a flavonoid study performed in France. The study analyzed flavonoid intake and cognitive decline in people 65 and older. Results showed that higher flavonoid intake was associated with improved performance on the Mini-Mental State Examination and that dietary flavonoid intake may protect against cognitive aging. He conducted a number of studies with the flavonoid luteolin. He stated that this particular flavonoid had very profound anti-inflammatory effects on microglial cells because it blocked LPS stimulation of IL-6. The more luteolin they were exposed to, the less AP1 activity they saw. This activation of AP1 was related to inhibition of JNK phosphorylation. Dr. Meggs asked what AP1 was. Dr. Johnson replied that AP1 was a transcription factor that sat in the cell cytoplasm and upon stimulation it was released so it could translocate into the cell nucleus where it would to bind to gene promoter sites. Dr. Golomb asked about foods that were rich in luteolin. Dr. Johnson said that celery and green peppers were rich in luteolin.

He described several luteolin studies, in both humans and animals. In humans and rats, IL-6 was

reduced. Dietary luteolin reduced MHC class II, IL-1β, and IL-6 mRNA in the hippocampus of aged mice and reduced MHC class II-positive microglia as well. Luteolin improved performance for memory tasks in animal models as well. He spoke of another study that showed that repeated stress actually activated microglia in discrete brain regions that then attracted peripheral monocytes to those brain regions. Dr. White asked if there were any reason to think that the age related changes in microglia and IL-6 were anything but degenerative, and that they were there for a protective purpose. He said unfortunately he was unsure. Dr. Golomb added that she thought that fatigue served an important purpose by reducing expenditures of energy on discretionary things people needed energy for to fight the infection.

Dr. Steele asked why he chose luteolin for his studies as opposed to other flavonoids. He said that the conference he went to that spoke of MS and flavonoids showed evidence that luteolin worked in other models and studies so that was why he chose it for his. She also asked if he had an idea of the persistence of the effect and how long the effects lasted. He indicated that he was unsure as they had not done studies along those lines but his sense was that the prior health status would return back again over time. Dr. Golomb asked if eating too much luteolin could lose its beneficial effect. He said that he had not studied a varied range of doses as it was a costly measure.

Dr. Steele said that there was a commercial product with a luteolin base which the manufacturers said inhibited mast cell expression of cytokines and it improved symptoms of chronic fatigue. Dr. Johnson said that he had not heard of the product but what the manufacturers claimed seemed consistent with his results.

Chairman Binns thanked Dr. Johnson for his presentation and Dr. Sullivan introduced the next speaker.

The effects of mindfulness practice on the neurobiology of pain processing and emotion regulation

Dr. Britta Holzel, Massachusetts General Hospital & Harvard Medical School

Dr. Holzel stated that the reported benefits of mindfulness were relaxation and well-being that last beyond the time spent meditating (See Appendix A – Presentation 9). She explained that studies had demonstrated improved concentration and memory functioning and had reported improved immune function, reduced blood pressure, and reduced cortisol levels. She said that in the area of PTSD, a preliminary study on mindfulness-based exposure therapy suggested that intervention appeared acceptable, veterans showed compliance, and that PTSD symptoms improved significantly. She explained that mindfulness was commonly defined as the non-judgmental awareness of experiences in the present moment and observing experiences with an attitude of acceptance, curiosity and openness.

The question that she was addressing in her research was what the neural mechanisms could be

that underlie the beneficial effects of mindfulness. She used functional MRI to look at the activation of brain regions during different cognitive tasks and she used structural MRI to look at the morphometry of the brain. She said that in the field of meditation, there were a number of studies that compared the structure of the brain between experienced meditators and people who had never meditated before. Some of the studies found specific areas of the brain to be different between experienced meditators and non-meditators. Specifically, studies showed greater gray matter in the meditators compared to the non-meditators in the hippocampus and the right insula. Dr. White asked if the effect was bilateral in the hippocampus. Dr. Holzel responded that it was indeed found in both sides.

Dr. Holzel then introduced a program called Mindfulness-Based Stress reduction (MBSR); an eight week group intervention program where participants met weekly with an instructor to learn mindfulness techniques. Structural MRI scans were acquired before and after the 8 week period. The results showed that there was an increase in gray matter concentration in the hippocampus in the intervention group. An increase in the gray matter in the posterior cingulate cortex, temporo-parietal junction, and the cerebellum were also found.

The MBSR program was also reported to reduce stress. Dr. Holzel administered the perceived stress scale before and after the MBSR program to her study participants. Results showed that there was a significant reduction in perceived stress after the intervention program. She used changes in the perceived stress score to perform a regression analysis and she found that decreased perceived stress correlated with decreased amygdala gray matter volume as well.

She also described another study which consisted of 17 meditators and 17 controls who received mildly painful electric shocks in the MRI scanner. The participants were instructed to encounter the pain in two different ways. The first way instructed was to encounter it with an attitude of mindfulness versus a baseline condition where the participants did not change the way they were addressing the pain. In terms of self-report ratings, she found that meditators experienced the same intensity of the pain, but rated the stimuli as less unpleasant. She found that with mindfulness, meditators were able to reduce the unpleasantness of the painful stimuli while the intensity of the stimuli remained the same. This suggested that the way they were approaching the unpleasantness was different. What Dr. Holzel reported was that during painful stimuli, while meditators were practicing mindfulness, there was increased activation in the right insula and decreased cognitive control in the lateral prefrontal cortex.

Dr. Meggs commented that her work gave the committee great hope for treatments for GWI. She said that while she was reading the symptom description for GWI, she felt that mindfulness would speak to a number of GW veterans' symptoms. Dr. Meggs urged her to put in an application for a CDMRP treatment grant for GWI.

Dr. Sullivan asked if Dr. Holzel looked at chronic pain and mindfulness with imaging techniques. Dr. Holzel said that she had not yet looked at this but behavioral studies had looked at that. She was not aware of any brain imaging studies but there were studies looking at symptom improvement with very good results.

Dr. Golomb asked if Dr. Holzel could go through the elements of the MBSR. Dr. Holzel said that it was structured in a way so that different types of practices are introduced in the 8 weeks of the program. It started with the body scan which was a practice where attention was guided through the body very systematically, tuning into sensations in the body. She stated that the program included very gentle yoga practices such as mindful stretching. The program also included stress information including physiology and learning to detect what a physical stress response is.

Chairman Binns thanked her for being her and appreciated her presentation and then Dr. Sullivan introduced Dr. Conboy.

The Effectiveness of acupuncture in the Treatment of Gulf War Illness

Dr. Lisa Conboy, The New England School of Acupuncture

Dr. Conboy explained that she was reporting the initial results of a treatment trial in acupuncture that was in the last 6 months of the trial. She said that the main objective of the trial was to find a successful treatment for GWI by gathering data to better understand the effectiveness of acupuncture in treating GWI (See Appendix A – Presentation 8). In a sample of veterans with GWI, she evaluated the effectiveness of an individualized acupuncture treatment protocol on the volunteers' most distressing GWI symptom. The type of acupuncture taught was to use individualized protocols and to tailor the treatment to the symptoms of the specific veteran. She used an unblinded randomized trial with a wait-list control design for this study. The active group received 6 months of biweekly treatment while the waitlist group received 2 months of waiting and then 4 months of weekly treatments.

She then discussed how Traditional Chinese Medicine (TCM) characterized GWI since there was no GWI in TCM but she said that TCM's individualized diagnosis and treatment was good for heterogeneous presentation of GWI. Dr. Conboy explained for the grant, she did a literature review of Chinese and Japanese literature looking specifically at exposure to neurotoxicants, and found good Randomized Controlled Trials (RCT) with specific treatment protocols. She said that there were a few TCM diagnoses that resembled GWI, and that was part of the training for the practitioners.

Dr. Jaeger asked about her views on laser acupuncture. She said that it was not a traditional technique and although she had read a few pilot studies on it, so she really could not comment on it.

She explained that recruitment was very challenging for this treatment trial and her staff had used

newspaper stories & advertisements, radio, cable TV, Yellow Ribbon Ceremonies, and had talked with the VA to recruit enough participants for the study. She said that there were 101 veterans enrolled and randomized, and expected to finish with 110 total participants.

Dr. Golomb asked what a yellow ribbon ceremony was. Dr. Conboy responded that it was a post-deployment gathering for vendors and people who had services of interest to veterans. The VA would be there, lawyers who specialize in veterans services would be there, as well as selective social services and other relevant agencies. Dr. Golomb asked if Dr. Conboy's study was a VA funded trial, and Dr. Conboy responded that it was a DoD funded trial.

She then discussed the measure yourself medical outcomes profile (MYMOP) which was cross-validated with the SF-36 and offered comparable results. The MYMOP was a patient centered scale that asked patients to list main and secondary symptoms (either physical or mental) and numerically define how good or bad the symptoms were on a scale from 1-10. The MYMOP was given at follow-up appointments, but pre-populated with the symptoms to see if the severity had changed over time. When she compared baseline to follow up changes in the higher dose treatment group: at 2 months, no significant change was found but at four and six months, there was a significant change. When she compared baseline to follow up changes in both treatment groups, at two and four months, there was no significant changes but at six 6 months there was a significant change.

Dr. Conboy believed that there were subgroups within GWI that acupuncture worked really well for and there were some that it did not. In terms of usability, she indicated that many veterans were very comfortable with recommending acupuncture to a friend or family member and wanted to continue with the study even after completion. She said that the next step was to apply for CDMRP investigator-initiated grant funding to continue this research. She also said she was interested in determining what types of acupuncture would work best for which symptoms, and in what dose.

Dr. Steele said that she liked that the veterans were engaged and willing to participate and that she could not wait to hear what the TCM diagnoses were for GWI. She asked if veterans at the Yellow Ribbon ceremonies were solely 1991 GW veterans. She said that she believed that for the RFA, they needed to be 1991 GW veterans. Dr. Conboy said that some GW veterans did not identify themselves as solely GW veterans since they could be involved in other deployments as well, and that the Yellow Ribbon campaign was great to finding those types of veterans coming back from more recent deployments. Dr. Golomb asked if there was an exclusion criterion for Dr. Conboy's study. Dr. Conboy responded no, and that they used the most general definition from the CDC to be very inclusive for this study. Dr. Golomb said it could be concerning because maybe another condition is causing the syndrome that was being treated, so they might not know if the treatment was actually targeting GWI or not based on this study.

Dr. Sullivan said it was amazing that Dr. Conboy had recruited 100 veterans for her treatment trial and that she was excited to see the upcoming final results. Major Nichols asked if Dr. Conboy had

contacts in other major cities so that this study could branch out to other areas besides Boston. Dr. Conboy said that VA's are hiring more acupuncturists so it could definitely branch out if VA wanted to.

Chairman Binns thanked Dr. Conboy for her presentation and Dr. Sullivan introduced the next speaker, Dr. Chenchen Wang.

Tai-Chi: A Mind body Exercise For Pain Relief and Well-Being
Dr. Chenchen Wang, Tufts University School of Medicine

Dr. Wang presented information on Tai Chi as a Mind-body Exercise for Pain Relief and Well-being. (See Appendix A – Presentation 10). She reported that about 2.5 million Americans practiced Tai Chi and the number was rapidly increasing.

She then spoke about FM and how there were limited treatment options for it. She said that aerobic exercise had been the most efficacious in her reading of the literature. The current theory of FM was that it was considered a disorder of the central nervous system. Other theories were that it is a stress related disorder caused by abnormalities in the hypothalamic-pituitary-adrenal axis.

She described Tai-Chi as a traditional martial art and that evolved from physical and breathing exercises in ancient times. Tai-Chi combined meditation with slow graceful physical movements and deep breathing and relaxation. Dr. Wang found that there were 47 studies focused on the benefits of Tai-Chi. She said that the reported benefits of the studies included improved balance and strength, cardiovascular and respiratory function, symptoms of arthritis, muscular strength and psychological well-being.

She then described her study of a randomized trial of Tai-Chi for FM. The goal of the study was to explore the effects of Tai Chi on musculoskeletal pain, sleep quality, psychological distress, functional impairment and health status in patients with FM. The intervention groups consisted of patients who practiced classical Yang style Tai Chi for 1 hour, twice a week for 12 weeks. Every session included warm up and review of Tai Chi principles, meditation with Tai Chi movement, breathing techniques, and relaxation techniques. The control group had an education and stretching component for the same length of time but did not practice Tai-Chi. The outcome measure used was the fibromyalgia impact questionnaire (FIQ) change scores from baseline to 12 weeks. The FIQ included measures of intensity to pain, physical function, fatigue, depression and anxiety and the score ranges from 0-100. The results showed that 92% of the participants completed the study and that mean FIQ scores decreased significantly over time in the intervention group.

Dr. Meggs asked where a normal person would be on the FM scale and she responded that since the

person would have no symptoms, it would be zero. She said that Tai-Chi was a safe and enjoyable exercise with high adherence and was effective for treatment of chronic pain. Results showed that it improved physical function, sleep quality, depression, and quality of life in people with chronic pain syndromes. She said that future medicine should be a multidisciplinary approach and integration of Eastern and Western Medicine as it is affordable, sustainable and equitable.

Dr. Golomb asked how someone would ascertain whether a practitioner was properly qualified and experienced to teach Tai-Chi. Dr. Wang said that she felt that instructors needed to have at least 10-15 years' experience and it was very important that they had experience with patients and could communicate with them. Dr. Wang said that it was challenging to find the right Tai-Chi instructors.

Dr. Meggs commented that they had seen a number of studies that showed improvement in treatments and it was great to see improvement, but the long term goal should be to cure all FM symptoms.

Dr. Sullivan thanked Dr. Wang for her presentation and she said that one of the issues with GWI patients was that if GW veterans tried strenuous exercise, they general experienced more pain. Tai-Chi was interesting because it is was not as strenuous and there were very positive results with fibromyalgia patients. She said it would be interesting to see how long the benefits could last from these treatments. Dr. Wang was currently looking at that to see how many times a week was most beneficial and how long the benefits lasted after the studies ended. Dr. Sullivan asked if she was going to be applying neuroimaging to her studies and Dr. Wang said that she was.

Chairman Binns thanked Dr. Wang for her presentation and then introduced LTC Knox to make a comment.

LTC Knox said that she was very angry yesterday and that she was still angry. She said that there were wonderful scientific presentations on the first day and that evidence was growing that low level chemical exposures caused damage to individuals and that GW veterans have suffered a long time. She said she served GW veterans and was honored to do so but it was coming to a cost to her own health. She said that it was very difficult for her to sit there day in and day out and listen to the evidence and then listen to the bureaucrats who did not want to move in step with the scientists. She decided to resume her seat on the Committee because of the veterans. She said that people needed veterans on the Committee to advocate for them. LTC Knox said that she was disappointed that VA did not seem to understand the needs of GW veterans particularly when the IOM's recent report gave good reviews of the current science and told scientists what they needed to do to solve the GWI problem and the DoD was continuing to support GWI research but for the VA to not accept the strategic plan that the RAC and VA staff had prepared was very upsetting. She wanted Mr. Gingrich and Secretary Shinseki to know that no one on the panel agreed with the changes that were unilaterally made to the strategic plan and she hoped that everyone in the panel would follow with

her in not accepting these unilateral VA changes and not signing off on the newly edited strategic plan. She said that Sec. Shinseki needed to listen to the Committee and that the little research money that VA had for GW research needed to be spent more wisely.

Chairman Binns thanked LTC Knox for her comments and announced a short break.

Structural MRI in Military Pesticide Personnel from the Gulf War

Dr. Kimberly Sullivan, Dr. Maxine Krengel, Boston University School of Public Health

Dr. Sullivan presented the results of her pilot study of structural MRI and cognitive functioning in pest-control personnel from the GW. She gave a brief introduction stating that GW veterans had reported lasting health symptom complaints since their return from the war in 1991 (See Appendix A – Presentation 11). She then discussed that acetylcholinesterase inhibitors such as organophosphate (OP) pesticides, anti-nerve gas pills (PB) and nerve agents are known to produce chronic neurological symptoms at sufficient exposures. Combinations of exposures to similarly acting pesticides and PB has been suggested as a likely cause of lasting health complaints in GW veterans and some military pest control applicator's exposures likely reached levels of concern for toxicity. Their exposures and unique knowledge of pesticides made them an ideal group to study.

Dr. Sullivan explained that troops used pesticides for personal use on skin and uniforms and as insect repellants, area sprays and fogs, pest strips and fly baits and as delousing agents for prisoners of war (POWs). Those who applied the pesticides were likely exposed to more pesticide products and at higher doses. They were also much more knowledgeable about pesticide types and usages. Pesticides were used widely in the Gulf War to protect the troops from pests such as sand flies, mosquitoes and fleas that can carry infectious diseases. A Health Risk Assessment conducted by DOD estimated that 41,000 GW veterans could have been overexposed to pesticides during the war. The DOD identified five pesticides of potential concern (POPC) that may have reached levels of concern in Gulf War veterans. The POPCs included the repellants, pyrethroids, organophosphates, carbamates, and organochlorines.

The most commonly used pesticide products during the Gulf War included repellants, fly baits, pest strips, sprayed liquids, sprayed powders and fogs. The general use pesticides included the repellants, fly baits and pest strips. The more controlled field use pesticides used by certified applicators included sprayed liquids, sprayed powders and fogs. Delousing of POWs was performed mostly by military police or certified applicators.

In a prior study, the Pesticide Cognition Study (PCS), a group of 159 pesticide controllers from the GW were assessed for cognitive functioning. Those in the high pesticide and high anti-nerve gas pill (PB) group reported significantly more health symptoms and performed less well on cognitive functioning measures. Results showed that GW veterans in the higher pesticide exposure group reported more total number of chronic health symptoms than the low pesticide

exposure group. When looking at the continuous performance test (a reaction time test and sustained attention test), she saw that the group with the highest exposures had the slowest reaction time response rates. She also found that individual pesticides including pest-strips, delousers, and flybaits were also found to be independently related to mood and information processing speed measures.

She then discussed the pilot pesticide MRI study and how this study utilized structural MRI and neuropsychological testing to investigate brain-behavior patterns in the same pest-control personnel from the GW. This sample included physicians, environmental science officers, entomologists, preventive medicine specialists, military police, field sanitation members and other pest controllers. Dr. Sullivan and Dr. Krengel traveled to four sites which included Texas, Florida, Missouri and Tennessee to recruit participants.

She said that the main hypothesis was that the pattern of neuropsychological function between the exposure groups would correlate with structural brain volumes and with reported health symptoms. Dr. Sullivan said that she focused on brain white matter in the study analyses because it was highly susceptible to the effects of neurotoxicants. GWI symptoms include fatigue, information processing speed and memory retrieval difficulties that are associated with WM disorders. Lower white matter volumes were found in two other studies of GW veterans related to exposure to low-level chemical weapons. She said that another system that she was interested in studying was the limbic system which was a circuit of highly interconnected midline structures in the brain that included the hippocampus. The battery of neuropsychological tests in this study included the cognitive domains of attention/executive functioning, memory, visuospatial, motor and mood. She described the Rey-Osterrieth Complex figure Test which was a test of visual memory. The California Verbal Learning Test was a test of verbal memory and the participants were asked to recall how many words they could remember after a list was read to them immediately and after a delay period. Overall, the data showed that brain white matter volumes were significantly correlated with total health symptoms reported. Brain white matter volumes were significantly correlated with the attention/executive system domain. Cerebral and cerebellar white matter and gray matter volumes were significantly lower in veterans over-exposed to pest-strips (dichlorvos) and the delouser lindane. Hippocampal volumes were significantly lower in veterans exposed to DEET and PB. This group also performed significantly worse on visual memory tests.

She concluded that although this was a small pilot study and needed to be replicated in a larger study sample, brain-behavior relationships appeared present in this study that correlated with her prior studies and with animal models of exposures that had been presented the prior day by Dr. Terry and others. These emerging brain-behavior relationships among brain imaging, neuropsychological functioning, health symptoms and environmental exposures suggested that biomarkers may be present for GWI that can be targeted for future therapeutics.

She indicated that her future research will look at brain behavior cross-talk pathways. She said that intranasal insulin could be a potential treatment for GWI and that her lab with Dr. Krengel and with Dr. Golier at the Bronx VA had received funding to do a treatment trial on intranasal insulin in GW veterans that would be starting soon. She explained that insulin is an important modulator of brain function and brain insulin receptors are located in the hippocampus and in the frontal cortex. She said that intranasal insulin did not alter peripheral glucose levels suggesting that it is safe, can be self-administered and does not change plasma glucose or insulin levels.

A member from the public said that he had insulin resistant metabolic syndrome and he asked if intranasal insulin would drive his blood insulin levels up. Dr. Sullivan responded that it could possibly alter it.

Mr. Hardie asked if all of the pesticides that she had identified as problematic were organophosphates. Dr. Sullivan said there were five classes of pesticides which were called pesticides of potential concern and there were five OPs in this group that were most of concern. She explained that the combination of chemicals is what was very concerning because of synergistic effects from these mixtures. Dr. O'Callaghan also agreed that researchers are dealing with a mixture of exposures which underlies the unique exposures that was present in the GW.

Maj Nichols asked if she or Dr. Steele had dealt with the Charleston Unit because when they were traveling overseas and coming back there was a lot of spraying that went on in the airplane and regulations were lax. Dr. Sullivan said she did not know of this unit, but she would like to get their information so that they could possibly be contacted.

Chairman Binns thanked Dr. Sullivan for her presentation and moved onto committee discussion.

Committee Discussion

Mr. James Binns, Chairman
Dr. Kimberly Sullivan

Chairman Binns summarized the Committee's concerns from the first day of the meeting. He said that he believed that everyone felt LTC Knox's frustration with the lack of commitment to GWI research evidenced in the decisions made at VA central office. He mentioned that this lack of commitment was all the more frustrating in view of the scientific progress being made in this area, as noted by Dr. Golomb and as exemplified by the presentations from the first and second day of the meeting. Chairman Binns said that the other central issue the Committee spoke about was that they could not accept the revisions of the new draft of the Strategic Plan as currently written.

He then read through a proposed recommendations related to the changes to the Strategic Plan and the other recent actions taken by VA staff. Chairman Binns noted that these were only brief examples of the issues with the new Strategic Plan.

Specifically, Chairman Binns stated that the goal of the Institute of Medicine, the Secretary of Veterans Affairs, and the United States Congress was to find treatments for GWI. The 2010 IOM Gulf War and Health Report called for "a renewed research effort with substantial commitment to well-organized efforts to better identify and treat multisymptom illness in Gulf War veterans." Secretary Shinseki declared on Feb. 27, 2010, that "At VA, we advocate for Veterans – it is our overarching philosophy and, in time, it will become our culture." In the Veterans Benefits Act of 2010, Congress directed VA to enter into an agreement with the Institute of Medicine "to carry out a comprehensive review of the best treatments for chronic multisymptom illness in Persian Gulf War veterans."

Despite these goals, some VA and Department of Defense staff members continue to fail to pursue them and to question whether Gulf War service-related health problems even exist. Chairman Binns went through several issues that the Committee discussed the previous day. He stated that the budget for VA Gulf War illnesses research was cut by two-thirds for FY2013, from $15.0 to $4.86 million and that this cut was never discussed with the Committee. The Gulf War Illness Research Strategic Plan had been gutted financially, and also the urgency, commitment, and the focus of the plan had been eliminated. The amount of research dollars being spent on GW health is being misrepresented in reports to the Secretary and to Congress and is being spent on studies that had little or nothing to do with GW veterans. The National Survey sent to Gulf War era veterans omitted the questions necessary to identify multisymptom illness and included excessive questions on stress and anxiety. The new IOM treatment study by healthcare practitioners experienced in treating Gulf War chronic multisymptom illness had been transformed by OPH into a literature review by a committee with no Gulf War expertise, who are being told that the illness is psychiatric. VA OPH has never arranged for an IOM study ordered by Congress in 2008 to determine the rate of multiple sclerosis in Gulf War veterans. ORD characterizes its Gulf War illnesses research program as "investigating whether" the health problems of Gulf War veterans are related to their service.

The Committee recommended that these failures and obstructive actions needed to be thoroughly investigated to identify the individuals responsible and that appropriate actions be taken to remove them from positions of authority and influence over GWI research.

Dr. Meggs, Dr. Steele and Mr. Hardie strongly supported the recommendations outlined by Chairman Binns. Mr. Hardie said that the Committee needed to make it clear that the intent of the recommendation was to help GW veterans. He said that right now VA was an unfortunate place for veterans, scientists, and advocates. Dr. White added that she strongly supported rejecting the Strategic Plan, and that she was very disappointed in the new changes. Chairman

Binns agreed with Dr. White's comments and that the only way this situation would change would be if there were changes in personnel who created these conflicts.

Dr. Steele asked what they would be doing with the current version of the Strategic Plan. Dr. Meggs suggested working with the January edition of the Strategic Plan instead of the new version. Chairman Binns said there were probably some nuances in the first draft that needed to be changed to make it a plan that could be adopted by VA, but that the Committee did not have confidence in the current process to be willing to go through the original document word for word. He concluded that he would like to work on this again, but with people who cared about the issue. Mr. Hardie said that the Committee had put forth a lot of effort, but the current plan did not show the concerted effort of the collective groups that worked on the plan. His sense all along was that everyone involved in this had written a comprehensive plan for GWI research that spanned bureaucratic structures and focused on outcomes that VA could feasibly focus on. He rejected the plan, and called for an investigation to find out who was responsible for the changes. He thanked everyone for their efforts and he hoped that VA leadership could eventually make this right.

The Committee agreed on the recommendations, subject to Dr. Steele's request for a few days to refine their language, as is customarily done.

Public Comments

Michael Lanning reported being a retired Staff Sergeant in the US Air Force. He handled liquid oxygen, liquid nitrogen and many other chemicals during his time in the military. He thanked the committee for inviting the public but he was disappointed in the politics with the VA and DoD. He had suffered for years from unrefreshed sleep even after practicing improved sleep hygiene. He also had trouble staying awake in the daytime and had symptoms of narcolepsy. He had lung nodules, and potentially bronchitis. He had a seventeen year old son who passed away from epilepsy and his eleven year old also had symptoms of unrefreshed sleep and was tired all the time. He said that the children of GW veterans need to be looked after also. He asked if it was possible in the future to simulcast meetings over the internet.

Dr. Sullivan said that unfortunately it was difficult for that to be done but the Committee regularly had a phone line that VA provided and the Committee would be happy to continue providing that for veterans.

Mr. Ed Brian, a retired army firefighter, was the next speaker. He had GWI and was compensated for it but received no treatment. He said that the GWI should have been included in the national survey, and he said there needed to be a survey for GWI. He said that GW veterans could not get any treatment because all the current therapies were for OEF/OIF veterans. He expressed that veterans' families also needed help and support as well. He said that VA needed

diagnostic biomarkers, basic treatments and counseling. He said that the RAC, OPH, and Environmental Health needed to work with the Office of Policy to get better funding and treatments. VA doctors were not treating and they were not compensating GW veterans properly. GW veterans needed answers and needed doctors to listen.

Jeffrey St. Julian was the next to speak. Prior to the Gulf War he was in the 25th infantry in Hawaii. He suffered from boils and sleep apnea following a series of vaccinations and now his daughter had been diagnosed with the same symptoms. He talked to some friends who also took the same vaccinations for preparation in going to the gulf. He asked if vaccinations affected the genetics of people. He also expressed that families also needed to be taken care of in addition to veterans.

Maj Nichols said that every time she thought progress in GWI was made, the walls got higher. She was concerned on how much higher they need to jump, for changes to be made. She said that veterans served the country, and now family members were having symptoms and their questions were not being answered. Their needs had not been met and the VA and the DoD were a big part of this. She said that veterans received a promise that they would receive their newsletter back for the GW vets which was very important. They needed the newsletter to come out and there was no coordination in the VA. They tried to get the VA to cooperate to get information out there. She said that it was important to work together and there was total dysfunction in the government. She concluded saying that veterans were not happy, they would stand up, they would verbalize this discontent.

A few veterans called in to speak. The first speaker had a bad phone connection and unfortunately it was inaudible. Dr. Sullivan indicated that she would be happy to accept a written public comment from this caller.

The next caller was Mr. David Lashell who was a retired air force veteran. He said that it came to his attention that Dr. Haley showed the most proof that the autoimmune systems had been damaged to the point of almost the inability to work or think for many veterans. He also said that his daughter had immune system and thyroid problems. His granddaughter had epilepsy and doctors could not control her seizures. He asked if there would be research on the children of GW veterans. He concluded thanked the Committee for their time.

Chairman Binns said that the Committee had a recommendation in the 2008 RAC report for additional research regarding the health conditions of families and that is one of the deficiencies in the current VA GWI research program. Dr. Steele said that she appreciated so many veterans speaking up about their concerns at this meeting. For the early years after the GW, family concerns were a big issue. There were registries for family, spouses and children. A large amount of information was collected, but unfortunately no information had ever been published

from the information collection. Another survey collected information about spouses and children and they found that there was an increased rate of birth defects but that was not followed up with a second round of the survey. There was a clinical study done from the first round of the survey but that information has also never been published. There was a lot of information collected, but it had never been published. In the 2008 and 2004 RAC reports, the Committee recommended that VA dig into whether or not there are excess problems, because the Committee did not know what the answer was and VA had the data to assess it.

Mr. Dave Lashell asked if there would be future research to get more information about family members. Dr. Steele responded that the Committee recommended getting it started but right now there was no study planned to do that. He then thanked her for her time.

GW Navy veteran, Wesley Crawford was the next caller to speak. He said that he would like to see a study done on the effects of modern toxicants created in places like the 9/11 attacks, as he saw limited research in this field. He felt that it could explain why recent war veterans are getting sick and could help future veterans. He said that with his symptoms he was treated like a pariah and felt that the government had betrayed him. He said he was not technically a Desert Storm veteran as the VA defined it so he was not receiving compensation because his ship served near Israel. He said he should not have these symptoms, but he was treated like he was lying when he complained of his symptoms.

Mr. Hardie mentioned that Wes Crawford raised a serious issue that the VA had yet addressed the GW veterans who served in Turkey, Israel, the Red Sea, and the Mediterranean during the war. He said that all of those veterans qualified for the Southwest Asia service medal and the DoD considered them as GW veterans, but VA had not accepted them as GW veterans for benefits. He said that was highly unacceptable since so many veterans were rejected compensation from VA, even though they were clearly GW veterans.

Dean Lockholm, another GW veteran was the next public comments speaker. He suffered from PTSD. He was in a coma in Desert Storm and has had rather serious medical problems since. He had a lot of problems through the VA and had to go through outside doctors for his medical care. He had a large range of symptoms that plagued him for 20 years. When he asked for tests from the VA, he was denied. He was now compensated for a rate of 100% for PTSD. He said it is very disappointing when a GW veteran or any veteran asks for recognition and is told that it was just stress. He stated that many veterans were not compensated and that compensation was what allowed a veteran to eat.

Angie McLamb was the next GW veteran to speak during the public comment session. She thanked the Committee for everything that they were doing, and stressed that sick GW veterans need a voice, and asked the Committee not to go away. She said that it was a hard battle but the

Committee could not quit because the veterans needed them.

Chairman Binns thanked everyone for their public comments and contributions and brought the meeting to close.

United States Department of Veterans Affairs

Diffusion Tensor Imaging in Gulf War Veterans with Chronic Musculoskeletal Pain

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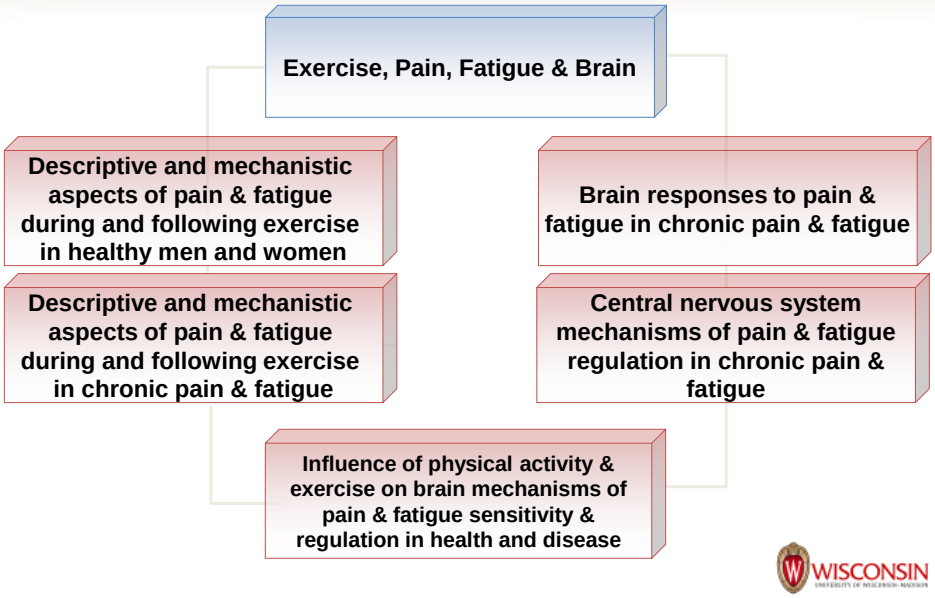
Exercise Psychology Laboratory



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Presentation Outline

www.veteransnewsnow.com

- Summary and update of previous presentation to RAC on GWI
- Preliminary diffusion tensor imaging (DTI) data
- Brief update of Gulf War Veteran resistance exercise training trial

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Chronic musculoskeletal pain in Gulf War Veterans

- 15% (100,000 of ~700,000) report chronic muscle pain symptoms (Kang et al., 2000)
- This number has grown considerably with ~200,000 veterans reporting symptoms consistent with Gulf War Illness (Research Advisory Committee on Gulf War Veterans' Illnesses (2004))
  - CMP - one of three major factors of Gulf War illness (Fukuda et al., 1997).
  - Reported twice as frequently (OR=3.06) in Gulf War Veterans (GVs) than non-GVs (Kang et al., 2000; Thomas et al., 2006)
  - Follow-up data indicate that symptoms have not resolved & that the health of GVs with GWI continues to worsen (Blanchard et al., 2006; Li et al., 2011; Ozakinci et al., 2006; Thomas et al., 2006)

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Can central nervous system dysregulation explain the persistent symptoms experienced by GVs with GWI?

- Data in FM and emerging data in GVs with CMP/GWI suggest yes?
  - Enhanced sensitivity to & diminished inhibition of experimental pain stimuli (Cook et al., 2004; 2010; Kosek et al., 1996; Lautenbacher et al., 1994; Price et al., 2002; Staud et al., 2001)
  - Enhanced sensitivity post acute exercise (Exercise-Induced Hyperalgesia) (Cook et al., 2010; Kosek et al., 1996; Mengshoel et al., 1995; Vierck, Jr. et al., 2001)
  - Augmented neural responses to experimental pain stimuli (Cook et al., 2004; Gopinath et al., 2012; Gracely et al., 2002)
  - Altered connectivity among pain modulation brain regions (Cifre et al., 2012; Craggs et al., 2012; Napadow et al., 2010)

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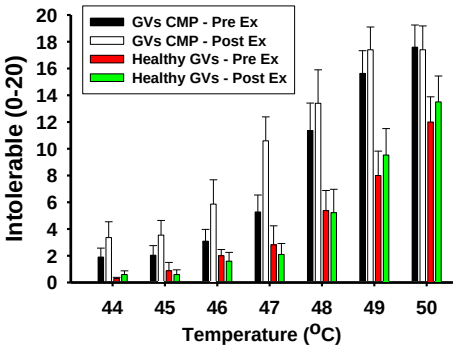
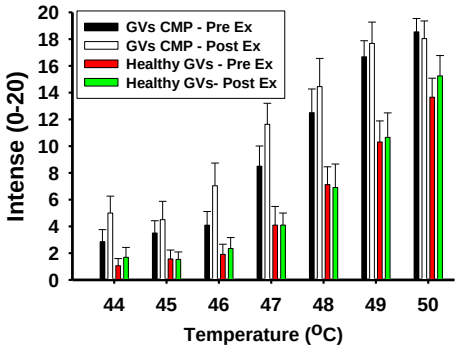
GVs w/ CMP are more sensitive to heat pain than healthy GVs and become more sensitive following acute exercise



Group*Trials*Time: $F_{6,20}=2.7$, $p<0.05$



Group*Trials*Time: $F_{6,20}=5.9$, $p<0.01$

Cook et al., 2010

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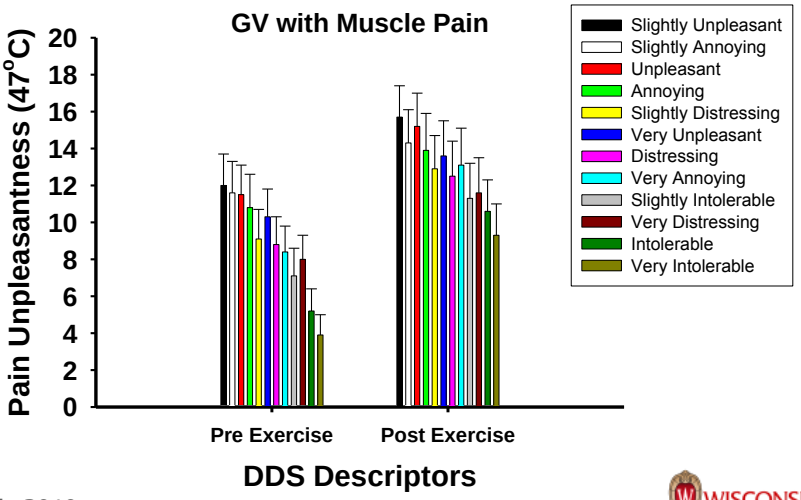
GVs with CMP demonstrated large increases in affective pain ratings from pre- to post-exercise



Cook et al., 2010

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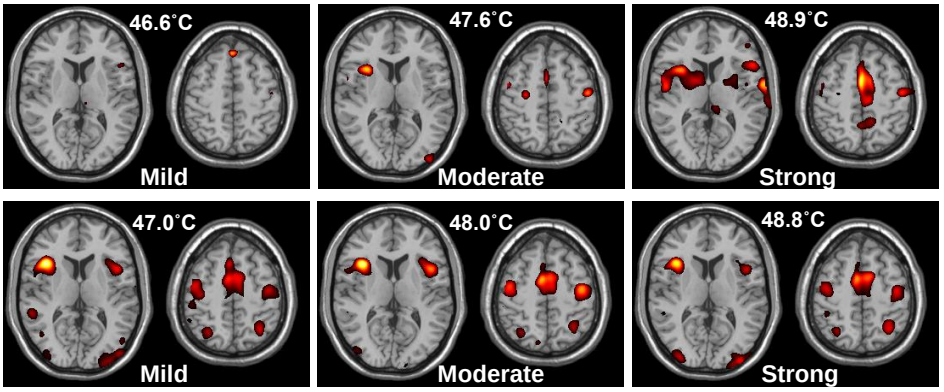
Functional MRI data demonstrating augmented brain responses to mild, moderate and strong pain stimuli in GVs with CMP



Stegner et al., In Preparation

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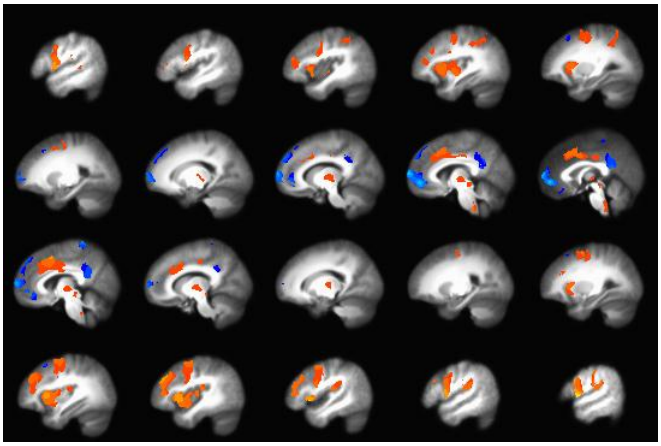
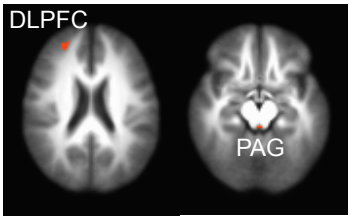
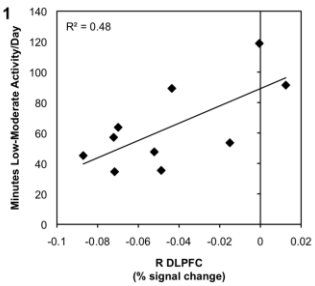
Relationships between physical activity and sedentary behaviors and pain processing

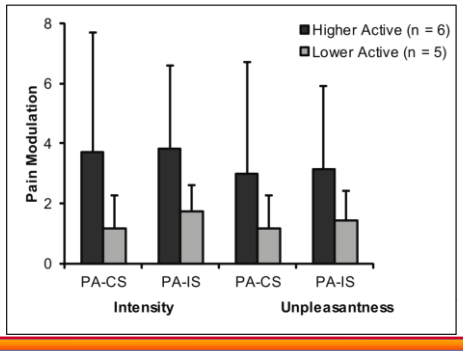


Using functional neuroimaging, we now have the opportunity to understand the mechanisms that underlie the effects of exercise on pain processing in humans.

Physical activity behaviors are positively associated with brain responses in regions involved in pain inhibition during pain modulation in FM

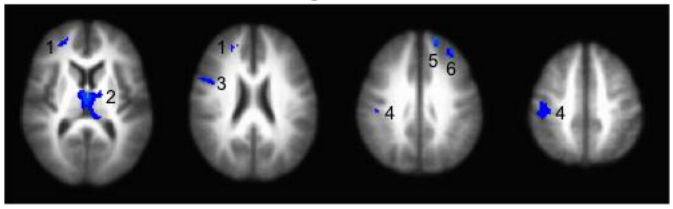


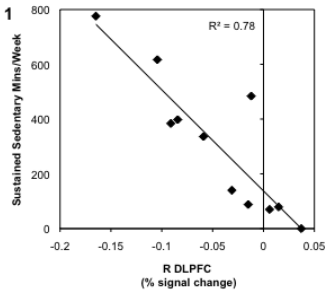


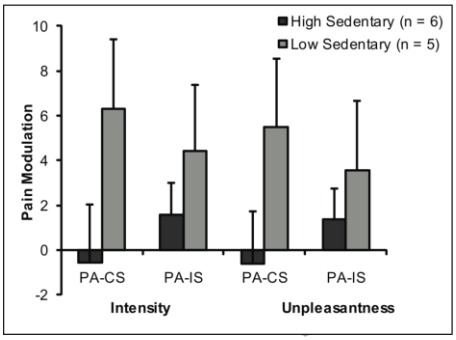


Ellingson et al., 2012

Sustained sedentary behaviors are negatively associated with brain responses during pain modulation



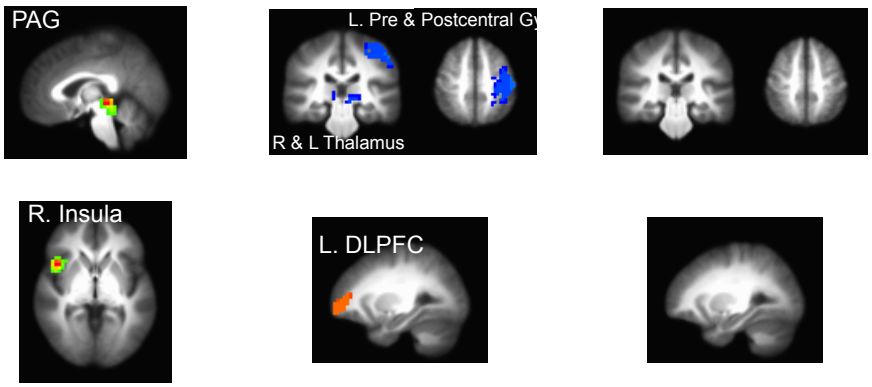




Ellingson et al., 2012

Functional Connectivity during Pain Stimuli

Seed Region | Controls | FM patients



Healthy controls demonstrated functional connectivity between regions involved in pain modulation and pain processing. These relationships were absent in FM patients.

Shields et al., 2012

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Take Home Points

- Patients with CMP are more sensitive to pain and are less efficient at regulating pain
- This may be in part due to poor communication between brain regions involved in descending pain control
- Augmented sensory processing and inefficient regulation may be one mechanism through which CMP/GWI may be maintained
- Diffusion Tensor Imaging is a method to measure the "integrity" of the neuronal connections (white matter tracts) between brain regions

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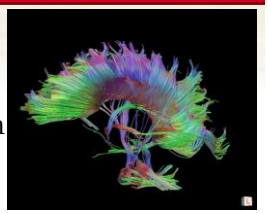
Diffusion Tensor Imaging



- An imaging modality that provides information about the diffusion of water in biological tissues
  - When water movement is random (e.g. tank of water), the movement is isotropic
  - When water movement is constrained (e.g. in a tube), the movement is anisotropic
- Healthy brain white matter is highly anisotropic, moving parallel to axonal fibers
  - Reduced anisotropy is thus interpreted as less axonal integrity & is indexed by 'fractional anisotropy' (FA)
  - Mean diffusivity (MD) is the inverse measure of axonal membrane density and is sensitive to cell edema & necrosis

FA=0

FA=.8

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DTI and Microstructure

	FA	AD λ_1	RD $(\lambda_2+\lambda_3)/2$	MD $(\lambda_1+\lambda_2+\lambda_3)/3$
Dense axonal packing	↑	–	↓	↓
High myelination	↑	↑	↓	↓
Large axonal diameter	↑	↑	↓	–
Axonal degeneration	↓	↓	↑	↑
Demyelination	↓	–	↑	↑

Sensitive to microstructural changes

Sensitive to Cellularity, edema, necrosis

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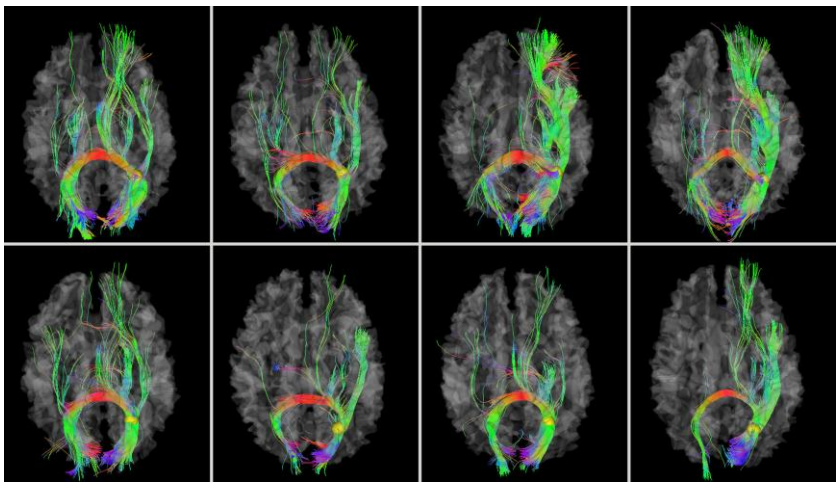
Tractogaphy



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Preliminary descriptive DTI data demonstrating decreased fractional anisotropy and increased mean diffusivity in GVs with CMP

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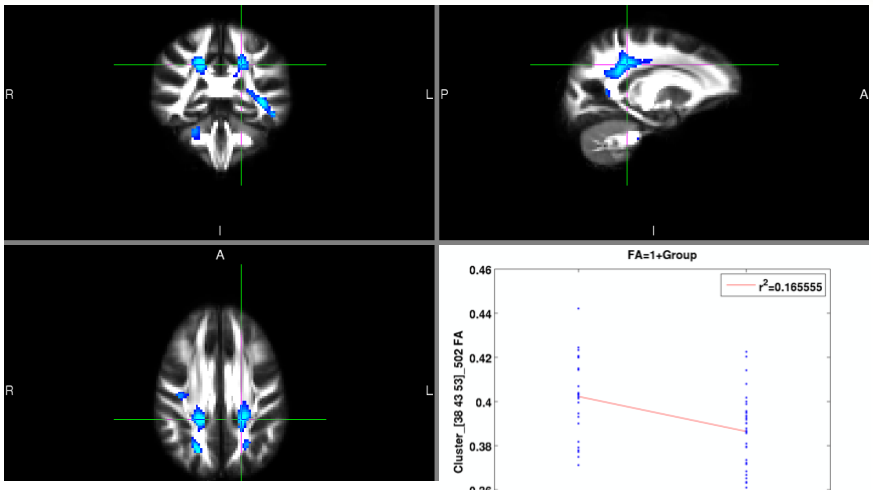
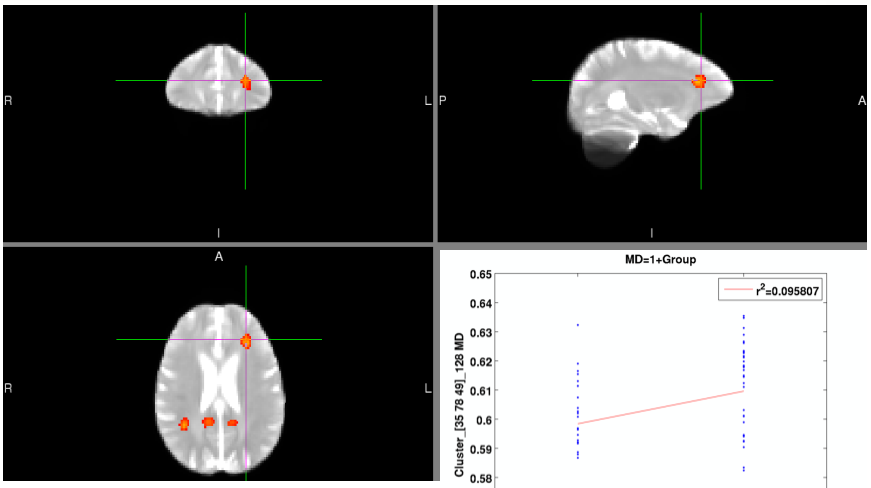
FA: GVs with CMP < Healthy GVs



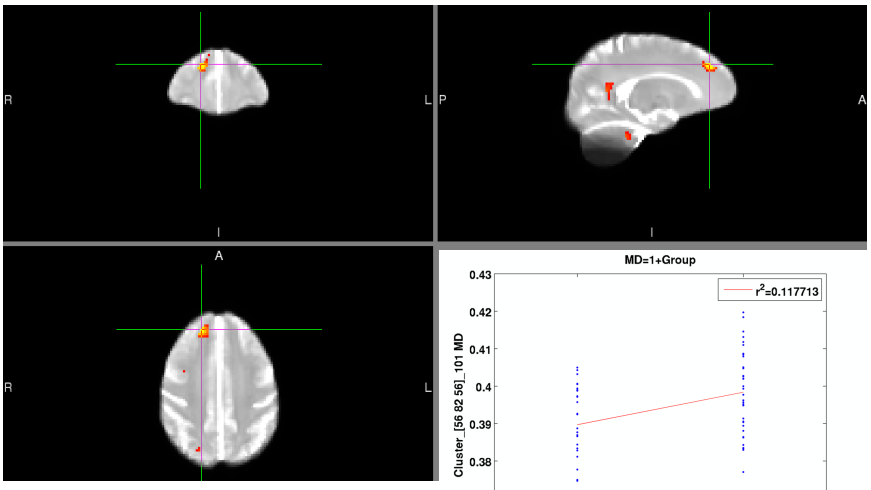
Cingulate gyrus (WM) and portions of the posterior corona radiata, postcentral gyrus and superior parietal lobule

MD: GVs with CMP > Healthy GVs



Anterior corona radiata and near the middle frontal gyrus (WM)

MD: GVs with CMP > Healthy GVs



Superior frontal gyrus (WM) & posterior cingulate cortex

Relationship to behavior

- Self-reported fatigue
- Pain sensitivity

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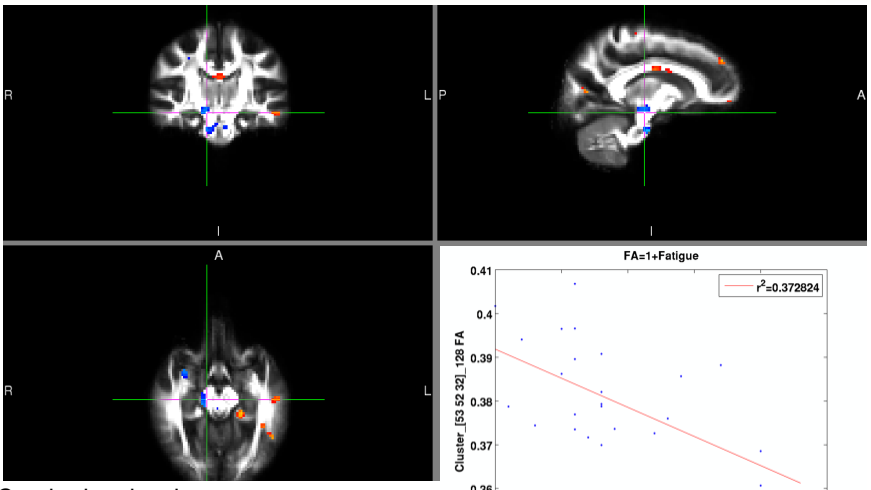
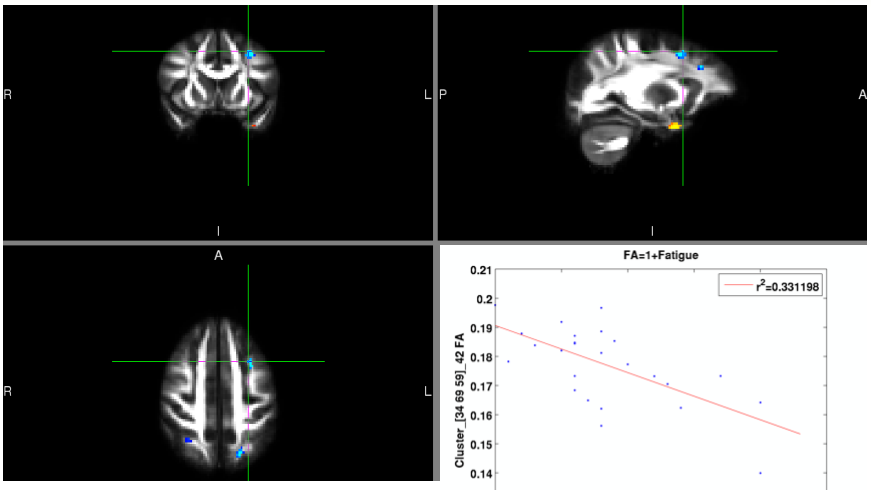
Relationship between FA and fatigue: GVs with CMP



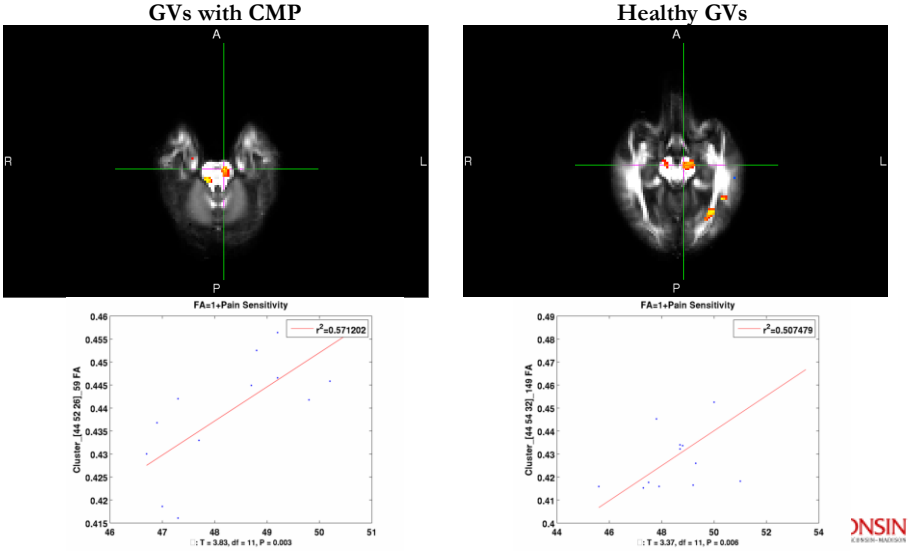
Cerebral peduncle

Relationship between FA and fatigue: GVs with CMP



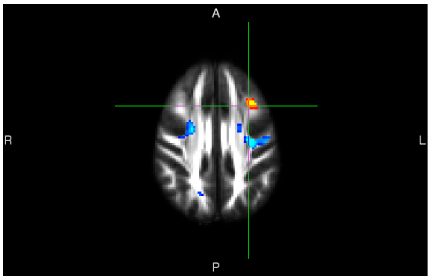
Middle frontal gyrus (WM)

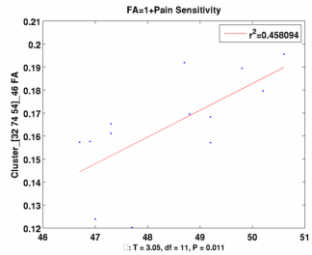
Relationship between FA and Pain Sensitivity: Corticospinal tract



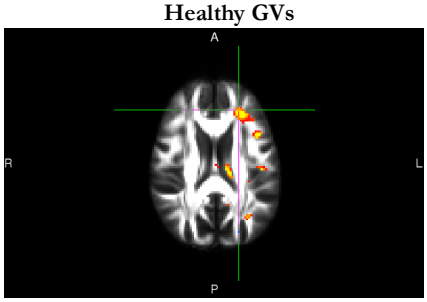
Relationship between FA and Pain Sensitivity: Middle frontal gyrus (WM)

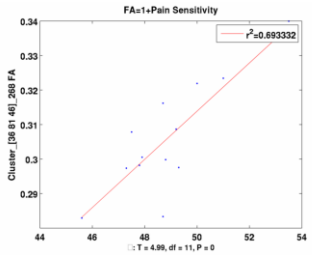
GVs with CMP





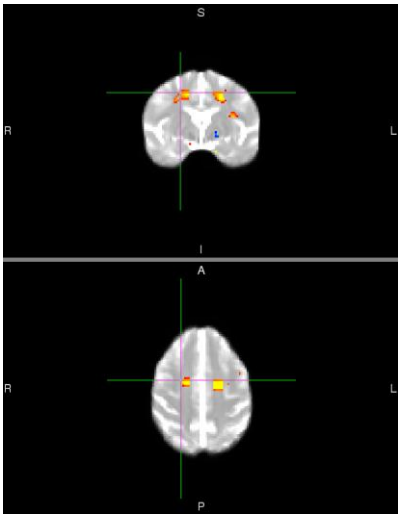
Healthy GVs



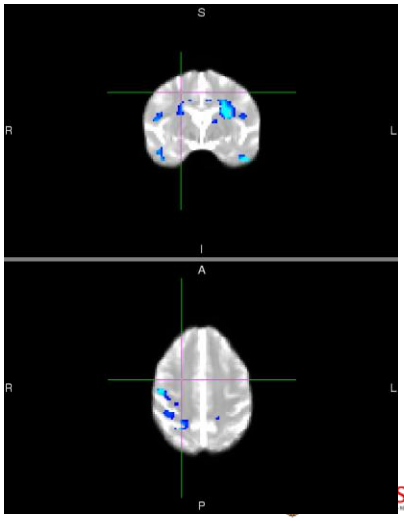


Relationship between MD and Pain Sensitivity: Superior corona radiata

GVs with CMP

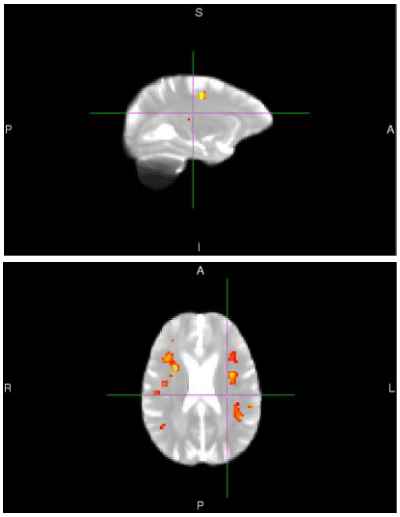


Healthy GVs

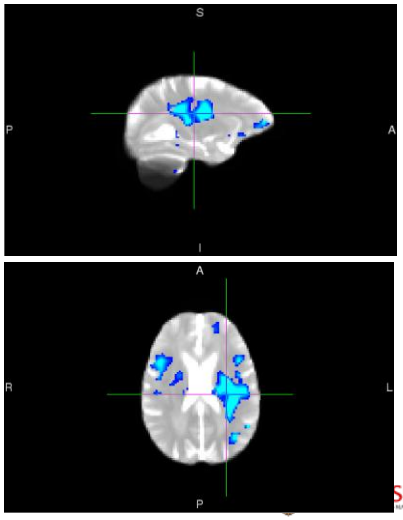


Relationship between MD and Pain Sensitivity: external & internal capsules, corona radiata, postcentral gyrus, precentral gyrus, longitudinal fasciculus

GVs with CMP



Healthy GVs



Initial interpretation of DTI data

- In general – GV with CMP show decreased white matter integrity (lower FA & higher MD) in several regions
- White matter density is associated fatigue and pain processing
- For MD there appears to be opposite relationships in GVs with CMP and healthy GVs suggestive of altered communication along spinal tracts that are involved in pain processing and modulation

A critical next step will be to determine whether potentially efficacious treatments of GWI influence brain structure and function and whether these changes predict illness improvement

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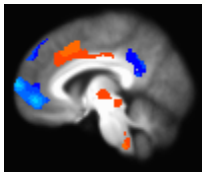
The impact of resistance exercise training on pain and brain function in GVs with CMP



Supported by: Department of Veteran Affairs Merit Review Award
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UW Exercise Psychology Lab

- Dane Cook, PhD
- Aaron Stegner, PhD
- Graduate Students
  - Morgan Shields, MS
  - Jacob Meyer, MS
  - Michael McLoughlin, MS
  - Lauren Newcomb, MS
- Study Coordinators
  - Stephanie VanRiper, BS
  - Alice Hoe, BS
  - Calisa Schouweiler, BS

Collaborators

- Waisman Center
- William S. Middleton Memorial Veterans Hospital

Funding:

- Dept. of Veterans Affairs
- National Institutes of Health

GWVI is a distinct brain disorder: Evidence from MEG

Apostolos P. Georgopoulos, M.D., Ph.D.

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University of Minnesota

Director of Brain Sciences Center
Minneapolis VA Medical Center

IOP PUBLISHING JOURNAL OF NEURAL ENGINEERING
J. Neural Eng. 4 (2007) 349–355 doi:10.1088/1741-2560/4/4/001

Synchronous neural interactions assessed by magnetoencephalography: a functional biomarker for brain disorders*

Apostolos P Georgopoulos[1,2,3,4,5,6,7,16], Elissaios Karageorgiou[1,2], Arthur C Leuthold[1,2,7], Scott M Lewis[1,3,7], Joshua K Lynch[1,2], Aurelio A Alonso[1,8], Zaheer Aslam[4,9], Adam F Carpenter[3], Angeliki Georgopoulos[10,11], Laura S Hemmy[4,12], Ioannis G Koutlas[1,13], Frederick J P Langheim[1,6,7], J Riley McCarten[3,12], Susan E McPherson[3,9], José V Pardo[4,9], Patricia J Pardo[1,4,7,14], Gareth J Parry[3], Susan J Rottunda[12], Barbara M Segal[10], Scott R Sponheim[1,9,14], John J Stanwyck[15], Massoud Stephane[4,9] and Joseph J Westermeyer[4,9]

September 2007

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J. Neural Eng. 7 (2010) 016011 (7pp) doi:10.1088/1741-2560/7/1/016011

The synchronous neural interactions test as a functional neuromarker for post-traumatic stress disorder (PTSD): a robust classification method based on the bootstrap

A P Georgopoulos[1,2,4,5,6,9], H-R M Tan[1,2,8], S M Lewis[1,3], A C Leuthold[1,2], A M Winskowski[1,6], J K Lynch[1,2] and B Engdahl[6,7]

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January 2010

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J. Neural Eng. **7** (2010) 066005 (8pp) doi:10.1088/1741-2560/7/6/066005

Post-traumatic stress disorder: a right temporal lobe syndrome?

B Engdahl[1,2,3], A C Leuthold[3,4], H-R M Tan[3,4,9], S M Lewis[3,5], A M Winskowski[1,3], T N Dikel[6] and A P Georgopoulos[3,4,5,7,8,10]

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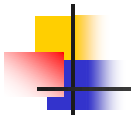
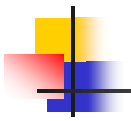
October 28, 2010



Outline of the Lecture

- Foundations: Neural communication
- Signal: Magnetoencephalography (MEG)
- Applications: Diagnosis of brain diseases
- GWVI: The latest application!

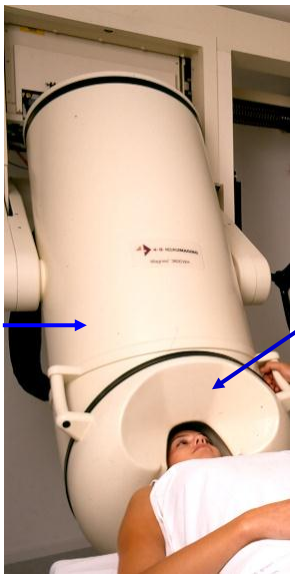


Neural Communication - 1

- The essence of brain function is communication among neural ensembles.
- Therefore, alteration in brain function should be reflected in disturbed communication.
- Conversely, disturbed communication can be informative about disordered brain function.

Neural Communication - 2

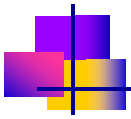
- Neural communication is accomplished by ongoing, dynamic interactions among multiple neuronal ensembles.
- These interactions can be positive or negative and can occur at different time lags.
- They can be estimated using the cross correlation function (CCF).



The MEG instrument at the Minneapolis Brain Sciences Center
(Magnes 3600WH, 4-D Neuroimaging, San Diego, CA)

MEG

- Measures magnetic signals in the brain
  - Direct (true) brain activity
  - High fidelity
  - High accuracy
  - High temporal resolution (ms)
- Ideal tool for measuring neural interactions

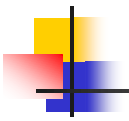


The MEG Signal

- MEG reflects integrated synaptic activity of neuronal populations → direct neural measure.
- It is not distorted and not delayed passing through tissues → faithful and instantaneous information about brain events.
- Provides outstanding temporal resolution (in milliseconds).

The Synchronous Neural Interactions (SNI) test

This test
assesses dynamic brain function
by evaluating neural interactions
at high temporal resolution
using MEG



The Test is:

- Simple (eye fixation only)
- Noninvasive (no sensors touching the head)
- Safe (just recording MEG activity)
- Short (~1 min in duration)
- Dynamic (temporal resolution of 1 ms)
- Robust (almost identical results from subject to subject)
- Sensitive to changes in brain function (excellent discriminating power for disease groups).

Data Acquisition

- Duration: 60 s (no task: subjects fixate a spot or keep their eyes closed)
- Data acquired @1017 Hz (hardware filters: 0.1-400 Hz)
- This yields 248 time series of ~60,000 values each

Data Analysis - 1

Data are analyzed as:

- Single trials
- Unsmoothed
- Unaveraged

Data Analysis - 2

Analyses are performed to estimate quantitatively the synchronous (i.e. zero-lag) interactions between signals from pairs of sensors to assess dynamic brain function.

- Step 1: Calculate all pairwise zero-lag cross-correlations
- Step 2: Calculate the partial zero-lag cross-correlations within the 248-sensor network

Data Analysis - 3

- To calculate any true (i.e. non-spurious) cross-correlation, the time series should be stationary (or quasi stationary) and non-autocorrelated

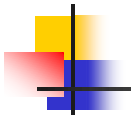
- If not, the CCF can be misleading by reflecting influences of the series themselves, unrelated to the true relations between the series

Data Analysis - 4

- Therefore, MEG time series are "prewhitened" by fitting an ARIMA (AutoRegressive Integrative Moving Average) Box-Jenkins model and taking the residuals
- This procedure yields practically stationary and non-autocorrelated series from which CCF is estimated

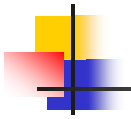
The Challenge

- Given 30628 values, find subsets of size k that could perfectly separate groups of subjects with various brain diseases



The Solution

- First pass (2007)
  - Genetic algorithms to search the immense space
  - Linear discriminant analysis to estimate percent correct classification
- Currently (2010)
  - Simple reduction of space parameters
  - Bootstrap-based classification



Initial Application to Six Groups

- Healthy control
- Alzheimer's Disease
- Schizophrenia
- Chronic alcoholism
- Multiple sclerosis
- Sjögren's syndrome (with brain involvement)

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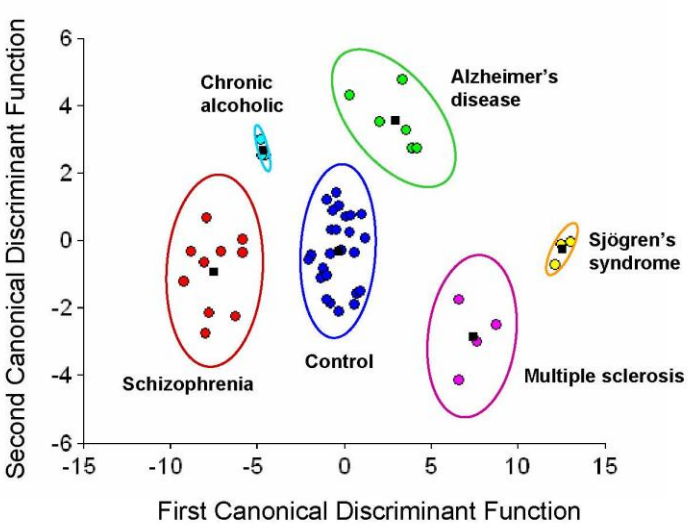
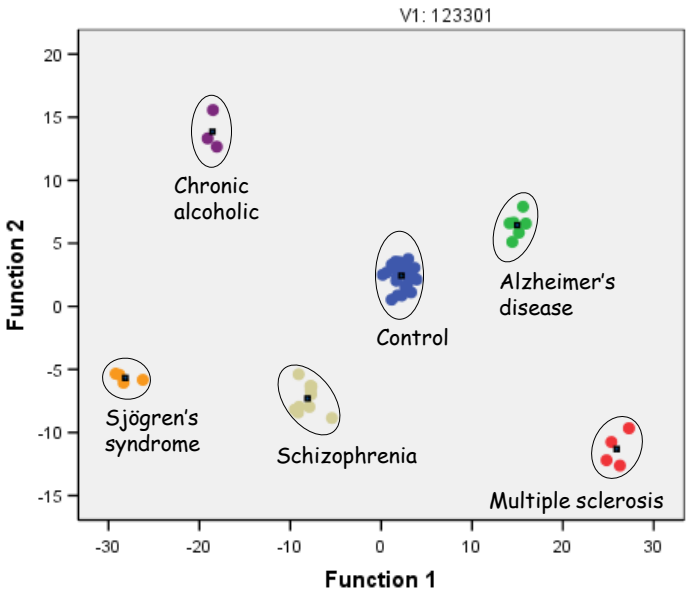
Discriminant Classification Analysis

- Linear discriminant analysis
- Robust, cross-validated leave-one-out method
- 100% correct classification of 52 subjects to one of 6 groups:
  - Healthy control
  - Alzheimer's Disease
  - Schizophrenia
  - Chronic alcoholism
  - Multiple sclerosis
  - Sjögren's syndrome
- Such sets are found using as few as 10 predictors and in numbers far in excess of those expected by chance

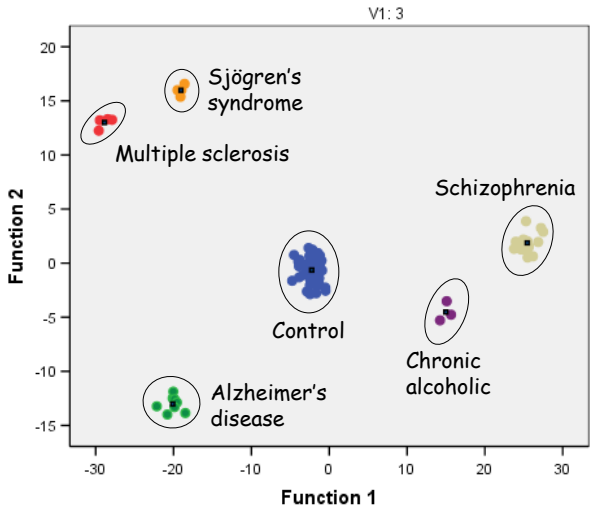


52 subjects, 20 predictors

Georgopoulos et al. (2007) J Neural Engineering 4: 347-355



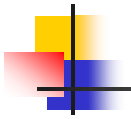
52 subjects, 40 predictors (another set)



79 subjects (Total N published = 146)

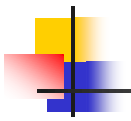
The Basic Science Behind the Test: Small-scale, High Temporal Resolution Synchronicity

- Our findings indicate a problem (in brain disease) with synchronous interactions among small neuronal populations
- A new basic science principle?



A new basic science principle

Fine-level synchronicity is a fundamental aspect of cortical function that is differentially disrupted by different disease processes, yielding a disease-specific signature.



Sources of Synchronicity

- Recurrent collaterals of pyramidal cells
- Thalamocortical afferents
  - Specific (parvalbumin)
  - Widespread, multifocal (calbindin)

Recurrent pyramidal cell collaterals

".. In the resting cortex, assemblies of idling neurons may be forced in synchronous grouped discharges by the diffuse interaction of interconnecting axon collaterals and cortical interneurons, synchronizing their spontaneous activity ..."

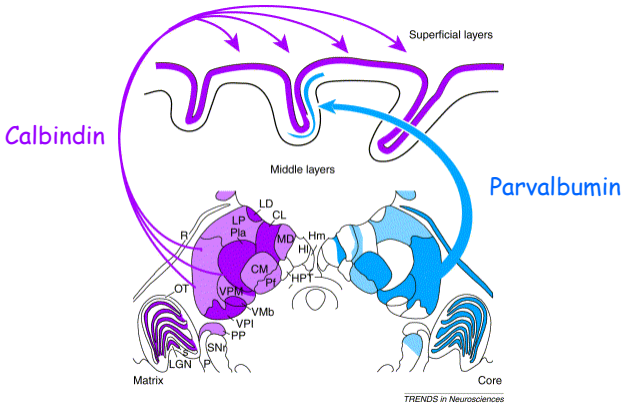
Stefanis, C. & Jasper, H. (1964)

Thalamocortical Synchrony

"Cortex is driven by weak but synchronously active thalamocortical synapses"

Bruno, R.M. & Sakmann, B. (2006)

Thalamocortical projections



Jones EG (2001) The thalamic matrix and thalamocortical synchrony. TINS 24:595-601

Future

The SNI test has the prospect of becoming the first routine test for:

- Assessing dynamic brain function
- Aiding in differential diagnosis
- Monitoring disease progression
- Evaluating the effects of intervention

Current studies: Targeted Subject Groups

Age 8-100+ y

Brain diseases

Alzheimer's disease	Fronto-temporal dementia
Autism	Gambling
Autoimmune disorders	**Gulf War Veterans Illnesses**
Bipolar disorder	Mild cognitive impairment
Chronic pain	Multiple sclerosis
Chronic alcoholism	Parkinson's disease
Depression	**Post-traumatic stress disorder**
Down syndrome	Schizophrenia
Fetal alcohol syndrome	Traumatic brain injury (mild)

Brain and PTSD

- Four steps in investigating brain and PTSD
  - 1. Prove it is a brain disease.
  - 2. Identify the specific brain abnormality.
  - 3. Quantify the brain abnormality and relate it to disease severity.
  - 4. Find out how the PTSD brain signature combines with other brain diseases in comorbidities

Brain & PTSD: Proof

- Find a brain measure that classifies PTSD and control subjects with high accuracy
  - Yes, the synchronous neural interactions
  - Georgopoulos et al. 2010
  - Current accuracy (80 PTSD, 284 controls):
    - ✓ 96% sensitivity
    - ✓ 98% specificity

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[6] Psychology Section, US Department of Veterans Affairs Medical Center (11B), Minneapolis, MN 55417, USA
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[8] Centre for Cognitive Neuroimaging, University of Glasgow, 58 Hillhead Street, Glasgow G12 8QB, UK

January, 2010

Brain & PTSD: Abnormality

- Discover the brain patterns that differentiate PTSD subjects from controls: PTSD brain signature
  - Yes, abnormal synchronicity
  - Engdahl et al. 2010
    - ✓ Right hemisphere
    - ✓ Node in temporal lobe

IOP PUBLISHING JOURNAL OF NEURAL ENGINEERING
J. Neural Eng. **7** (2010) 066005 (8pp) doi:10.1088/1741-2560/7/6/066005

Post-traumatic stress disorder: a right temporal lobe syndrome?

B Engdahl[1,2,3], A C Leuthold[3,4], H-R M Tan[3,4,9], S M Lewis[3,5], A M Winskowski[1,3], T N Dikel[6] and A P Georgopoulos[3,4,5,7,8,10]

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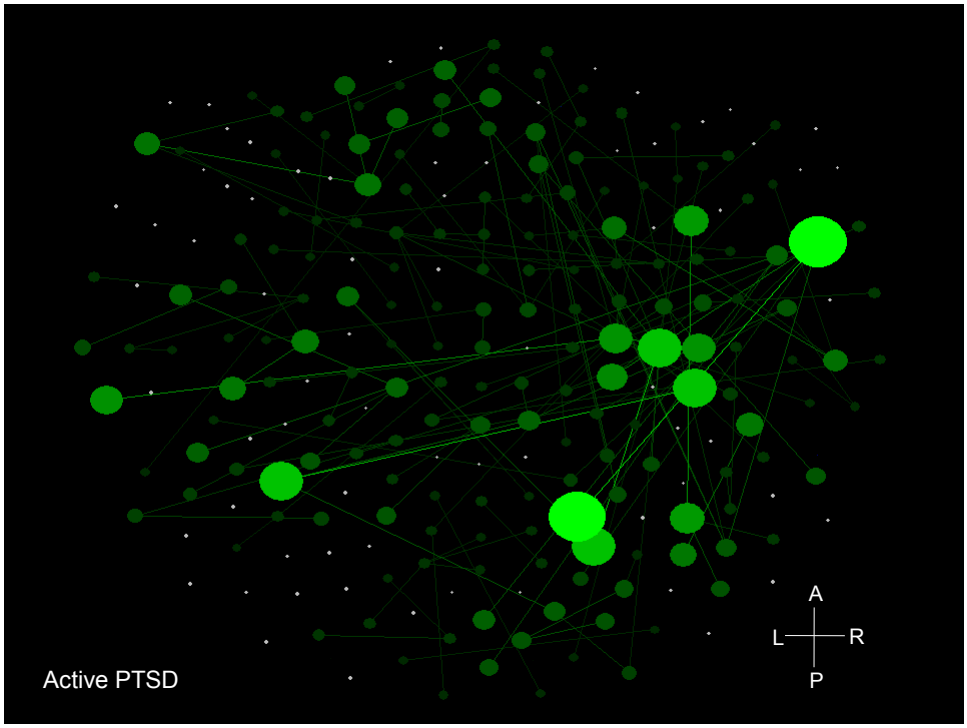
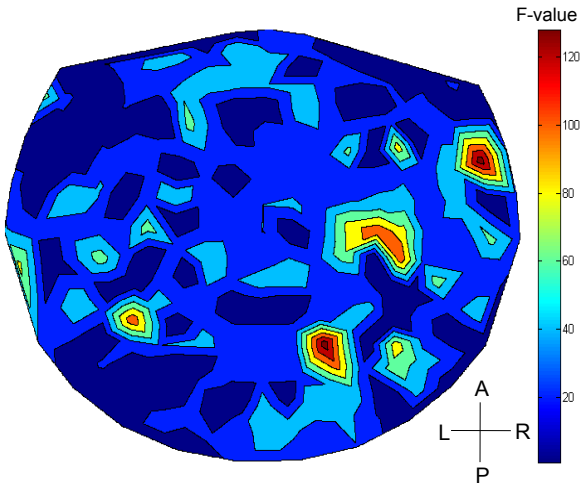
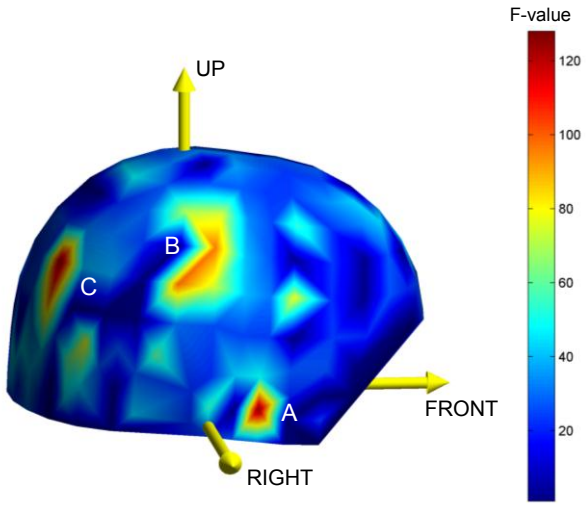
October 28, 2010





Active PTSD



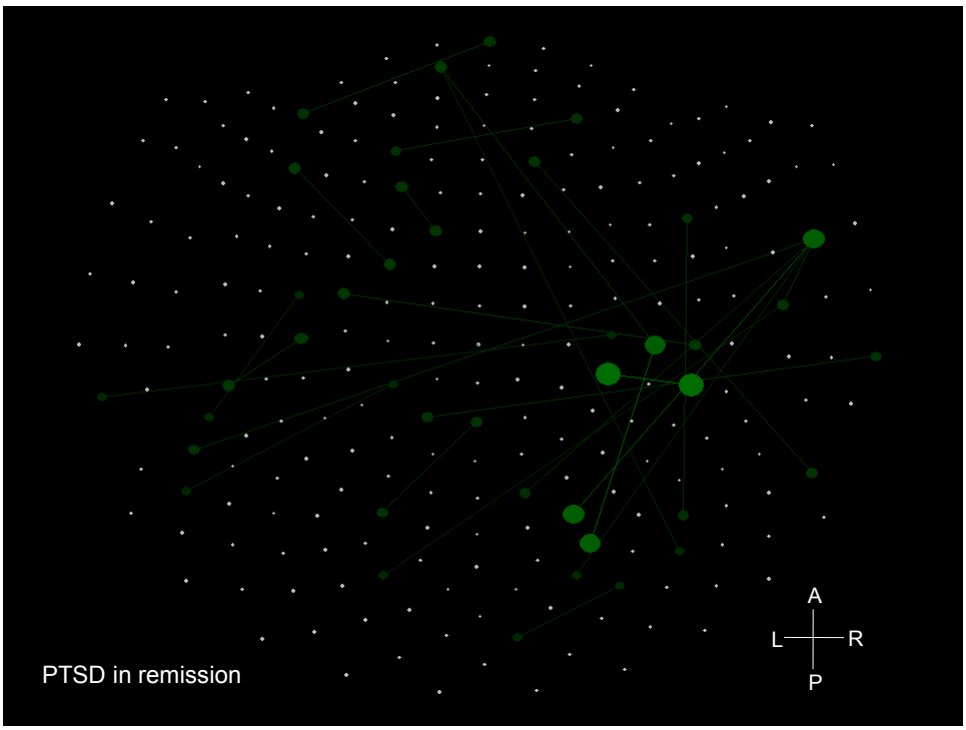
Active PTSD

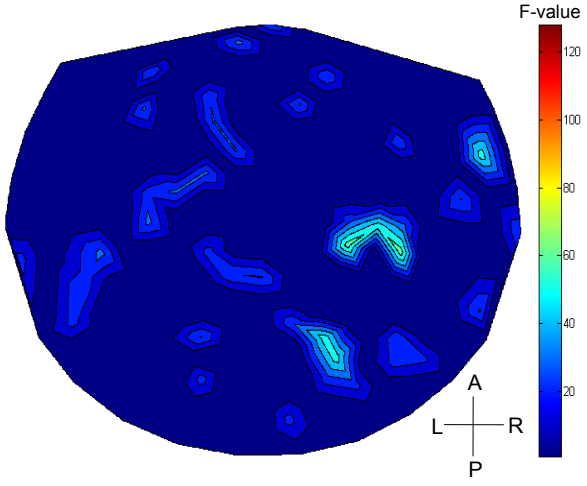
PTSD: A Temporal Lobe Syndrome

- These findings are consistent with observations by Penfield (1958), Gloor (1990), Banceaud et al (1994), Fried (1997), and others, that electrical stimulation of the temporal cortex in awake human subjects, mostly in the right hemisphere, can elicit the re-enactment and re-living of past experiences.
- Based on these facts, we attribute our findings to the re-experiencing component of PTSD and hypothesize that it reflects an involuntarily persistent activation of interacting neural networks involved in experiential consolidation

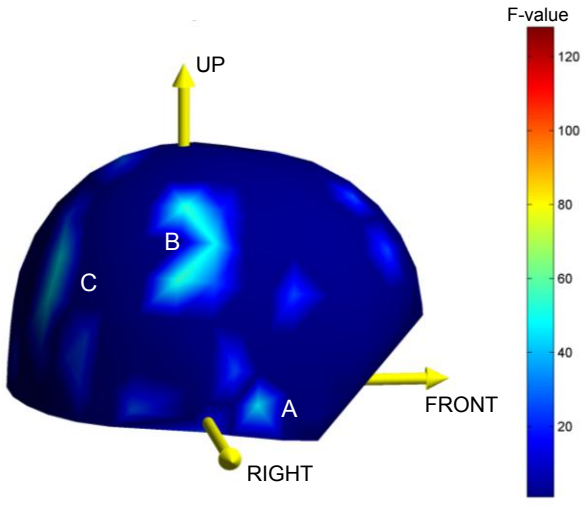
Brain & PTSD: Quantification

- Show that your measure varies with PTSD severity
  - Yes, SNIs much attenuated in PTSD in remission
  - Engdahl et al. 2010

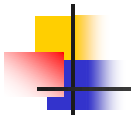




PTSD in remission

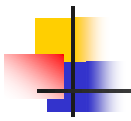


PTSD in remission



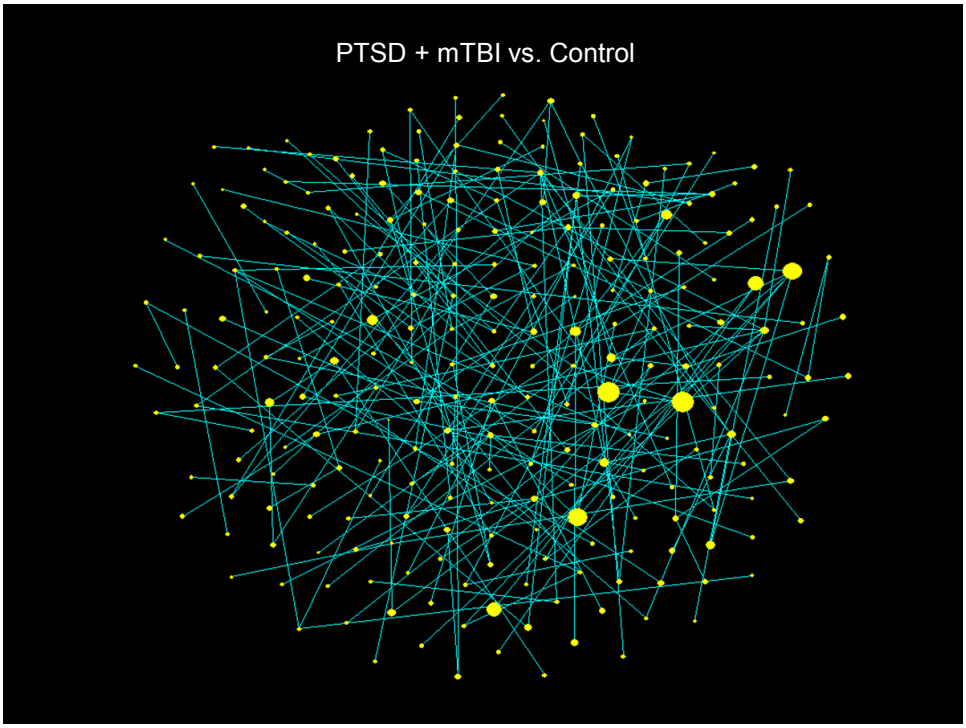
Brain & PTSD: Comorbidities

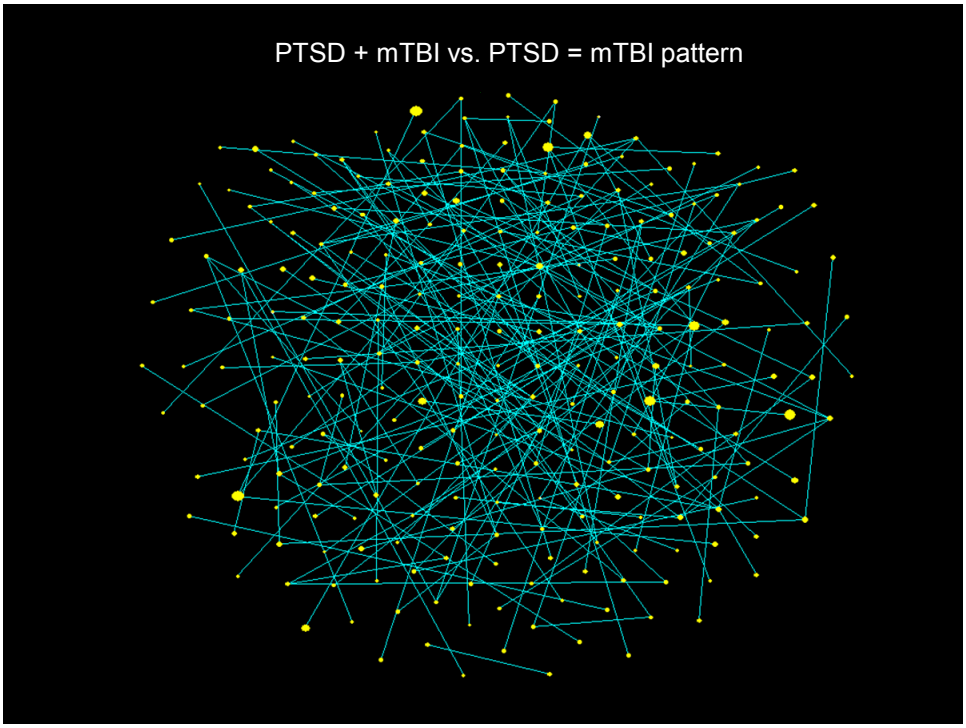
- How does PTSD brain signature combines with other brain diseases?
  - Yes, PTSD keeps its own signature!
  - mTBI (paper in preparation)

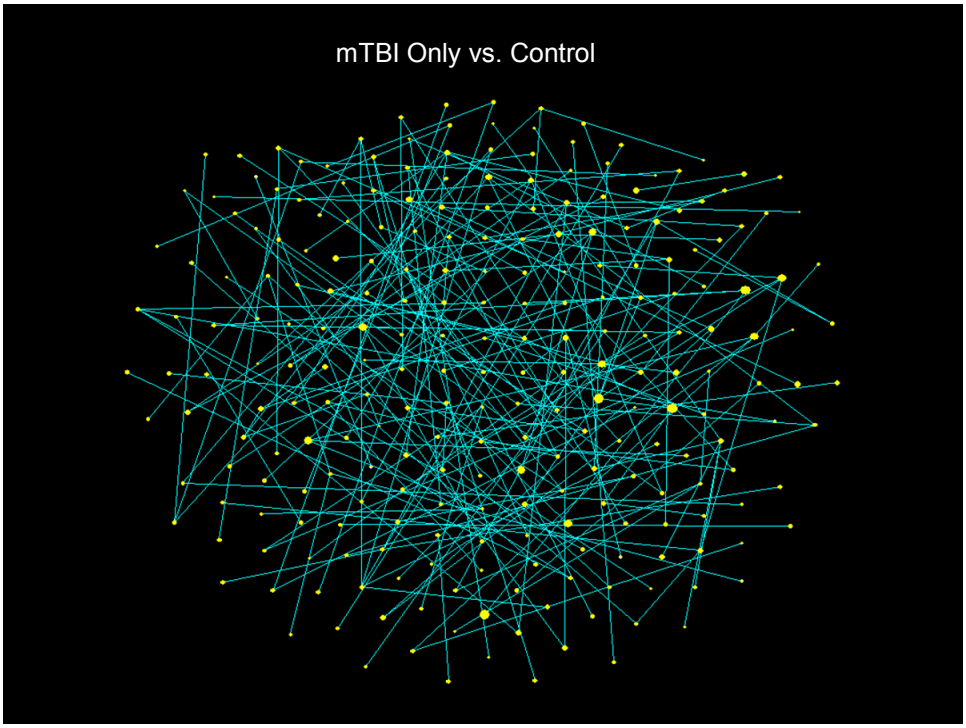


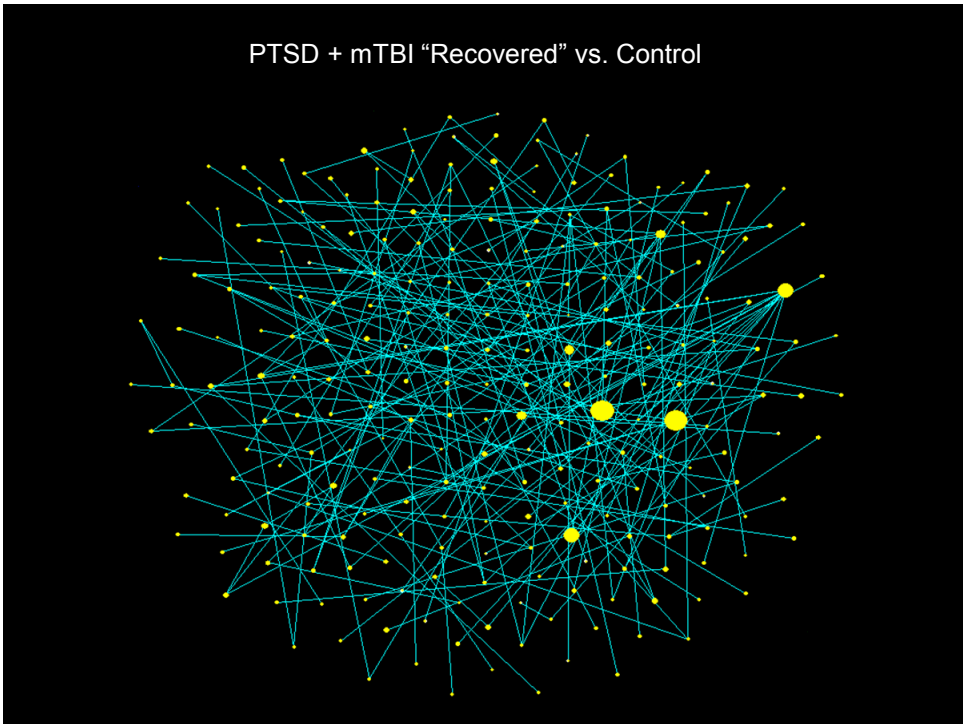
PTSD & mTBI

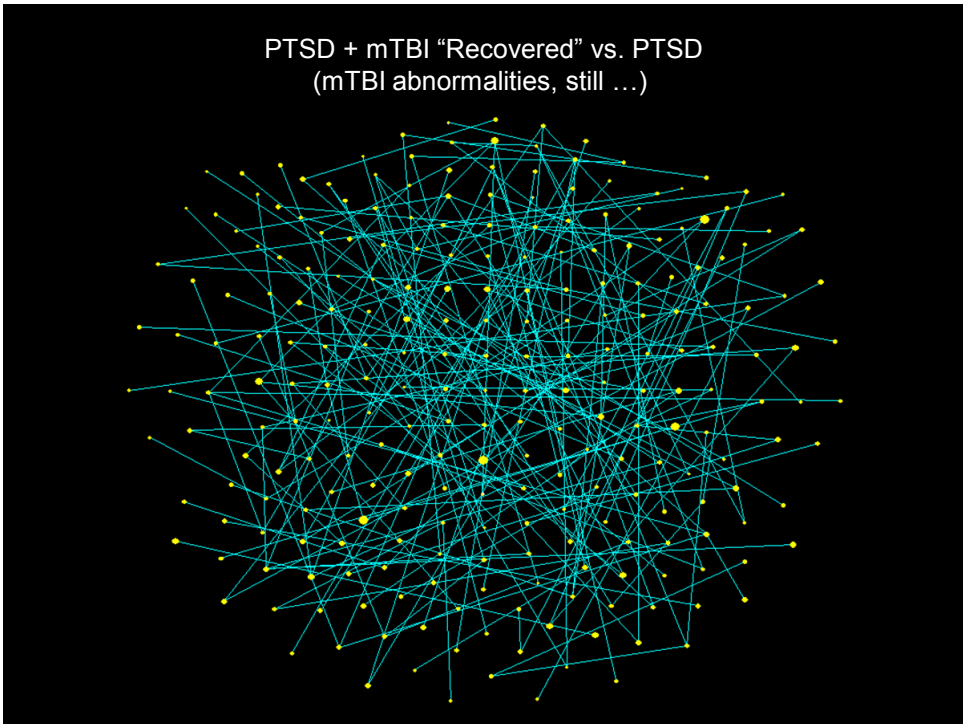
- Preliminary studies of subjects with
  - PTSD + mTBI
  - mTBI
  - PTSD + "recovered" mTBI

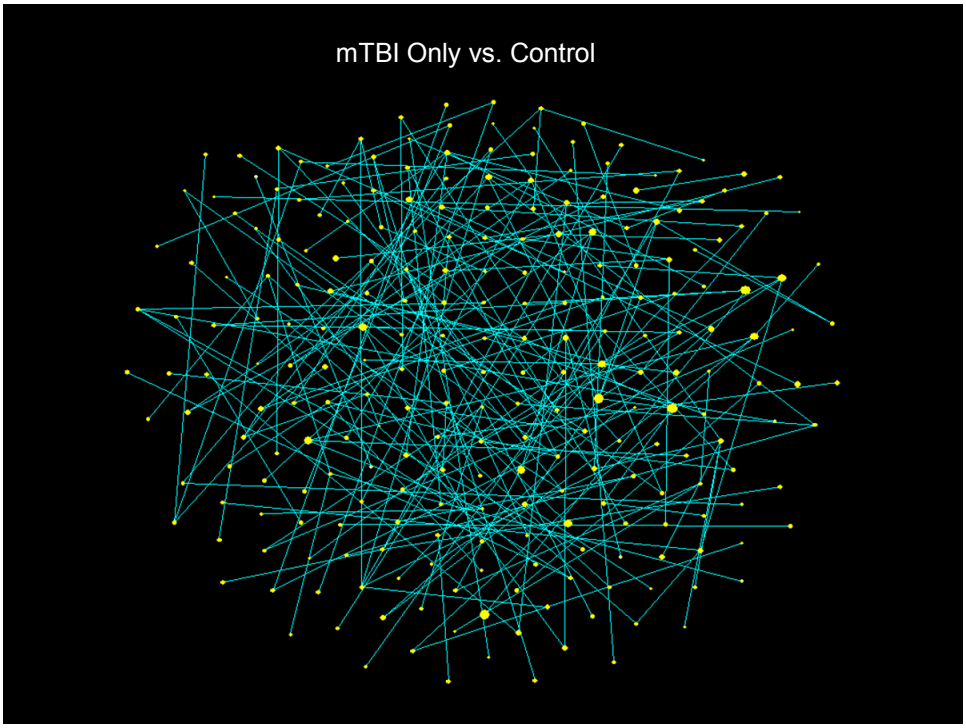

PTSD + mTBI vs. Control


PTSD + mTBI vs. PTSD = mTBI pattern


mTBI Only vs. Control


PTSD + mTBI “Recovered” vs. Control


PTSD + mTBI “Recovered” vs. PTSD
(mTBI abnormalities, still …)


mTBI Only vs. Control

PTSD: Conclusions

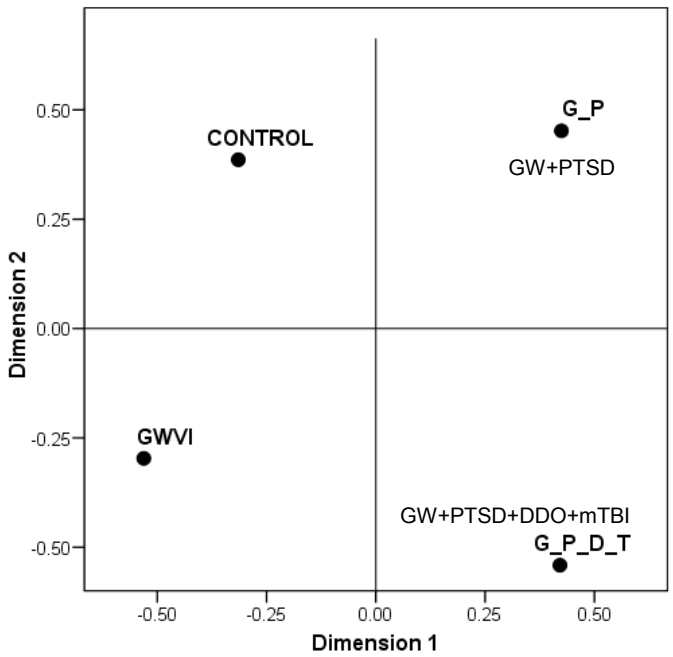
- PTSD is a brain disease
- It involves abnormal dynamic communication of brain areas mostly in the right hemisphere
- This miscommunication is graded with PTSD severity
- The SNI can aid in differential diagnosis, severity scaling and monitoring the effects of treatment
- The PTSD miscommunication pattern is additive to other abnormal brain patterns (e.g. due to mTBI)

GWVI – 1

- Goal: To apply the SNI test and evaluate potential abnormalities in neural communication in GWVI, as compared to control GWV
- Pilot study funded by the VA (started 10/1/11)
  - 13 GWV control
  - 28 GWVI (20 meeting both Fukuda CDC and Kansas GW criteria; 8 meeting only Fukuda criteria)
  - 11 GWVI with comorbidities (mental health, mTBI)
  - Investigators: L. James, PhD; B. Engdahl, PhD; A. Leuthold, PhD; S. Lewis, MD, PhD; A.P. Georgopoulos, MD, PhD

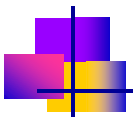
GWVI - 2

- SNI test: 30,628 partial correlations (PC) per subject
- Comparison of PC distributions between groups using the Kolmogorov-Smirnov test
- Distributions different from each other (P<0.001)
- Mapping of conditions: Multi-Dimensional Scaling (MDS)



GWVI - Conclusions

- GWVI is a distinctly separate entity
- The current study needs to be extended to larger numbers
- Detailed examination of subgroups with comorbidities
- Identification of a "core" brain abnormality?
- The MEG/SNI approach can lead to firm outcomes



The support of the

Department of Veterans Affairs and the University of Minnesota

is gratefully acknowledged

The End

Τέλος

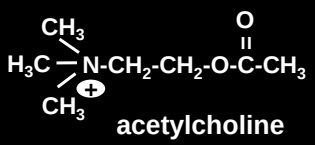
Functional Consequences of Repeated Organophosphate Exposure: Potential Non-Cholinergic Mechanisms

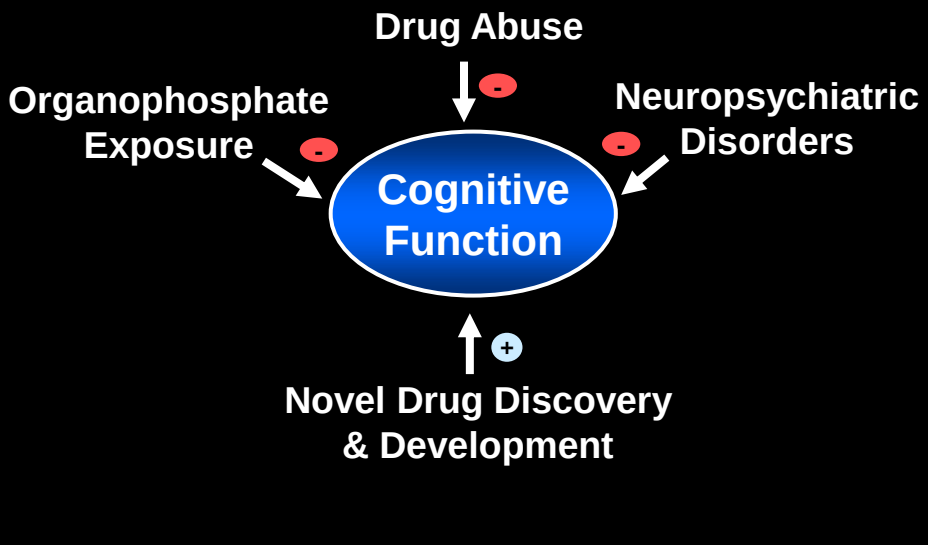
Alvin V. Terry, Jr., Ph.D.

Professor of Pharmacology and Toxicology

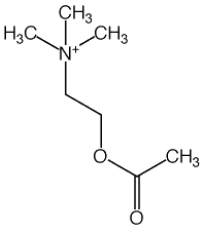
Georgia Health Sciences University

Terry Lab Interests

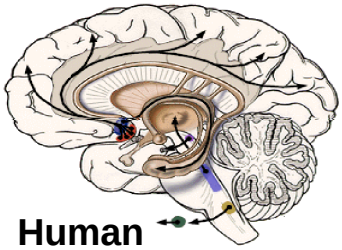




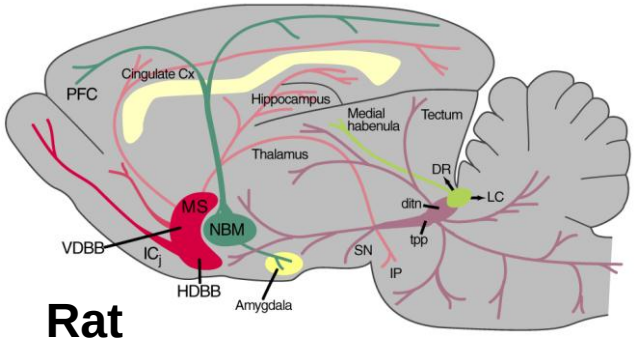
Central Cholinergic Pathways



Acetylcholine



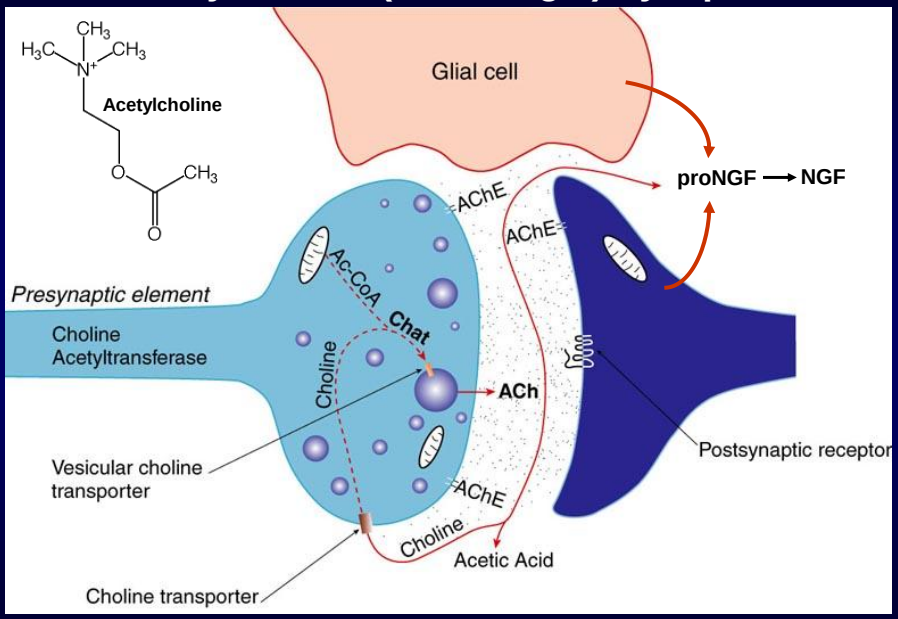
Human



Rat

Source: "Fundamental Neuroscience", Second Edition, Copyright, 2003, Academic Press

Acetylcholine (cholinergic) Synapse



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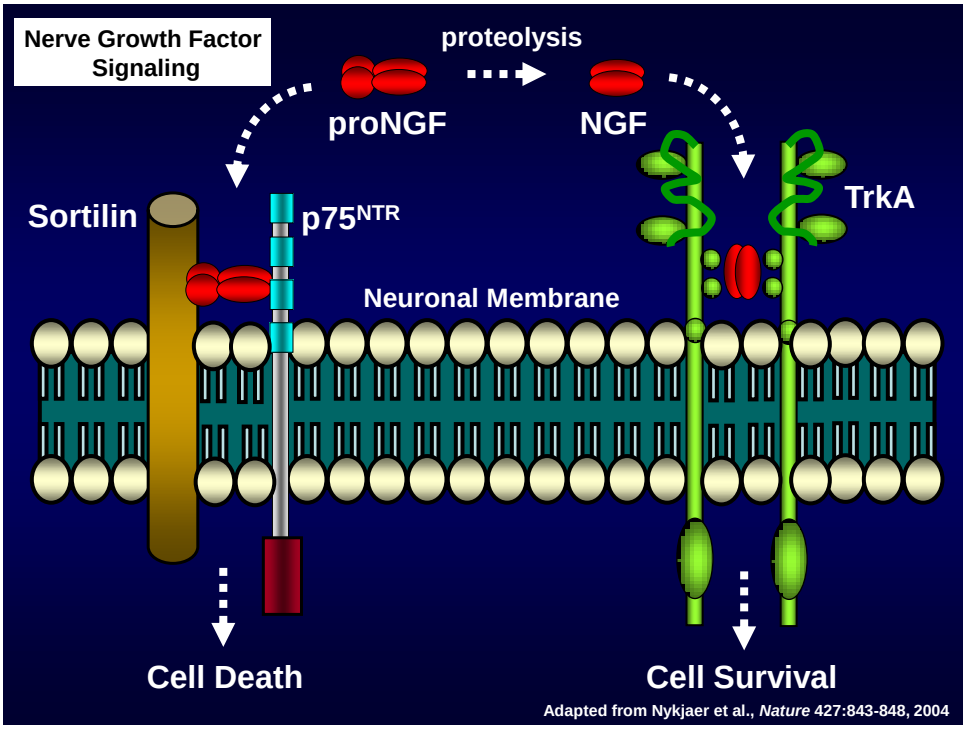
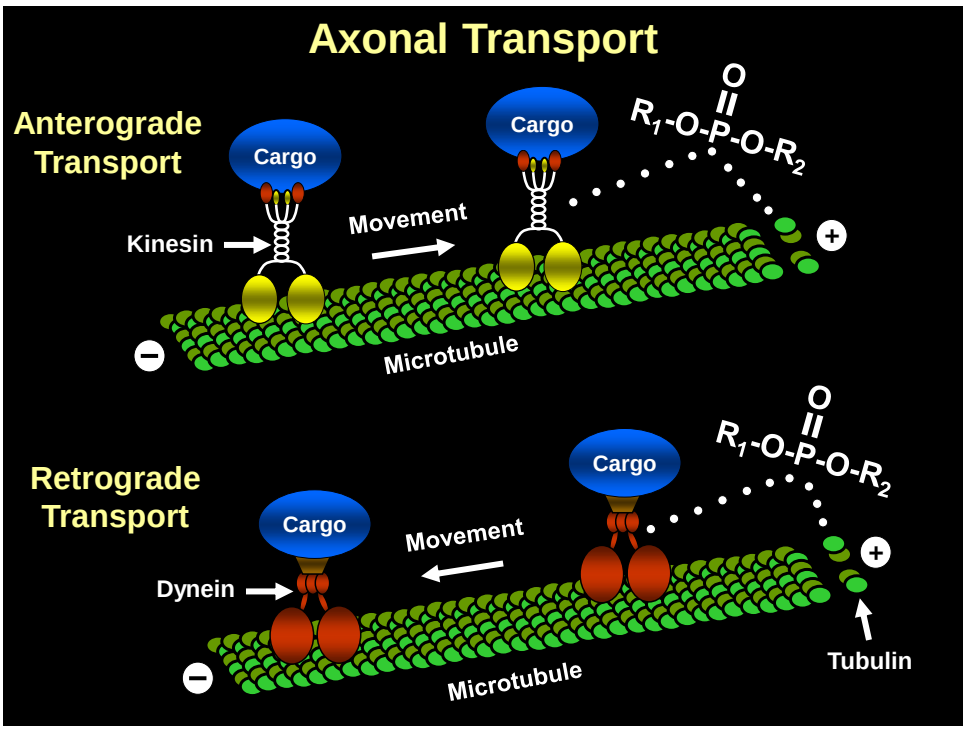
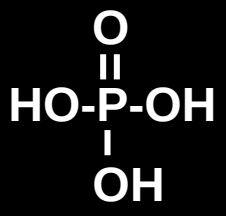

Nerve Growth Factor Signaling
proteolysis
proNGF
NGF
Sortilin
p75NTR
TrkA
Neuronal Membrane
Cell Death
Cell Survival
Adapted from Nykjaer et al., Nature 427:843-848, 2004

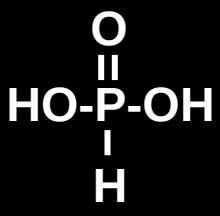

Axonal Transport
Anterograde Transport
Cargo
Kinesin
Movement
Microtubule
Retrograde Transport
Dynein
Tubulin

Organophosphates

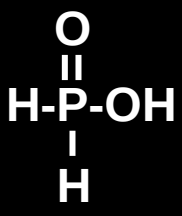
Chemicals Derived From:



Phosphoric Acid



Phosphonic Acid



Phosphinic Acid

Organophosphate-Based Chemicals Found in:

- Insecticides (e.g., malathion, parathion, diazinon, chlorpyrifos)
- Chemical Warfare ("nerve") Agents (e.g., soman, sarin, tabun, VX)
- Ophthalmic Agents (e.g., echothiophate, isoflurophate)
- Antihelmintics (e.g., trichlorfon)
- Herbicides (e.g., tribufos, merphos)
- Solvents, Plasticizers, and Extreme Pressure Additives for Lubricants

Reviewed, Katz and Brooks, 2010

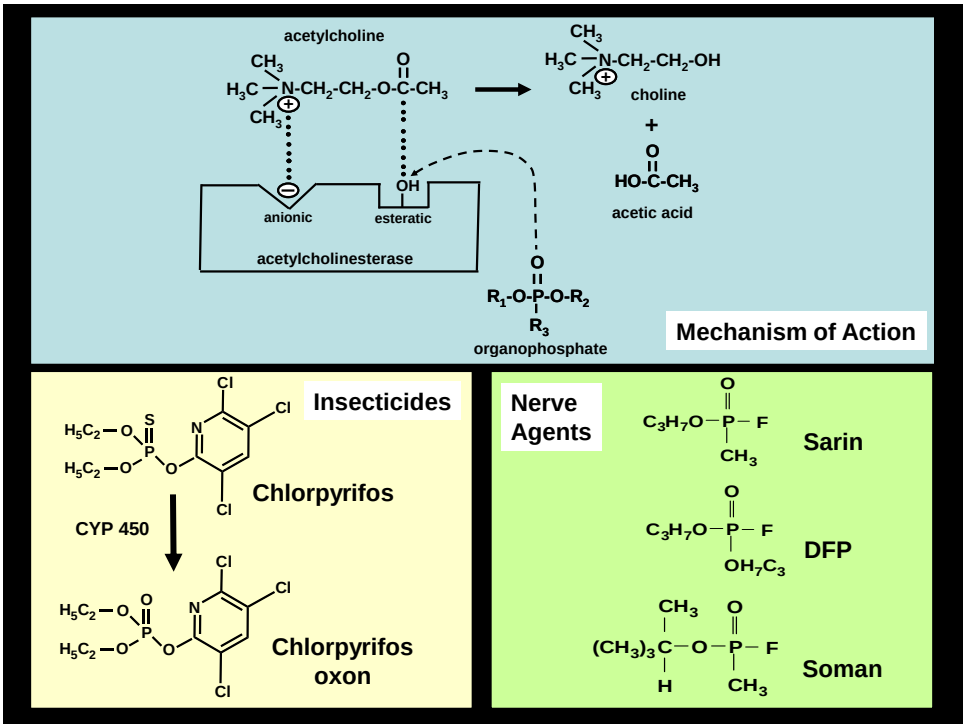
Gulf War Illness and OPs

- Exposure to one or more acetylcholinesterase inhibitors appears to offer a particularly plausible explanation for several of the neurological-based symptoms of GWI (Golomb et al., 2008)
- An estimated 41,000 military personnel in the first gulf war were exposed to insecticides that contained either carbamate or OP-based AChEIs (Fricker et al., 2000; US Department of Defense, 2003)
- As many as 100,000 military personnel may have been exposed to low (i.e., non-acutely toxic) levels of sarin/cyclosarin following the destruction of an Iraqi munitions storage complex at Khamisiyah, Iraq, in March 1991 (Berardocco, 1997).

OP-Pesticide Use in the First Gulf War

- Fly Bait
  - azamethiphos
- Pest Strips
  - dichlorvos
- Sprayed Liquids
  - chlorpyrifos, diazinon, malathion
- Fogs
  - chlorpyrifos, malathion

Source: http://www.gulflink.osd.mil/pest_final/index.html.



Organophosphate Toxicity

- **Acute**
  - Muscarinic (postganglionic parasympathetic) "DUMB-BELS": diaphoresis and diarrhea, urination, miosis, bradycardia, bronchospasm, emesis, lacrimation, salivation.
  - Nicotinic (neuromuscular junction)- muscle fasciculations, weakness, paralysis, respiratory failure; (CNS)- seizures or CNS depression/coma.
- **Chronic and/or Repeated Low-Level Exposures***
  - Anxiety, depression, psychotic symptoms, deficits in short-term memory, learning, attention, information processing, eye-hand coordination and reaction time, and extrapyramidal symptoms.

* Data primarily from case reports and retrospective epidemiological studies.

Overall Objectives

- Determine the consequences of repeated, "subthreshold" exposures to representative organophosphates on cognitive function in animal models.
  - Information processing and attention
  - Spatial Learning
  - Recognition Memory
  - Working Memory
- Determine the consequences of repeated, low-level exposures to representative organophosphates on neurobiological substrates of cognitive function
  - Cholinergic Markers
  - Neurotrophins
  - Axonal Transport
- Identify therapeutic targets for drug development

Study Algorithm

OP-Free Washout

Cognitive Function
- Water Maze
- Novel Object Recognition
- Prepulse Inhibition
- 5C-SRTT
- Radial Arm Maze

Cholinergic Markers
- Enzyme Assays
- Receptor Autoradiography
- Western Blot

Neurotrophins (NGF)
- Western Blot
- Immunohistochemistry

Axonal Transport
- Mitochondrial Movement
- βAPP Immunohistochemistry
- Mn^{2+} Enhanced MRI

Summary of Previous Chlorpyrifos Studies (repeated Subthreshold exposures)

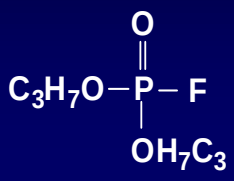
- Impairments in spatial learning
- Impairments in Prepulse Inhibition of the auditory startle response
- Decreased expression of cholinergic marker proteins in the brain
- Decreased expression of neurotrophin-related proteins in the brain
- Impairments of anterograde and retrograde axonal transport ex vivo

Terry et al., *J. Pharmacol Exp Ther* 305: 375-384, 2003.

Terry et al., *J. Pharmacol Exp Ther* 322: 1117-1128, 2007.

Recently Published Studies

Chlorpyrifos



DFP

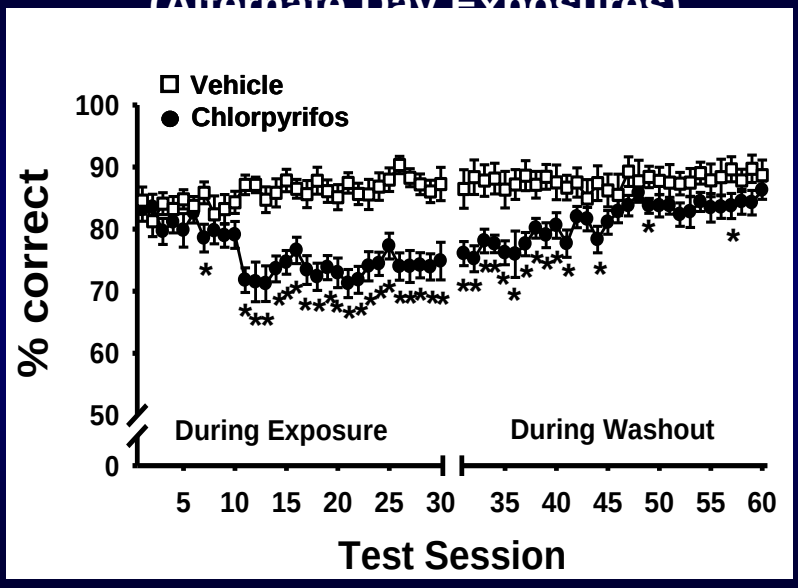
The Rat, Five Choice Serial Reaction Time Task (5C-SRTT)

Continuous Performance Task (CPT)
AX Type

Hit Lever ↓

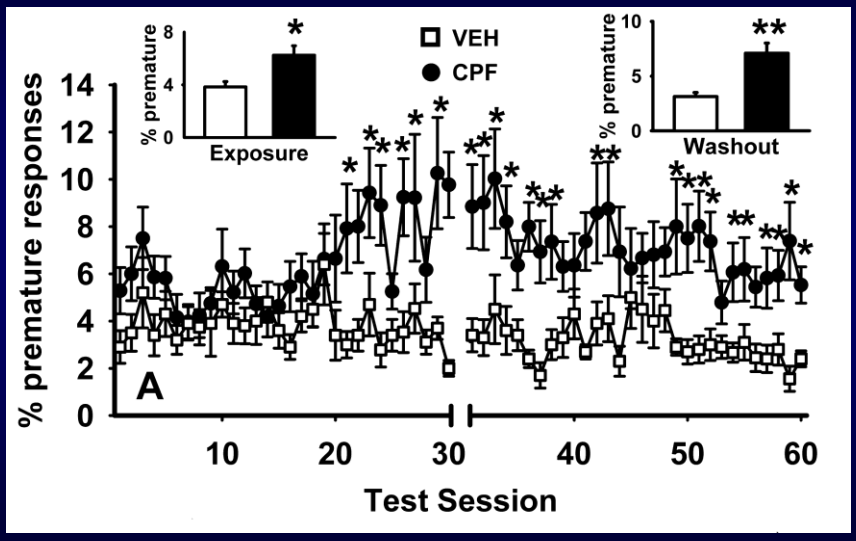
A H X J A K XO I Y A U B A X

5C-SRTT-Chlorpyrifos
(Alternate Day Exposures)



Middlemore-Risher et al., Neurotoxicology and Teratology 32: 415–424, 2010

5C-SRTT-Chlorpyrifos (Alternate Day Exposures)



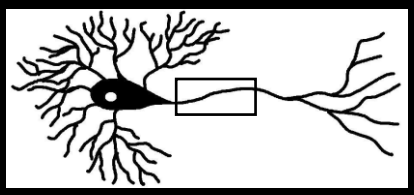
Middlemore-Risher et al., Neurotoxicology and Teratology 32: 415–424, 2010

5C-SRTT-Chlorpyrifos Experiments Conclusion

- Repeated exposures to subthreshold levels of chlorpyrifos lead to protracted impairments of sustained attention and an increase in impulsive behaviors in rats.

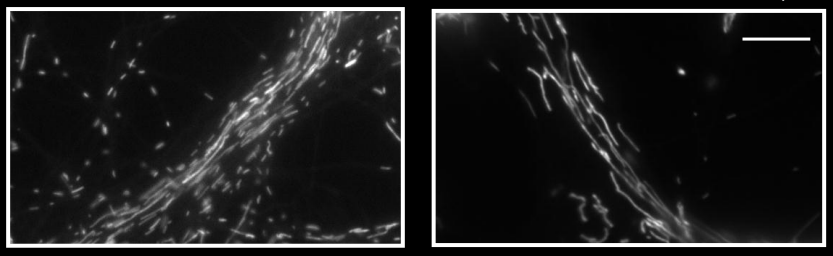
Middlemore-Risher et al., Neurotoxicology and Teratology 32: 415–424, 2010

MitoTracker® Imaging Measurements



Movement = mean # moving/μm
Length= average length in the ROI
Number= # of mitochondria/μm

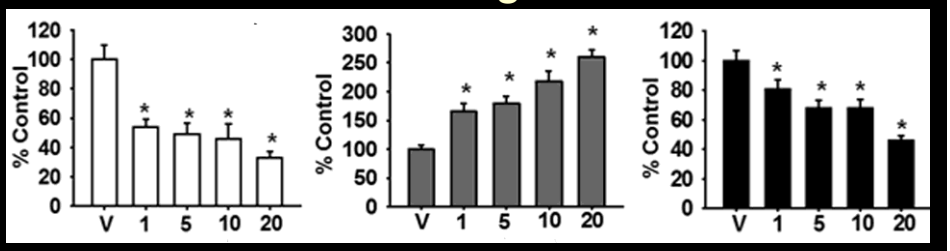
Scale bar= 100 μm



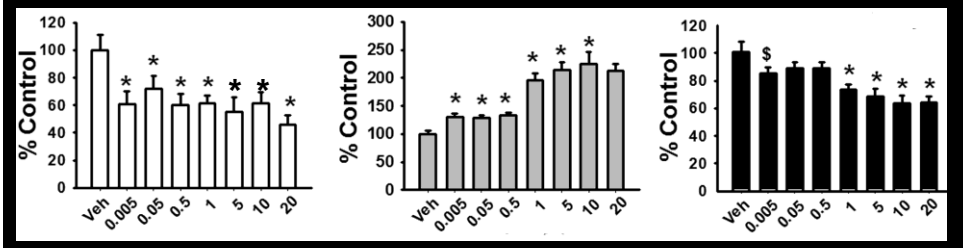
Vehicle **CPF oxon (5.0 nM)**

Middlemore-Risher et al., *J Pharm Exp Ther* 339:341-349, 2011

Movement Length Number



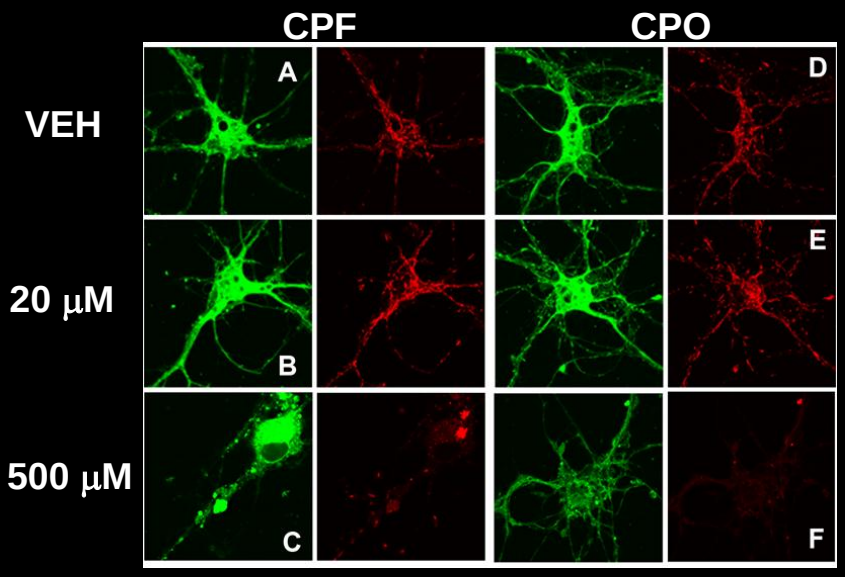
Chlorpyrifos (μM)



Chlorpyrifos oxon (μM)

Middlemore-Risher et al., *J Pharm Exp Ther* 339:341-349, 2011

DePsipher™ Assay

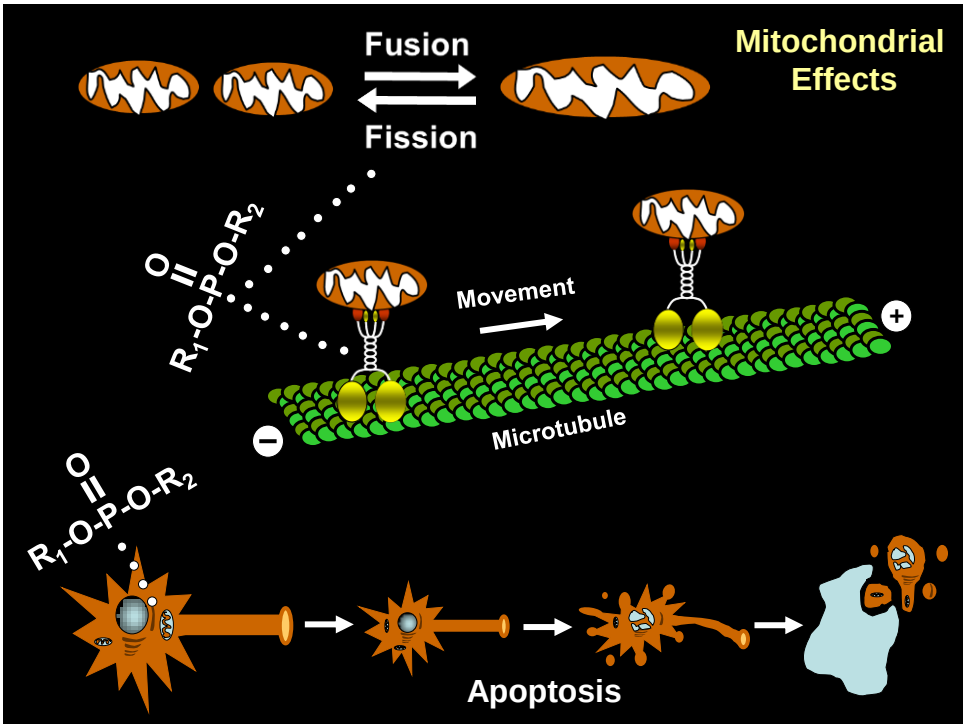


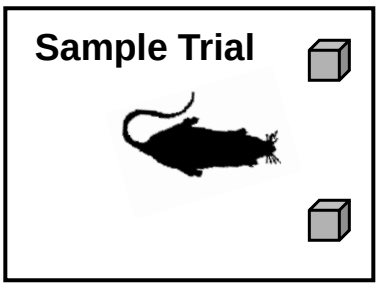
Middlemore-Risher et al., *J Pharm Exp Ther* 339:341-349, 2011

Summary (CPF & CPO in Neuronal Culture)

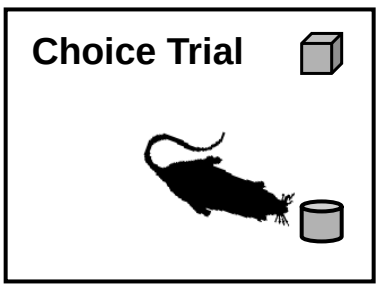
- Concentration-dependent decrease in the transport of mitochondria in axons, an increase in mitochondrial length, and a decrease in mitochondrial number (indicative of increased fusion versus fission events)
- The neuronal changes occurred at OP concentrations that did not inhibit AChE activity, they were not blocked by cholinergic antagonists, and they did not appear to be associated with directly toxic effects on mitochondria (i.e., alterations in ATP production, mitochondrial membrane potential, superoxide production).
- The results suggest that an underlying mechanism of OP-based alterations in neurological function might involve alterations in mitochondrial dynamics and/or their transport in axons.

Middlemore-Risher et al., *J Pharm Exp Ther* 339:341-349, 2011



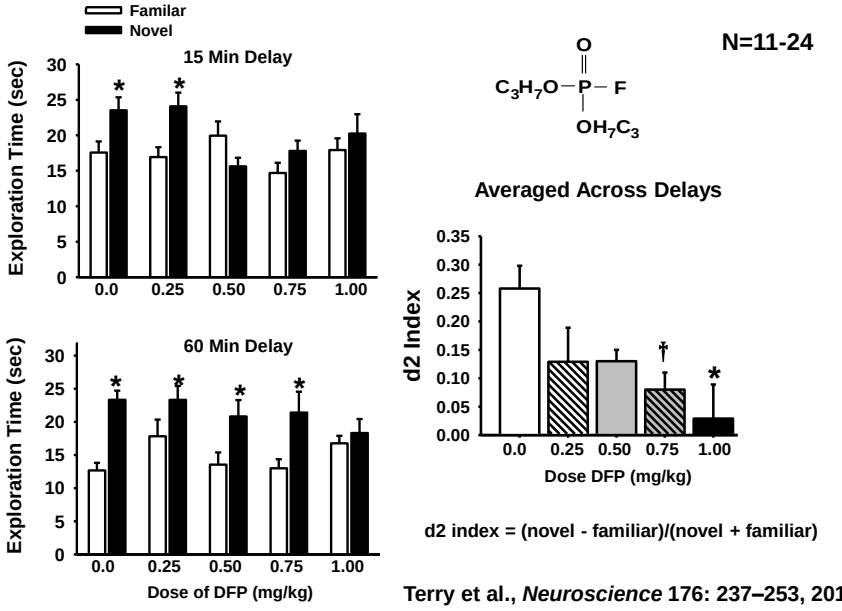


Delay



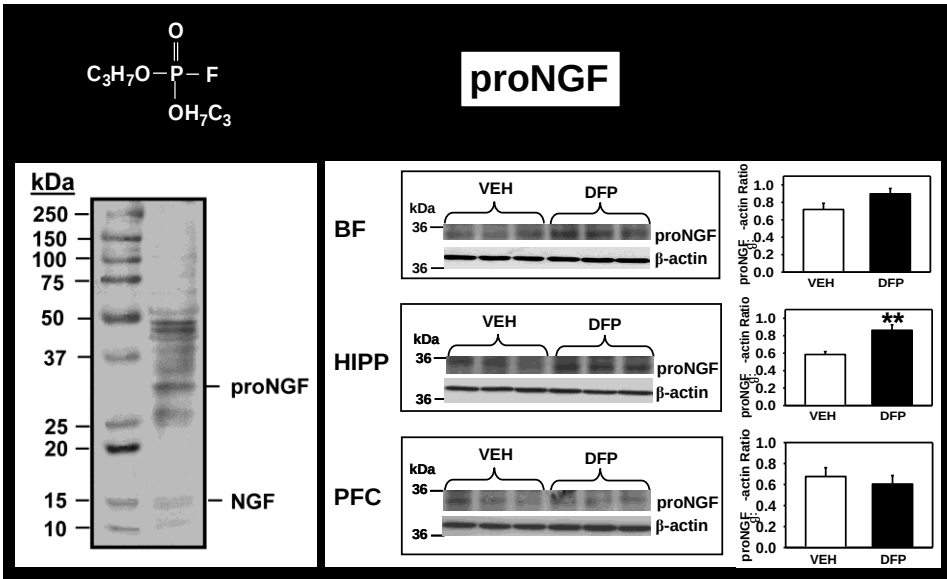
Spontaneous Novel Object Recognition

Spontaneous Novel Object Recognition

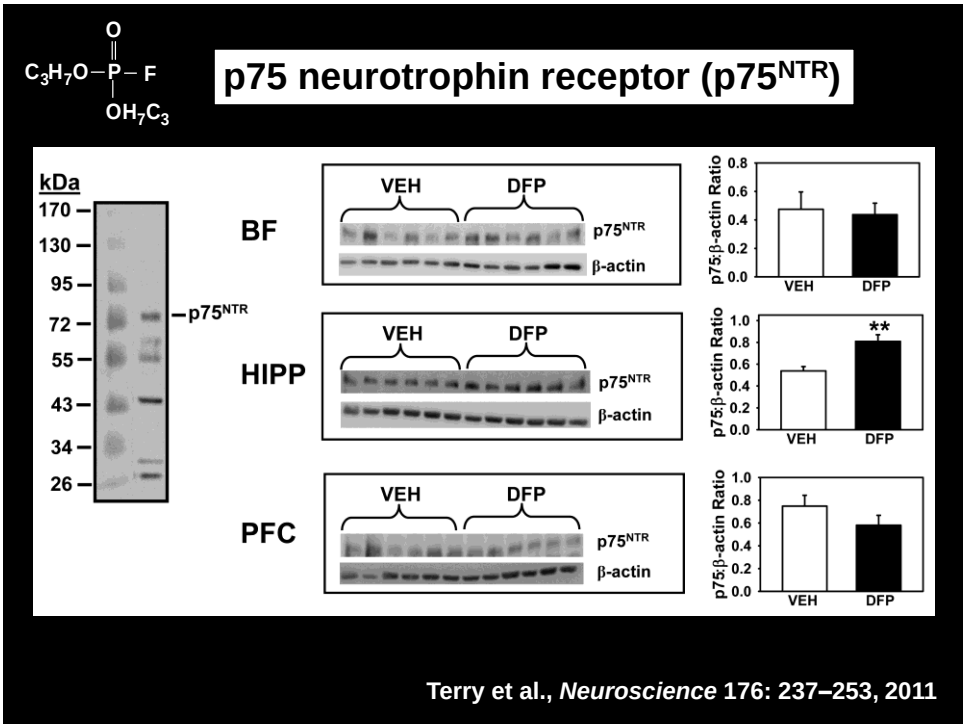


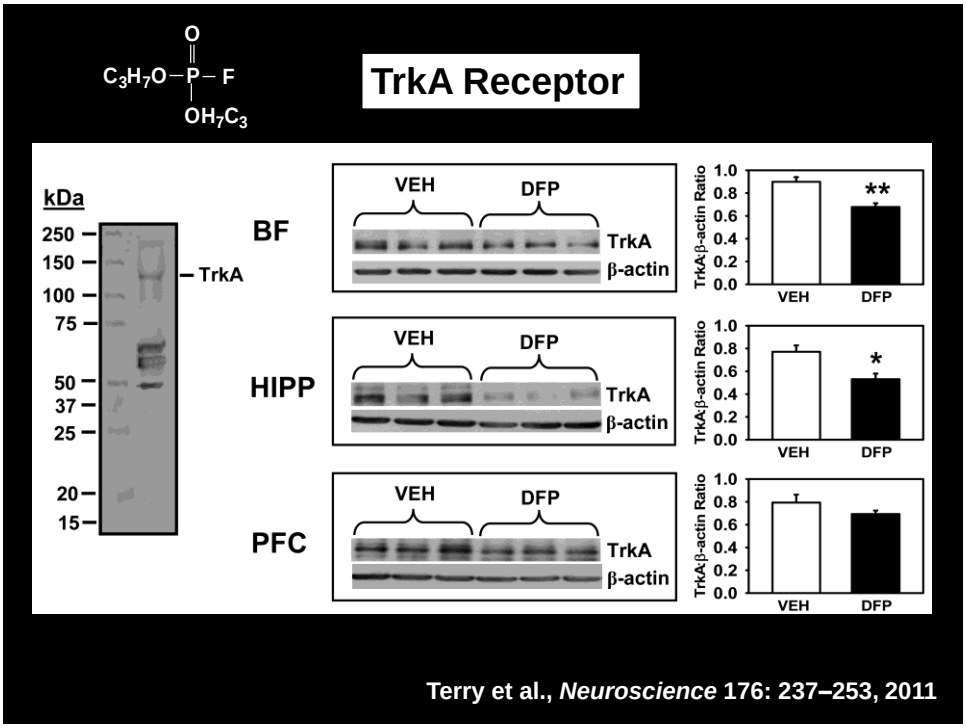
Terry et al., *Neuroscience* 176: 237–253, 2011

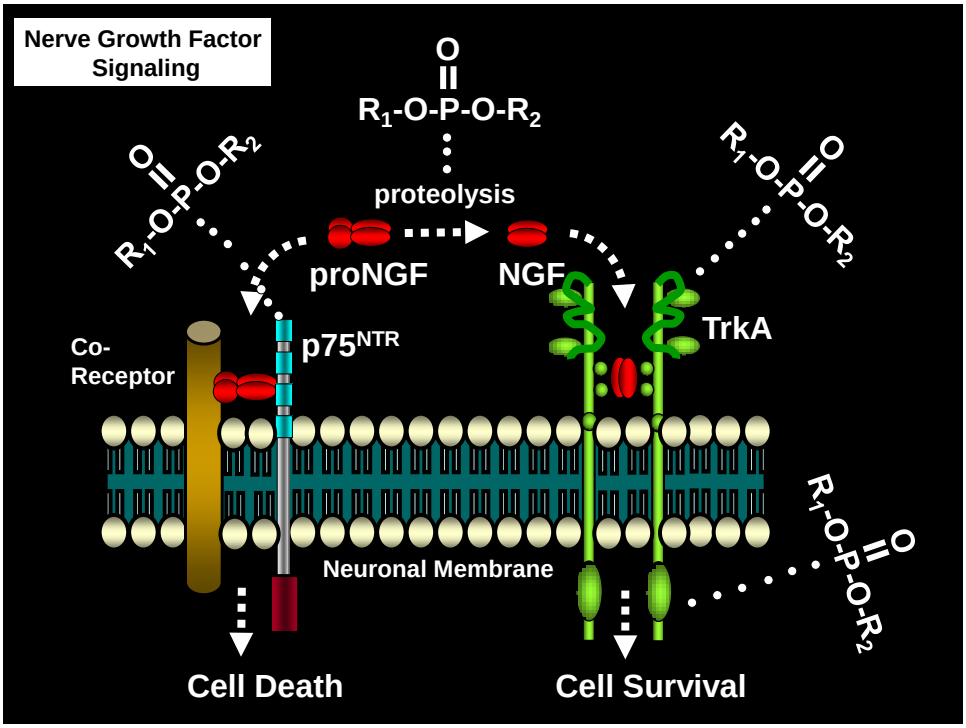
proNGF



Terry et al., *Neuroscience* 176: 237–253, 2011


C3H7O–P(=O)(F)–OH7C3
p75 neurotrophin receptor (p75NTR)
kDa
170
130
95
72
55
43
34
26
p75NTR
BF
HIPP
PFC
VEH
DFP
p75NTR
β-actin
p75:β-actin Ratio
0.0
0.2
0.4
0.6
0.8
1.0
**
Terry et al., Neuroscience 176: 237–253, 2011


C3H7O–P(=O)(F)–OH7C3
TrkA Receptor
kDa
250
150
100
75
50
37
25
20
15
TrkA
BF
HIPP
PFC
VEH
DFP
TrkA
β-actin
TrkA:β-actin Ratio
0.0
0.2
0.4
0.6
0.8
1.0
**
*
Terry et al., Neuroscience 176: 237–253, 2011



DFP Experiments (Conclusion)

- Intermittent, subthreshold exposures nerve agent OPs can lead to protracted deficits in specific domains of cognition (i.e., spatial learning and recall, recognition memory)
- The cognitive deficits may be related to persistent functional changes in brain neurotrophin and cholinergic pathways.

Terry et al., *Neuroscience* 176: 237–253, 2011

Neurotoxicology and Teratology 34 (2012) 1–8

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Chronic impairments in spatial learning and memory in rats previously exposed to chlorpyrfos or diisopropylfluorophosphate

A.V. Terry Jr. [a,b,*], W.D. Beck [a], S. Warner [b], L. Vandenhuerk [b], P.M. Callahan [a,b]

[a] Department of Pharmacology and Toxicology, Georgia Health Sciences University, Augusta, Georgia, 30912, United States
[b] Small Animal Behavior Core, Georgia Health Sciences University, Augusta, Georgia, 30912, United States

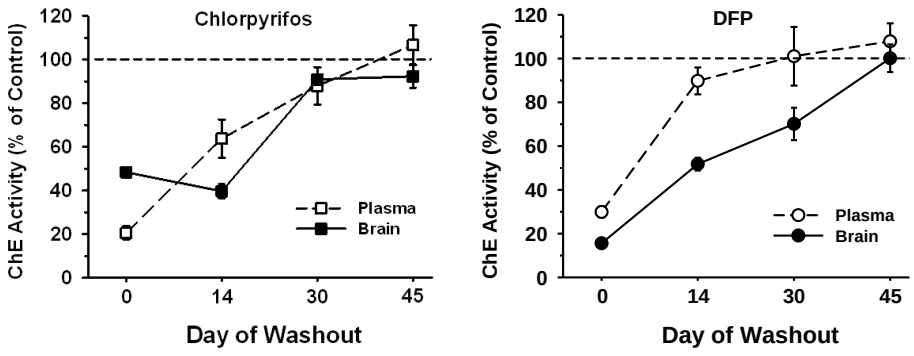
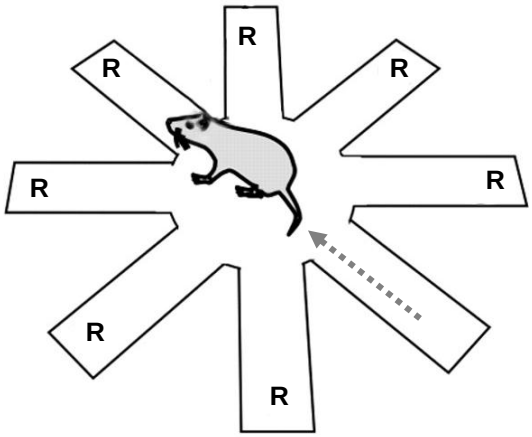


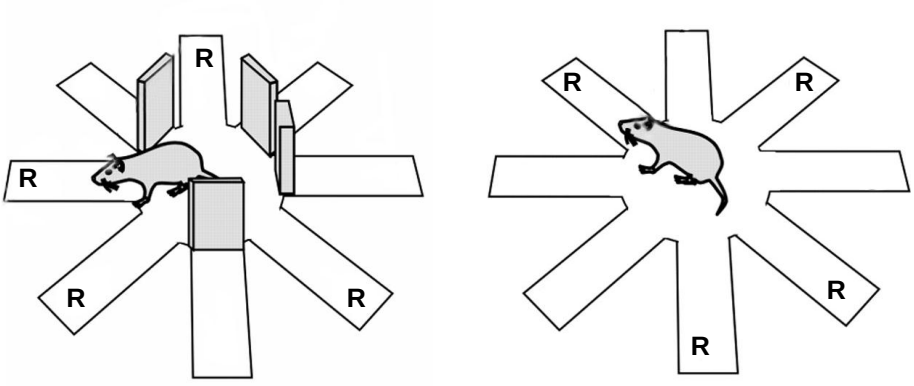
Fig 1. The effects of repeated exposures to CPF 18.0 mg/kg (Left) or DFP 0.75 mg/kg (Right) on cholinesterase activity in the plasma and brain at various time points during a 45 day OP-free washout period. Data (mean ± SEM) are presented as % of vehicle-matched control levels. (N=3-6).

Terry et al., *Neurotoxicology and Teratology* 34:1-8, 2012

8-Arm Radial Maze
(Win-Shift Task)



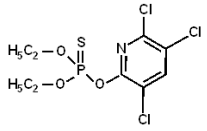
8-Arm Radial Maze
(Delayed Non-Match-to Sample)



Training Phase
(Forced 4)

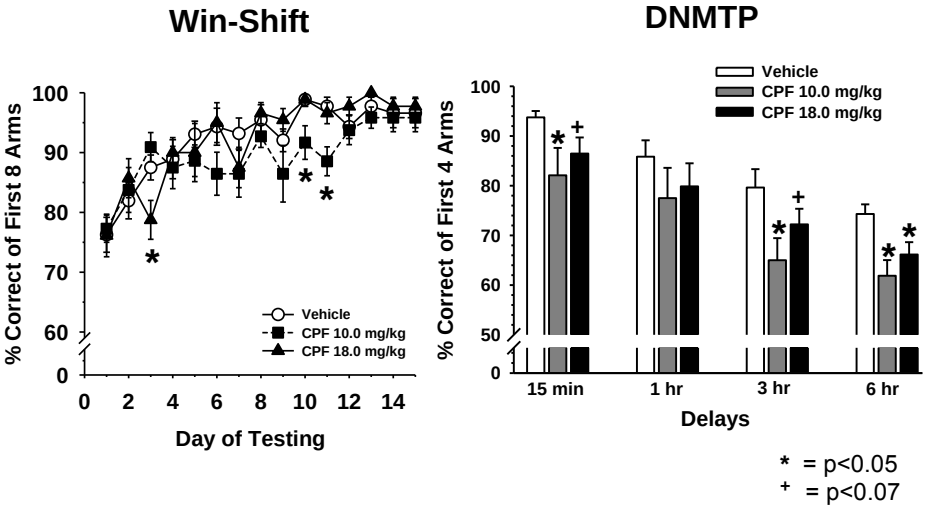
Delay

Test Phase
(Free 8)

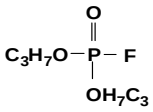


Radial Arm Maze

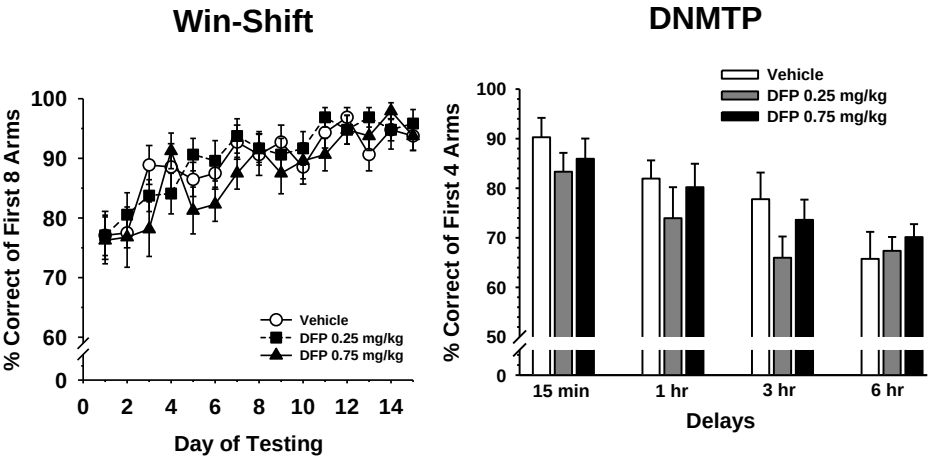
N=8-12



*** Behavioral Testing Began on day 50 of the OP-washout period**



Radial Arm Maze



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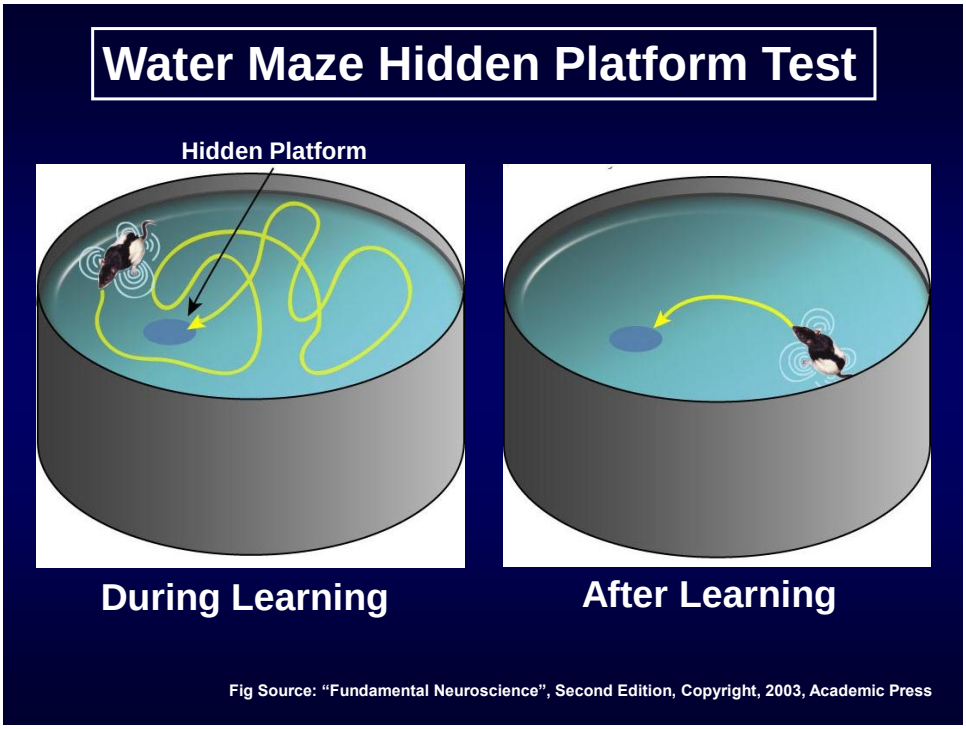
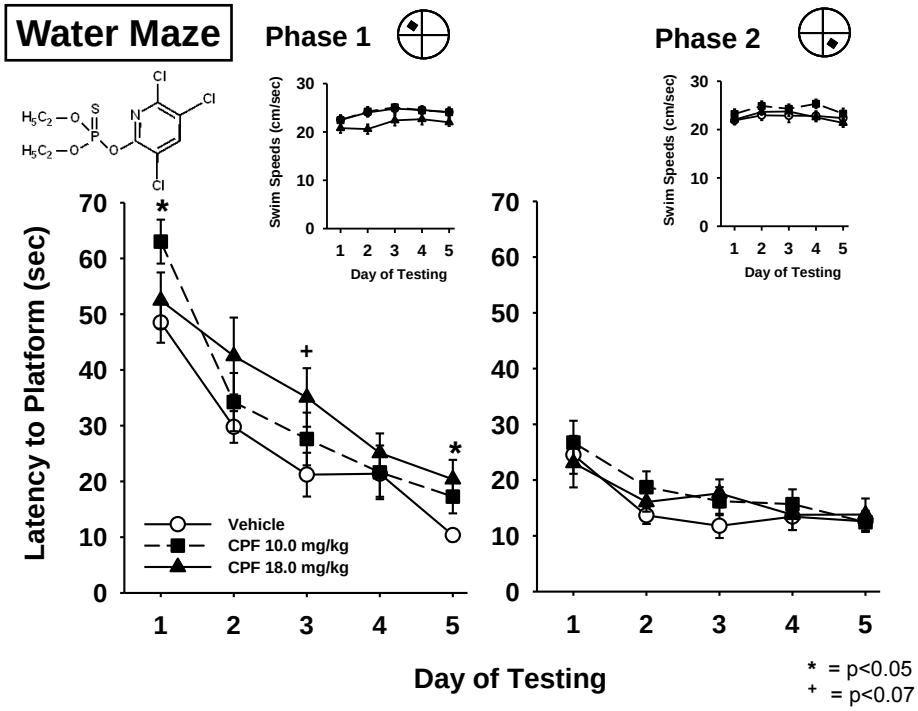
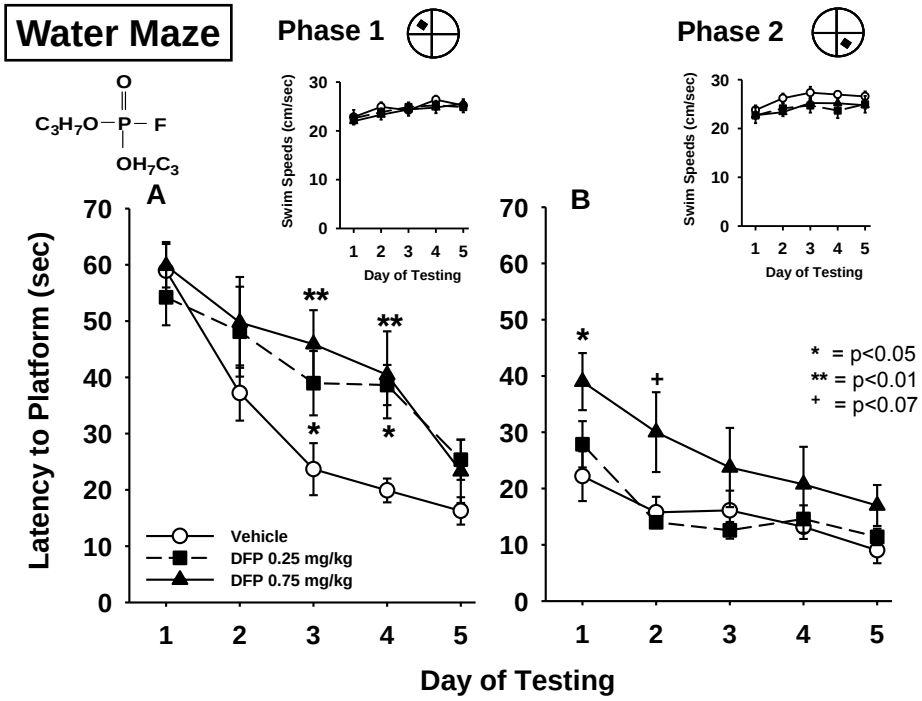
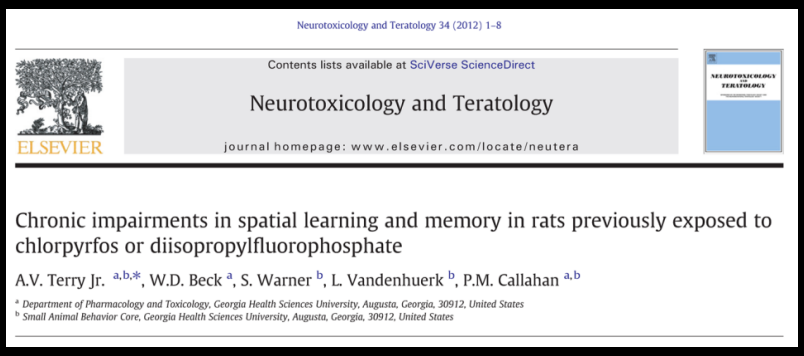

Water Maze Hidden Platform Test
Hidden Platform
During Learning
After Learning
Fig Source: "Fundamental Neuroscience", Second Edition, Copyright, 2003, Academic Press


Water Maze
Phase 1
Phase 2
Swim Speeds (cm/sec)
Day of Testing
Latency to Platform (sec)
Vehicle
CPF 10.0 mg/kg
CPF 18.0 mg/kg
Day of Testing
* = p<0.05
+ = p<0.07





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Chronic impairments in spatial learning and memory in rats previously exposed to chlorpyrfos or diisopropylfluorophosphate

A.V. Terry Jr. [a,b,*], W.D. Beck [a], S. Warner [b], L. Vandenhuerk [b], P.M. Callahan [a,b]

[a] Department of Pharmacology and Toxicology, Georgia Health Sciences University, Augusta, Georgia, 30912, United States
[b] Small Animal Behavior Core, Georgia Health Sciences University, Augusta, Georgia, 30912, United States

Conclusion

"Repeated, subthreshold exposures to CPF and DFP may lead to chronic deficits in spatial learning and memory (i.e., long after cholinesterase inhibition has abated) and that insecticide and nerve agent OPs may have differential effects depending on the cognitive domain evaluated".

Current and Future Studies

- Specific Aim #1: Determine the consequences of repeated subthreshold exposures to representative OPs on axonal transport in the living rat brain.
  - Manganese-Enhanced Magnetic Resonance Imaging (MEMRI) Studies
- Specific Aim #2: Determine the consequences of repeated subthreshold exposures to representative OPs on myelin in the living rat brain.
  - Diffusion tensor imaging (DTI)
  - Black Gold II Histology

Approved DOD-CDMRP Proposal (GW110073) "Organophosphate-Related Alterations in Myelin and Axonal Transport in the Living Mammalian Brain"

Summary/Conclusions

- Repeated, subthreshold exposures to both insecticide and nerve agent OPs lead to protracted impairments of attention and memory-related behavioral tasks in animals.
- Insecticide and nerve agent OPs may have differential effects on specific domains of cognition.
- The mechanisms underlying OP-related impairments of cognition may involve deleterious effects on mitochondrial morphology and movement, axonal transport, and neurotrophin signaling.

Potential Therapeutic Strategies

- Cholinergic-Based Compounds
- Glutamate Receptor Antagonists
- Mitochondrial-Targeted Antioxidants
- Drugs that Increase Axonal Transport?
- Drugs that Improve Neurotrophin Function
- Cytokine-Based Treatments

Reviewed, Terry, 2012, *Pharmacology and Therapeutics* 134:355-365

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Terry-Lab Personnel

- **Pharmacology**
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  - Samantha Warner
  - Leah Vandenhuerk
  - Rosann Schade
  - Nancy Kille
  - Elizabeth Hutchings

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- Adviye Ergul, M.D., Ph.D.
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- Gary Schwarz
- NIH/NIEHS ES012241

Cognitive Effects from Organophosphate Exposures

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Funding: NIH R21 ES017223 (Diane S Rohlman, PI)
NIH R01 ES016308 (W Kent Anger & Pamela J Lein, MPI)

Collaborators:
WK Anger, PJ Lein, FM Farahat, M Lattal, JR Olson, MR Bonner, RA Fenske, K Galvin, TM Farahat, A Ismail, G Abdel Rasoul, O Hendy, M El Batanony,

Conflict of Interest: OHSU and Dr. Rohlman have a significant financial interest in Northwest Education Training and Assessment, LLC, a company that may have a commercial interest in the results of this research and technology. This potential conflict of interest was reviewed and a management plan approved by the OHSU Conflict of Interest in Research Committee was implemented.

Studies examining low-dose exposures

- Range of occupational groups in different countries (> 20 studies)
  - Pesticide workers, sheep dippers, greenhouse workers, tree-fruit farmers, farmworkers and residents on farms
  - US (migrant farmworkers), Ecuador, Egypt, South Africa, Spain, Brazil, UK, United Arab Emirates, Israel
  - Adults and adolescents occupationally exposed

- Majority of studies observed neurobehavioral differences in occupational groups

Studies examining low-dose exposures

Not all studies have found deficits associated with exposure (Maizlish 87, Rodnitzky 75, Daniell 92, Ames 95)

Results are not consistent across studies

Table 2. Studies that have used variants of the digit span test to assess pesticide exposure.

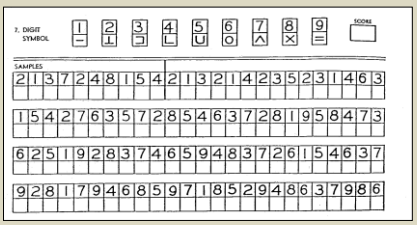
Study	Method	Outcome
Bazylewicz-Walczak et al. 1999	Polish NCTB	–0
Cole et al. 1997	NCTB	~
Farahat et al. 2003	Unknown	+
Fiedler et al. 1997	WAIS-R	–0
Kamel et al. 2003	BARS	+
London et al. 1997	NCTB	–0
Nishiwaki et al. 2001	NCTB	~
Reidy et al. 1992	WAIS-R	~
Rohlman et al. 2001b	BARS	+
Rosenstock et al. 1991	WAIS-R	+
Stephens et al. 1995	Unknown	–0
Stephens et al. 1996	NES	–0
Wesseling et al. 2002	NCTB	~
Yokoyama et al. 1998	Japanese WAIS	–0

Abbreviations and symbols: +, poorer performance in exposed group; ~, nonsignificant trend observed with poorer performance in exposed group; 0, no significant difference between control and exposed groups; NES, Neurobehavioral Evaluation System; WAIS-R, Weschler Adult Intelligence Scale–Revised.

Why are there variations in neurobehavioral performance?

Method – Procedure – Population

- Range of methods used (computer/paper, parameters)
- Cross sectional designs (may not provide information about previous exposures)
- Small sample size (N < 100)
- Populations with low education, limited writing/computer, language/culture



Why are there variations in neurobehavioral performance?

Exposure Classification

- Pesticide Source Information: pesticide use, home inventory, proximity to agricultural field, job classification
- Environmental Monitoring: indoor air, dust samples (vehicle/home), surface wipes
- Biomarkers: **plasma ChE**, **urinary metabolites**

Usually can't establish the exposure history

Do repeated low-dose exposures cause neurotoxicity in humans?

Review of 24 studies indicate deficits in exposed vs. controls in several functional domains:

Motor Speed/Coordination (10 studies)
Finger Tapping, Pegboard, Aiming

Information Processing Speed (8 studies)
Simple Reaction Time, Syntactic Reasoning

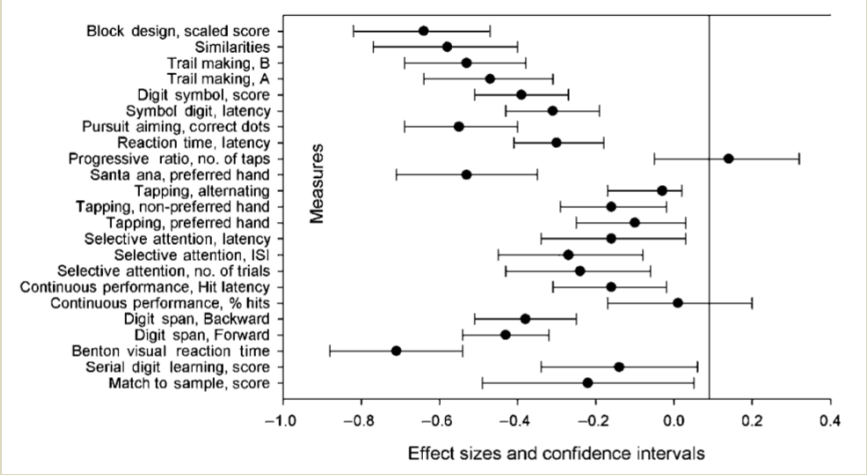
Complex Visual Motor/Executive Function (12 studies)
Digit Symbol, Symbol-Digit, Trailmaking

Attention/Short-term Memory (9 studies)
Digit Span

Memory (6 studies)
Benton Visual Retention
Match to Sample

Rohlman et al., 2011, *Neurotoxicology*

Do repeated low-dose exposures cause neurotoxicity in humans?



Ismail et al., 2012, *Occup Environ Med*

Do repeated low-dose exposures cause neurotoxicity in humans?

- **Weight of evidence**
  - (19 of 24 studies) suggests that occupational exposures to OPs are associated with neurobehavioral deficits
- **However,**
  - A relationship between OP dose and behavioral deficits has not been defined in humans
  - Only 2 of 24 studies have demonstrated a link between neurobehavioral performance and current biomarkers of OP exposure: blood cholinesterase (ChE) activity and urinary levels of OP metabolites

Potential reasons for the lack of correlation between biomarkers of OP exposure and neurobehavioral deficits

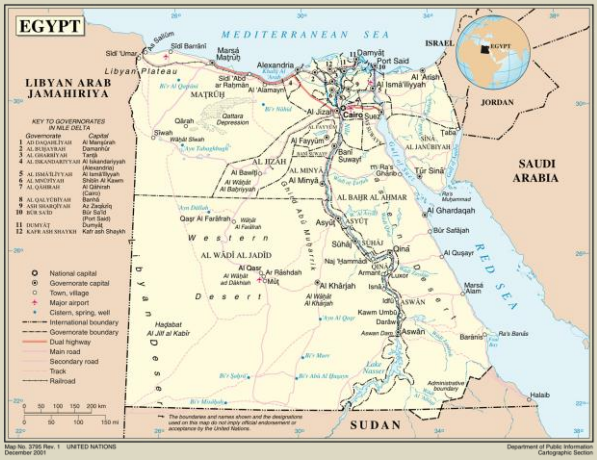
- **Exposure assessment**
  - Incomplete information on pesticide formulations
  - Lack of detailed data on workers' exposure history
- **Biological mechanisms**
  - Genetic differences in the expression and/or activity of enzymes that metabolize OPs or proteins that scavenge OPs differentially influence peripheral *versus* central outcomes.
  - ChE inhibition may not be mechanistically related to chronic OP neurotoxicity

Hypotheses

- OP-induced neurobehavioral deficits are dose-related
- Biomarkers based on alternative, non-cholinergic mechanisms may be better predictors of OP neurotoxicity or improve prediction when used in conjunction with ChE inhibition
  - ***oxidative stress***
  - ***inflammation***

Setting of Human Studies

Agricultural workers involved in OP (chlorpyrifos) application to cotton fields located in Menoufia, Egypt situated in the Nile River delta north of Cairo

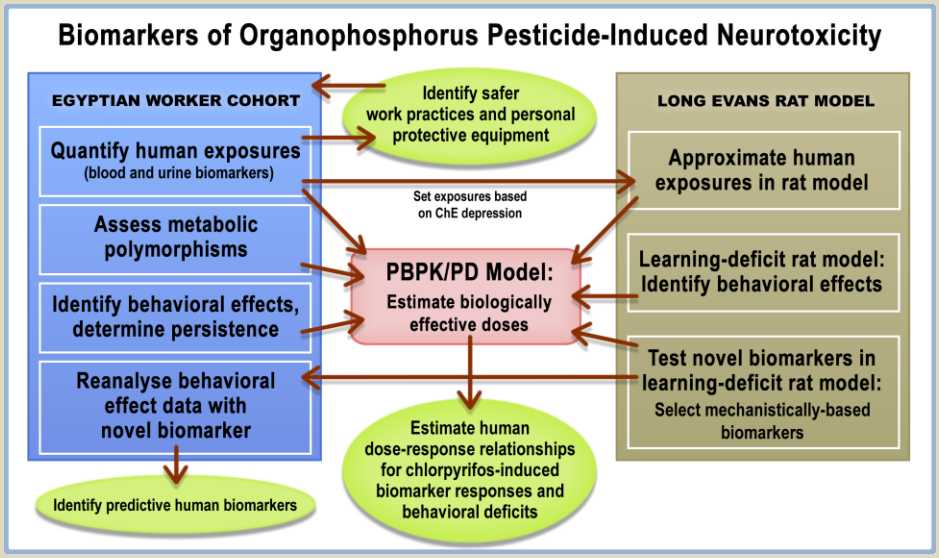


Occupational Cohort

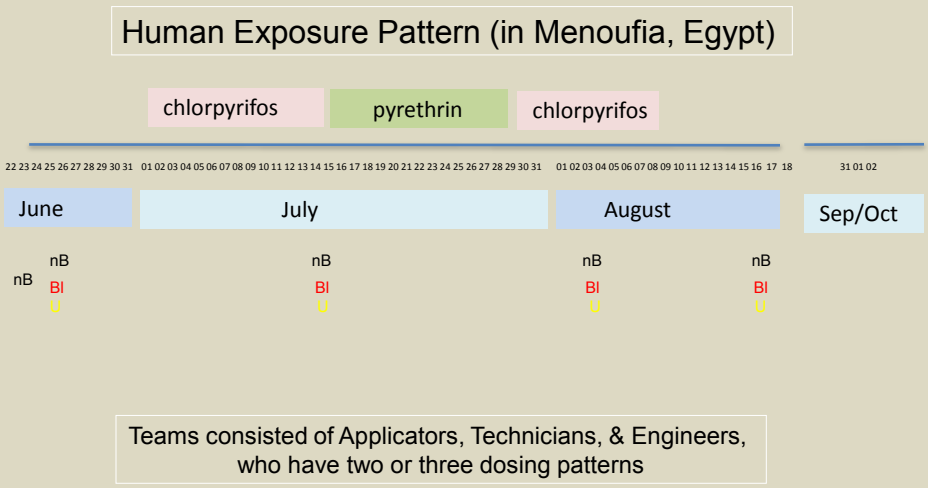
Egyptian Cotton Workers

- **Applicator** – applies CPF using a backpack sprayer
- **Technician** – walks with an applicator to direct the path of the applicator and point out heavy insect infestation
- **Engineer** – periodically walks the fields but more often directs application from the edge of the fields

Experimental Strategy

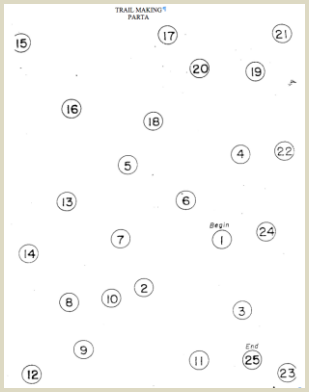


Typical pesticide application schedules to cotton fields in Menoufia Egypt



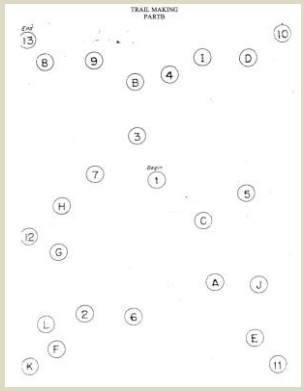
Neurobehavioral Studies in Occupational Cohort: Trailmaking test *

A – draw line from 1 to 2 to 3…



Test of complex visual scanning with a motor component and is sensitive to many types of brain damage (esp. part B).

B – draw a line from 1 to A to 2 to B to 3 to C …



* Farahat et al. (2003) found deficits on this test (both A & B) in engineers + technicians vs. Ministry of Agriculture controls. Significant differences found in 5 of 5 studies of OP-exposed workers in which the Trailmaking test has been used.

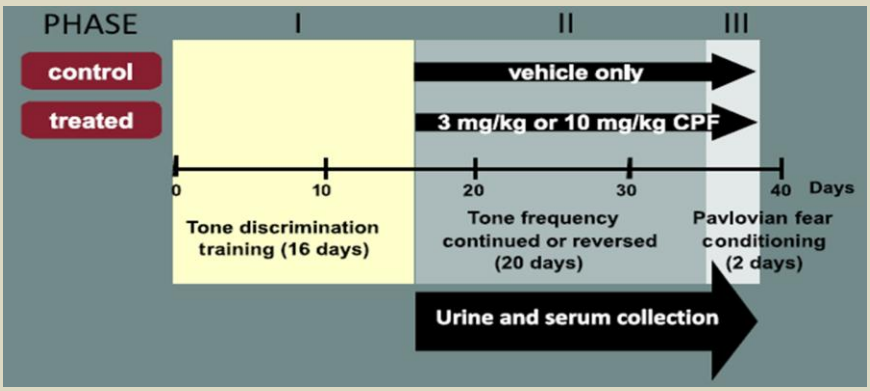
Analysis of Neurobehavioral Data

- **Generalized Estimating Equations (GEE),** a regression analysis that tests for the effects of variables on non-independent repeated measures
  - gave people the same Trailmaking test 4-5 times (when learning was expected to improve performance) during (July, Aug) and after (October) chlorpyrifos applications.
- **Variables**
  - Age
  - Years of education
  - Cholinesterase inhibition (based on June ChE measure) on days of testing
  - TCPy on days of testing
  - Years working for the Ministry of Agriculture
  - Job title (Applicator, Tech, Engineer) < only significant factor

Long Evans Rat Model Based on Human Exposure Data

- CPF exposure in Egyptian cotton workers is primarily dermal, so administered CPF daily via subcutaneous injection
- Preliminary dose range finding studies identified doses that upon repeated daily s.c. injections produced levels of **blood cholinesterase reduction in rats comparable to that found in the Egyptian workers at the end of chlorpyrifos application cycle**
  - *3 and 10 mg/kg daily (s.c.)*

Experimental design in rat studies



Ongoing biomarker analysis in rat models of occupational CPF exposure

- **Current biomarkers**
  - Plasma ChE, urinary TCPy
- **Oxidative stress***
  - **F2-isoprostanes (brain and urine)**
  - **Prostaglandin E2 (brain)**
- **Inflammation**
  - GFAP and Iba1 immunoreactivity (brain)
  - Inflammatory cytokines (brain, blood)
  - C-reactive protein (blood)

**** Isoprostane and PGE2 analyses performed by Dejan Milatovic and Miki Aschner, Vanderbilt University***

Gulf War Veterans' Illnesses Biorepository Brain Bank (CSP501B)

Christopher B. Brady, Ph.D.
Neil W. Kowall, M.D.

Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC)
VA Boston Healthcare System

Research Advisory Committee on Gulf War Veterans' Illnesses Meeting
June 18-19, 2012, Boston, MA

VAB Brain Bank Background

- The VA National Registry of Veterans with ALS and VA Biorepository Brain Bank (VABBB) were developed by VA in response to findings that linked ALS to deployment to the Persian Gulf and military service in general
- The VABBB (CSP 501) is coordinated at the Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC) at VA Boston Healthcare System(VABHS)
- Veterans/next-of-kin receive regular follow-up from VABBB staff
- Tissue is analyzed, processed and stored at the Southern Arizona Core Tissue Laboratory (SACTL) at the Southern Arizona VA Healthcare System (SAVAHCS) in Tucson, AZ
- Diagnostic neuropathological analyses are conducted at the VAs in Bedford/Boston, MA
- Tissue/data releases to investigators are ongoing

National Coverage

VABBB has consented Veterans from 47 states

VABBB National Tissue Recovery Network

Red markers – VA pathology department; Blue markers – non-VA diener

VABBB Enrollment / Recovery Rate

VABBB has a:

55% success rate in consenting referrals

100% success rate in tissue recovery when we have been contacted and next-of-kin wants to proceed

88% of recovered tissue is high quality (RIN > 4) for research

Gulf War Veterans' Illnesses Biorepository

- Given the development of the VABBB as a national tissue recovery model, this model was adapted to develop the Gulf War Veterans' Illnesses Biorepository (GWVIB) 2-year pilot study (CSP501B)

- New challenges for the development of the GWVIB were:
  - GWVIB open to all 1990-1991 Gulf War Veterans regardless of whether they receive care at VA
  - Research tissue needs of investigators
  - Recruitment and enrollment procedures
  - Data acquisition and management
  - Ongoing follow-up

GW Veterans by Enrollment Priority *

Table HC-1: Cohorts by Enrollment Priority Group – FY 2009

Priority Group	Pre-9/11	Deployed to Persian Gulf	Gulf War	Stabilization Period
1. S/C 50% +	373,820	104,775	78,493	38,220
2. S/C 30% - 40%	260,877	67,626	48,100	27,797
3. S/C 10%-20%/POW/Special	403,332	96,364	69,237	38,666
4. AA/Housebound or Catastrophic	11,559	2,725	2,269	693
5. NSC Below Income	337,646	72,148	50,528	28,379
6. All Other Not Req to Make Co-Pay	194,796	44,159	37,315	10,131
7. Non-Compensable 0% S/C-Below GMT	1,229	290	219	98
7. NSC Vets-Below GMT	12,125	2,281	1,673	860
8. Noncompensable 0% S/C-Above GMT	31,000	8,492	6,513	2,946
8. Noncompensable 0% S/C-Above GMT > 1_16_03	6,705	1,487	1,080	577
8. Noncompensable 0% S/C-Above GMT > 6_15_09	140	32	24	11
8. NSC Vets-Above GMT	244,172	56,333	42,042	19,802
8. NSC Vets-Above GMT > 1_16_03	56,902	10,745	7,997	3,934
8. NSC Vets-Above GMT > 6_15_09	1,396	253	190	94
90. Vet User Not Enrolled	16,034	2,212	1,240	1,202
91. Non-Vet User Not Enrolled	20,900	3,932	2,289	2,183
Unknown*	4,543,397	655,499	414,128	317,018

Source: Official DoD military personnel records matched against VA healthcare data.

Notes: 1) The Pre-9/11 column represents the overall unique total. All other categories are sub-cohorts of the Pre-9/11 cohort; 2) All cohort data is as of FY09; and 3) Acronyms: AA = aid and attendance, FY = Fiscal Year, GMT = geographic means test, NSC = Nonservice-connected, POW = prisoner of war, and S/C = service-connected.

*Unknown records indicate no matches.

** Gulf War Era Veterans Report: Pre-9/11, February 2011*

GW Veterans by VISN*

Table HC-14: Unique Veterans by VISN for All Cohorts – FY 2009

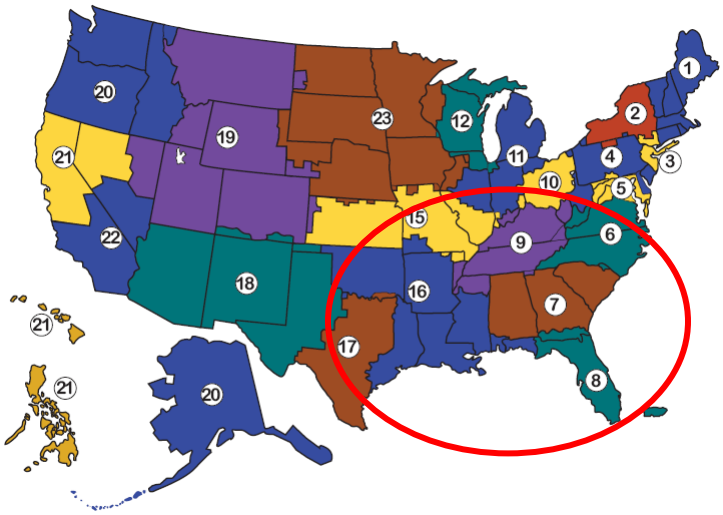
VISN	Pre-9/11	Deployed to Persian Gulf	Not Deployed to Persian Gulf	Gulf War	Stabilization Period	Desert Shield	Desert Storm	Post-Desert Storm	Al Jubayl	Non-Al Jubayl	Khamisiyah	Non-Khamisiyah
1	30,558	5,389	25,169	4,016	1,885	2,730	3,117	3,596	<10	3,114	898	2,698
2	20,300	3,903	16,397	3,025	1,259	2,106	2,380	2,762	<10	2,378	678	2,084
3	20,994	3,611	17,383	2,827	1,103	1,944	2,244	2,553	<10	2,241	647	1,906
4	38,485	7,883	30,602	6,169	2,521	4,206	4,874	5,553	<10	4,867	1,484	4,069
5	29,717	6,404	23,313	4,907	2,142	3,332	3,855	4,499	<10	3,852	1,220	3,279
6	67,784	19,713	48,071	15,951	5,583	12,116	13,031	14,483	49	12,982	3,727	10,756
7	83,756	22,176	61,580	18,432	5,713	13,941	15,375	16,901	67	15,308	5,431	11,470
8	80,003	17,784	62,219	13,523	6,230	9,416	10,364	12,241	12	10,352	2,984	9,257
9	49,658	12,889	36,769	10,856	3,043	7,862	8,983	10,037	48	8,935	3,149	6,888
10	27,635	6,098	21,537	4,745	1,971	3,390	3,752	4,284	<10	3,748	1,099	3,185
11	36,027	7,881	28,146	6,313	2,360	4,499	5,025	5,716	<10	5,018	1,418	4,298
12	32,068	6,822	25,246	5,174	2,328	3,661	4,092	4,681	<10	4,087	1,061	3,620
15	35,103	8,419	26,684	6,765	2,395	4,852	5,500	6,155	12	5,488	1,807	4,348
16	87,389	21,040	66,349	16,553	6,649	11,595	13,207	15,001	29	13,178	3,848	11,153
17	62,614	15,747	46,867	12,300	4,869	9,120	10,129	11,292	<10	10,123	4,070	7,222
18	48,582	12,139	36,443	8,750	4,821	6,030	6,950	7,918	<10	6,941	2,124	5,794
19	34,678	7,458	27,220	5,357	2,890	3,721	4,197	4,763	10	4,187	1,252	3,511
20	49,025	10,692	38,333	7,606	4,278	5,292	5,885	6,773	13	5,872	1,536	5,237
21	40,230	8,970	31,260	6,321	3,882	4,301	4,703	5,559	<10	4,694	981	4,578
22	54,909	15,014	39,895	9,563	7,823	6,681	6,916	8,011	28	6,888	863	7,148
23	41,845	8,439	33,406	6,354	2,874	4,563	5,139	5,688	16	5,123	1,484	4,204

Source: Official DoD military personnel records matched against VA healthcare data.

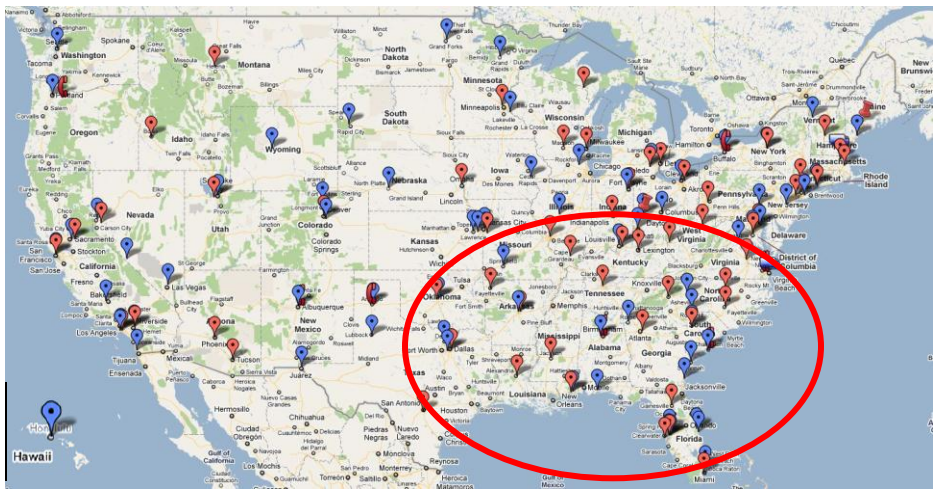
Notes: 1) The Pre-9/11 column represents the overall unique total. All other categories are sub-cohorts of the Pre-9/11 cohort; 2) Unique Veterans count at a VISN but can be counted in multiple VISNs; 3) All cohort data is as FY09; and 4) Acronyms: FY = Fiscal Year, VISN = Veterans Integrated Service Network.

** Gulf War Era Veterans Report: Pre-9/11, February 2011*

VA VISNs



VABBB National Tissue Recovery Network



Red markers – VA pathology department; Blue markers – non-VA diener

Research Tissue Needs of Investigators

- The value of postmortem CNS tissue had already been established via feedback from the RAC-GWVI and the literature:
  - Accurate diagnoses of neurodegenerative diseases can only be obtained through post-mortem pathology
  - Necessary for clinicopathological correlation
  - Human tissue is required to study human disease and to test the relevance of results from animal models
  - High quality DNA, RNA, and protein required for accurate and reproducible results
  - May aid in the understanding of disease, the discovery of new diagnostic targets, and the development of therapeutics

Research Tissue Needs of Investigators

- The need for non-CNS tissue had not been established
- Collecting non-CNS tissue presented considerable logistical hurdles
- Poll conducted of 33 VA Gulf War Researchers did not presently support the need to collect non-CNS tissue
- Based on this feedback it was decided to begin the GWVIB as a CNS tissue biorepository
- Non-CNS tissue collection could be considered in the future if the need arises

GWVIB Site Responsibilities

- Boston-MAVERIC/Bedford VA
  - Operations and data coordinating center
  - Recruitment/enrollment/follow-up
  - Pager coverage/tissue recovery coordination
  - Medical informatics
  - Data management
  - Diagnostic neuropathology
- Tucson- SACTL
  - CNS tissue processing/storage
  - CSF processing/storage
  - Tissue data management

Recruitment

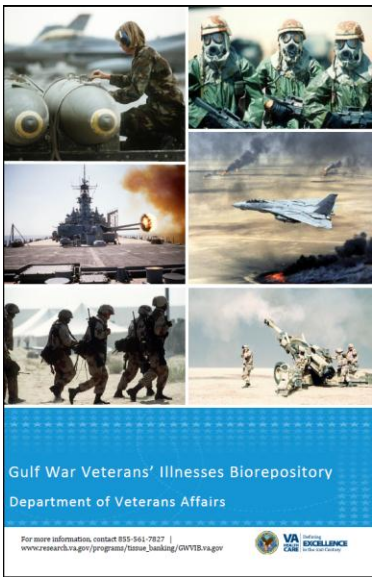
- Web site *

  (www.research.va.gov/programs/tissue_banking/GWVIB.va.gov)
- Brochure
- Nationwide toll-free number- 855-561-7827 *
- Postings on GW Veteran web sites and newsletters
- Outreach to GW Veteran organizations

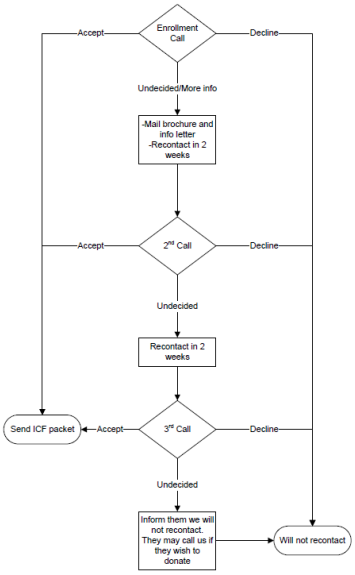
* Web site and toll-free number "go live" on 7/9/12

Web Site

Brochure



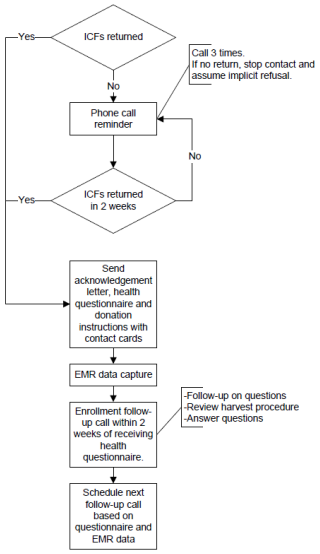
Recruitment



Informed Consent

- Purpose of study
- Broad based consent
- Ongoing data collection/recontact
- Permission to be contacted for other studies
- Use of results
- Confidentiality
- Next-of-kin consent

Enrollment



Data Acquisition

- Data collected at enrollment
  - Health history, GW symptom checklists (e.g., Kansas, Fukuda), military and occupational neurotoxicant exposures, etc. via mailed questionnaire
  - Medical history from VA electronic medical record if present
- Data collected during semi-annual or annual follow-up
  - Updated medical history and contact information via telephone and mailed questionnaires

Health Questionnaire

Domains assessed:

- Demographics and physical features
- Gulf War Veterans' illnesses symptom checklists
  - Gulf War illness by Kansas case definition and chronic multisymptom illness by Fukuda case definition
- Military and occupational exposures (SNAC-Short Form)
- Health history and healthcare use
- Family health history
- Military service and combat exposure
- Tobacco and alcohol use

Tracking and Tissue Recovery

- Semi annual or annual follow-up to monitor health
- Portfolio development:
  - Contact VAMCs as primary tissue recovery site
  - Private hospitals, dieners, coroners, if VAMC unavailable
  - Employ funeral home for transport
  - Send specimen box to tissue recovery facility
- Brain, spinal cord & cerebrospinal fluid recovery
  - 24/7 coverage with delivery to Tucson by special door-to-door courier service

Tissue Processing and Storage
(Tucson and Boston)

Specimen Receipt (recording code #, age, gender, PMIs, cause of death)

⇩

Grossing (digital imaging, dry ice freezing, formalin fixation/FFPE blocks)

⇩

Tissue Monitoring (Luxol/H&E slides; QC: tissue pH, RNA integrity)

⇩

Storage (frozen, FFPE blocks, slides; barcode labeling, database input)

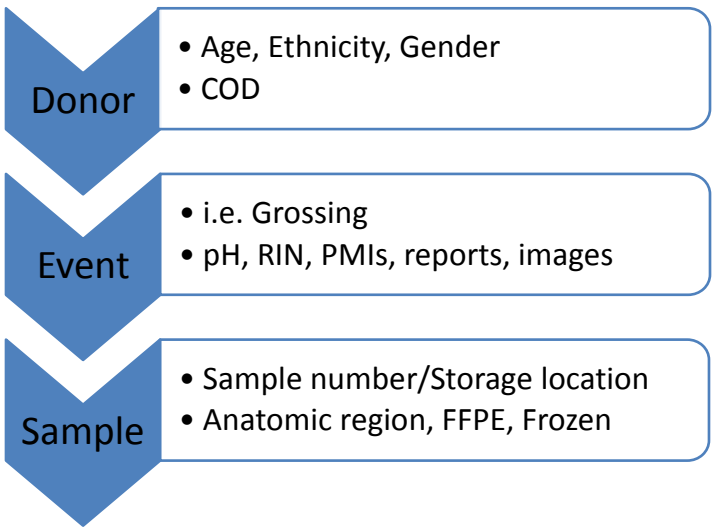
⇩

Neuropathology report (gross report; diagnostic)

⇩

Distribution (request review, inventory assessment, database tracking)

Tissue Metrix Data Storage



Distribution of specimens

- Tissue request form
  - Description of review process for investigators
  - Specific aims, IRB approval, analyses to be conducted, tissue needed
- Review committee composition
  - Standing committee composed of members from all biorepository sites, VACO and outside experts
  - Membership is published
- Review procedures and criteria
  - Initial submissions checked for completeness and forwarded to committee
  - Monthly meeting by conference call to review submissions
  - Committee reviews and scores application
  - Investigator notification timeline
- Distribution procedures

VAB Staff

Boston

- Neil Kowall, M.D., Principal Investigator
- Christopher (Kit) Brady, Ph.D., Co-investigator
- Maxine Krengel, Ph.D. , Co-investigator
- Shelley Amberg, M.P.H., Project Coordinator
- Sally Perkins, M.S., Project Manager
- Latease Guilderson, M.S.W., Research Assistant

Bedford/Boston

- Ann McKee, M.D., Site PI and Chief Neuropathologist
- Thor Stein, M.D., Ph.D., Neuropathologist

Tucson

- Stephen Renner, M.D., Site PI
- Katrina Trevor, Ph.D., Co-investigator
- Jim Averill, Data Manager
- Sean Walker, Molecular Biology Specialist

Thank you!

The GWVIB (CSP501B) is funded by the
VA Biomedical Laboratory Research and Development Service

GULF WAR RESEARCH PORTFOLIO

VHA OFFICE OF RESEARCH AND DEVELOPMENT / Victor Kalasinsky

June 18, 2012

VA HEALTH CARE Defining EXCELLENCE in the 21st Century

Gulf War Research Funding – DoD, HHS, VA

10-Year (FY 2001-2010) Funding Trends for GW Research in Millions of Dollars

Department	FY 2001	FY 2002	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010	Total Costs FY '01-'10
DoD	$ 31.6	$ 18.8	$ 16.4	$ 11.1	$ 10.1	$ 10.1	$ 3.4	$ 11.7	$ 10.4	$ 3.1	$ 126.70
HHS	$ 1.0	$ 0.8	$ 1.0	$ 0.5	$ 0.5	$ 0.4	$ 0.4	$ 0.4	$ 0.0	$ 0.0	$ 5.00
VA	$ 8.6	$ 4.5	$ 5.7	$ 7.6	$ 9.5	$ 13.0	$ 22.1	$ 21.9	$ 16.6	$ 13.9	$ 123.40
TOTAL	$ 41.2	$ 24.1	$ 23.1	$ 19.2	$ 20.1	$ 23.5	$ 25.9	$ 34.0	$ 27.0	$ 17.0	$ 255.10

(DoD estimate for FY 2010 does not include CDMRP funds.)

Gulf War Research Funding – DoD, HHS, VA

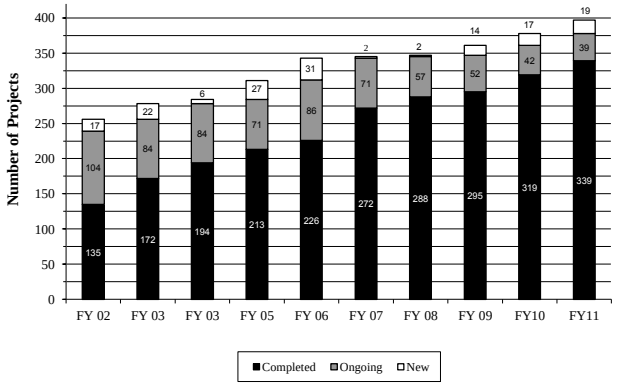
10-Year (FY 2002-2011) Funding Trends for GW Research in Millions of Dollars

Department	FY 2002	FY 2003	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010	FY 2011	Total Costs FY '02-'11
DoD	$ 18.8	$ 16.4	$ 11.1	$ 10.1	$ 10.1	$ 3.4	$ 11.7	$ 10.4	$ 10.2	$ 3.2	$ 105.40
HHS	$ 0.8	$ 1.0	$ 0.5	$ 0.5	$ 0.4	$ 0.4	$ 0.4	$ 0.0	$ 0.0	$ 0.0	$ 4.00
VA	$ 4.5	$ 5.7	$ 7.6	$ 9.5	$ 13.0	$ 22.1	$ 21.9	$ 16.6	$ 13.9	$ 6.0	$ 120.80
TOTAL	$ 24.1	$ 23.1	$ 19.2	$ 20.1	$ 23.5	$ 25.9	$ 34.0	$ 27.0	$ 24.1	$ 9.2	$ 230.20

(DoD estimate for FY 2011 does not include CDMRP funds.)

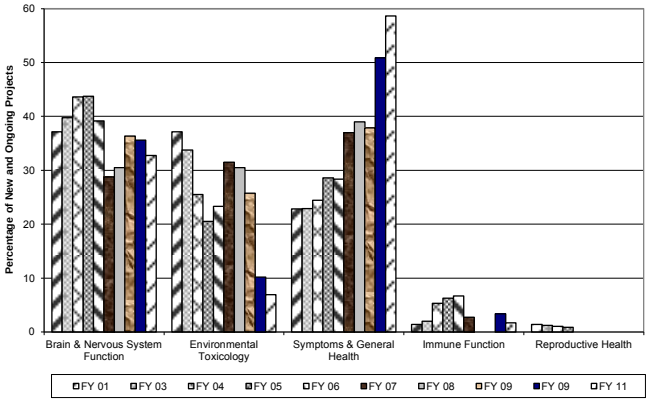
Funded Gulf War Research Projects – DoD, HHS, VA

Cumulative Number of Funded Projects (FY2002 – FY2011)



Topic Areas Gulf War Research Projects

Annual Distribution of Topic Areas for New and Ongoing Projects



Recent Gulf War Research Projects

Completed in FY2010:

- **Effects of Gulf War Illness on Brain Structure, Function and Metabolism: MRI/MRS at 4 Tesla**
- **Immunologic Mechanisms and Biomarkers in Gulf War Illness**
- **Diarrhea-Predominant Irritable Bowel Syndrome in Persian Gulf Veterans**
- **Behavior of Neural Stem Cells in a Rat Model of GWS**
- **Multiple Sclerosis in Gulf War Veterans**

Completed in FY2011:

- **Tissue Factor and Gulf War-Associated Chronic Coagulopathies**
- **Autonomic Functions of Gulf War Veterans with Unexplained Illnesses**
- **Motor Neuron Function of Gulf War Veterans with Excessive Fatigue**
- **Genetic Epidemiology of ALS Veterans**
- **Testing the Feasibility of MC CBT for Veterans with IBS**
- **A Pilot study of CPAP Adherence Promotion by Peer Buddies with Sleep Apnea**
- **Transcription factors regulating sensory gene expression and pain pathways**

Active Gulf War Research Projects

Active:

- **Bacterial Overgrowth Associated with Chronic Multi-Symptom Illness Complex**
- **Differential Gene Expression in Pathologies Associated with Neuronal Hyperexcitability: Links to Gulf War Illness**
- **Imaging Pain Modulation in Gulf War Veterans with Chronic Muscle Pain**
- **Bacterial Host Defense Mechanisms in Polyaromatic Hydrocarbon Carcinogenesis**
- **Somatic hypersensitivity in Veterans with IBS**
- **Lipoic Acid Therapy for Experimental Autoimmune Encephalomyelitis**
- **Multiple Antigenic Peptides to Alter the Course of Autoimmune Disease**
- **Immunoregulation of Myelin Specific T Lymphocytes**
- **Central Mechanisms Modulating Visceral Sensitivity**
- **Evaluation of MEG Synchronous Neural Interaction Test in PTSD**
- **Neuroprotection and Myelin Repair Mechanisms in Multiple Sclerosis**

Active Gulf War Research Projects

Active:

- **Sleep Neurobiology and Circuitry**
- **Prevention of Hippocampal Neurodegeneration Due to Age and Apnea**
- **Epigenetic Mechanisms Relevant to the Pathogenesis of ALS**
- **A randomized controlled trial of a mindfulness based intervention for Gulf War Syndrome**
- **Impact of exercise training on pain and brain function in Gulf War Veterans**
- **Nanoparticle Coupled Antioxidants for Respiratory Illness in Veterans**
- **Understanding Pain of Gastrointestinal Origin in Women that Serve in OEF/OIF**
- **Randomized Trial of a Formal Group Program for Fatigue in Multiple Sclerosis**
- **Memory and Mood Enhancing Therapies for Gulf War Illness**
- **MEG Synchronous Neural Interactions (SNI) in Gulf War Veterans**
- **rTMS for the Treatment of Chronic Pain in GW1 Veterans**

Gulf War Research – Requests for Applications (RFAs)

Biomedical Laboratory Research & Development (BLR&D):

BX-12-011
Award for Research on Gulf War Veterans' Illnesses (GWVI)
BX-12-012
Pilot Projects for Research on Gulf War Veterans' Illnesses (GWVI)

Clinical Science Research & Development (CSR&D):

CX-12-011
Award for Research on Gulf War Veterans' Illnesses (GWVI)
CX-12-012
Pilot Projects for Research on Gulf War Veterans' Illnesses (GWVI)
CX-12-013
Award for Research on Treatments for Gulf War Veterans' Illnesses (GWVI) – (clinical trial)

Gulf War Research – Other Activities

- **Cooperative Studies Program (CSP)**
- **Institute of Medicine (IOM) – Treatments for Gulf War Veterans' Illnesses**
- **Gulf War Veterans' Illnesses Task Force (GWVI-TF)**
- **Annual Report to Congress**
- **Research Meeting (Fall, 2012)**
- **Gulf War Research Strategic Plan**

Office of Public Health

Victoria J. Davey PhD, MPH, RN
Chief Officer

Gulf War Veterans' Illnesses Research Advisory Committee Meeting
June 18-19, 2012

PUBLIC HEALTH

VA HEALTH CARE Defining EXCELLENCE in the 21st Century

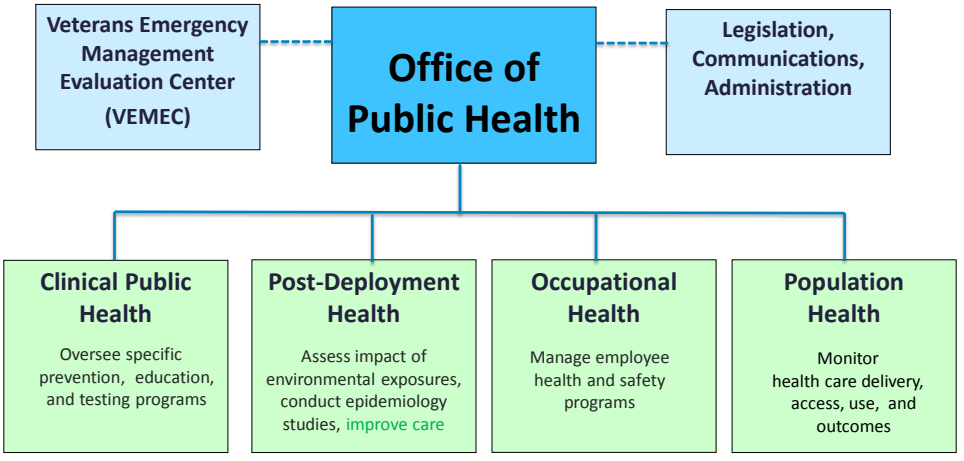
"Patients are in control of their health care, and the system is designed around the needs of the patient."

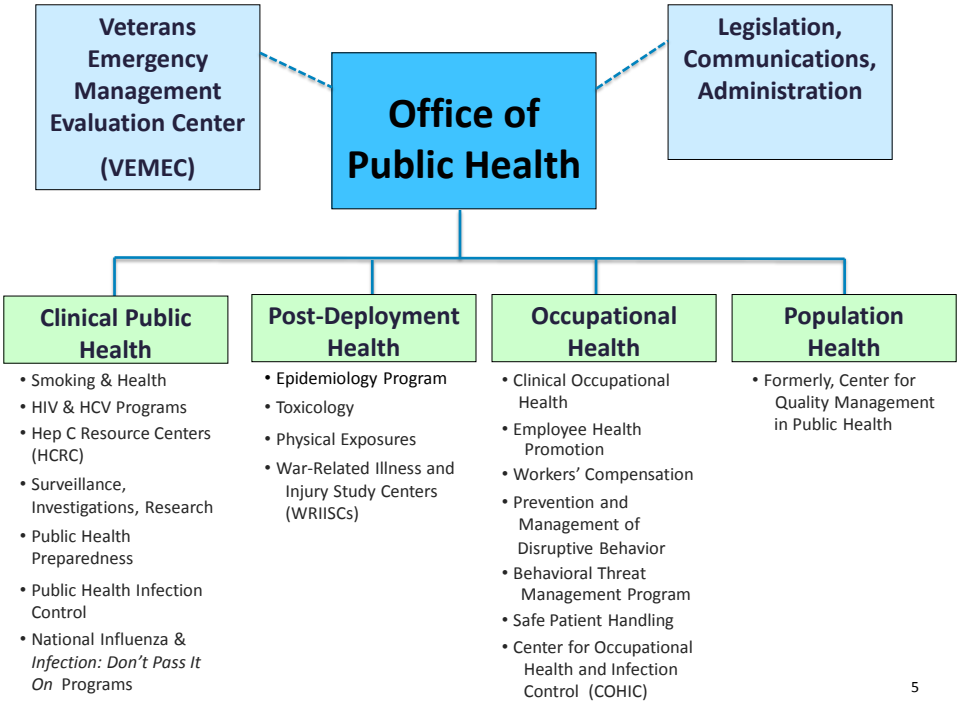
Robert A. Petzel, M.D.
Under Secretary for Health
Department of Veterans Affairs

Functions of Population/Public Health

- Broad look at health of Veterans as whole (by cohort such as era)
- Conduct surveillance
  - Post-deployment health
  - Emerging health issues
  - Diseases
- Assess and report
  - Health status of Veterans overall
  - Impact of VHA interventions to improve health, decrease disparities
- Use data to make decisions
  - Risk determinations
  - Screening/diagnosis standards
  - Treatment standards
  - Policy
  - Provider/Veteran education & outreach

Organizational Structure




Veterans Emergency Management Evaluation Center (VEMEC)
Office of Public Health
Legislation, Communications, Administration
Clinical Public Health
• Smoking & Health
• HIV & HCV Programs
• Hep C Resource Centers (HCRC)
• Surveillance, Investigations, Research
• Public Health Preparedness
• Public Health Infection Control
• National Influenza & *Infection: Don't Pass It On* Programs
Post-Deployment Health
• Epidemiology Program
• Toxicology
• Physical Exposures
• War-Related Illness and Injury Study Centers (WRIISCs)
Occupational Health
• Clinical Occupational Health
• Employee Health Promotion
• Workers' Compensation
• Prevention and Management of Disruptive Behavior
• Behavioral Threat Management Program
• Safe Patient Handling
• Center for Occupational Health and Infection Control (COHIC)
Population Health
• Formerly, Center for Quality Management in Public Health
5


Clinical Public Health Focus
• National programs for HIV and hepatitis C
• Smoking and health policy and education
– Counseling
– Evidenced-based care for tobacco cessation
– Integrating tobacco cessation into PTSD care
• Biosurveillance
– e.g., seasonal influenza, H1N1, Dengue, Gulf Coast oil spill
– Emerging diseases & other significant pathogens
• Epidemiologic investigations and look backs
– Prostate biopsy, endoscopes, dental, surgical, provider behavior
"STEP UP" TO PREVENT FLU
Get Checked
Say yes to the test
HIV Testing Saves Lives. Learn More.
Infection: Don't Pass It On
Helping Smokers Quit
Video Length: 04:51
VETERANS HEALTH ADMINISTRATION
6

Post-Deployment Health Focus

- Conduct surveillance and studies on environmental and occupational exposures of Veterans during military service
  - Research is one tool used by OPH
- Evaluate existing and new research to provide policy recommendations
- Oversee War Related Illness and Injury Study Centers
- Maintain Environmental Health Registries (e.g., Gulf War)
  - Inform and provide outreach to Veterans
  - Advise and educate clinicians

Specific Initiatives for Gulf War Veterans

- Follow-up Study of a National Cohort of Gulf War and Gulf Era Veterans
  - Third in a series of surveys to learn how the health of 1990-91 Gulf War-era Veterans has changed over time
- War Related Illness and Injury Study Centers (WRIISC)
  - Provide comprehensive clinical evaluations and exposure assessments of Veterans
  - Patient satisfaction with the most recent visit is consistently between 95% and 100%
  - Conduct research on disease causes and treatments (e.g., effects of exposures on cardiopulmonary function and the treatment of chronic pain)
  - Serve as educational resource for combat Veterans, their family members and loved ones, and Veteran health care providers
  - Provide training for clinicians
- Gulf War Registry
  - Entry into health care and enables communication and outreach

Recent Accomplishments of Office of Public Health

Accomplishments and Ongoing Initiatives, 2009-2012 Public Health (10P3)

- Using our expertise as the largest U.S. provider of care for persons with HIV and hepatitis C
  - Through VHA initiated legislative change & program initiatives - HIV testing has doubled from 2009-2011
  - Offer and educate on latest, best treatments available for HIV, hepatitis C
- Conducting lookback and epidemiologic investigations across the VHA health system
  - Endoscopes, dental equipment, infection control breaches, surgical infections, provider behavior
- Establishing an expert group on Veteran population health
  - Assess and report on overall health status, impact of interventions through collaboration with other VHA programs
  - Using data to determine standards for screening, diagnosis, treatment

Accomplishments and Ongoing Initiatives, 2009-2012 Public Health (10P3) (continued)

- Reducing infections
  - Preventing influenza with vaccinations, hand and respiratory hygiene, staying home when sick
  - Developing a health care associated infection and influenza surveillance system (HAIISS) to monitor at national, VISN and facility levels
  - Promulgating a national hand washing initiative
- Strengthening public health preparedness
  - Actively collaborating within VHA, with VA, with states, and across government
  - Establishing the Veterans Emergency Management Evaluation Center (2010; VEMEC) working with VHA's Office of Emergency Mgmt (OEM) and VA Operations, Security, & Preparedness (OSP)

Accomplishments and Ongoing Initiatives, 2009-2012 Public Health (10P3) (continued)

- Ensuring a healthy, productive workforce
  - Providing employee occupational health support and consultation
  - Developing and implementing national electronic Employee Medical Folder, the electronic Occupational Health Recording Keeping System (OHRS)
  - Improving safe patient handling through distribution of equipment and dissemination systems - reducing injuries for both staff and patients in collaboration w/ Nursing, PCS, OQSV, Safety/Engineering
  - Preventing, assessing and advising on behavioral threats, disruptive behaviors
  - Promoting employee health & wellness through lifestyle changes and healthy choices (2K Walk at 150 VA locations; also collected essential items for homeless Veterans)
  - Managing and improving tracking and outcomes for Workers Compensation
  - Ongoing projects including:
    - Project BREATHE—design and production of a new and improved N95 level respirator for health care providers
    - Respiratory Protection Effectiveness Clinical Trial (ResPECT)

Accomplishments and Ongoing Initiatives, 2009-2012
Public Health (10P3)

Walking workstations for employees

Campaign to reduce health care associated infections through handwashing

Flu prevention – promoting vaccination for Veterans & staff

PUBLIC HEALTH
www.publichealth.va.gov

New pocket card to assist providers with Veterans' concerns about military exposures

Numerous collaborations & provision of guidance on tobacco cessation – esp. for mental health & substance abuse populations

Providing information for those exposed to Agent Orange

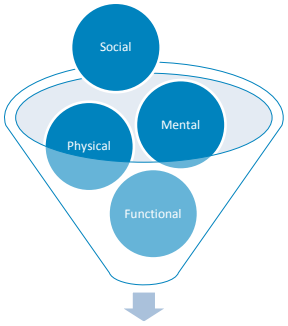
Safe patient handling equipment in use

VA2K walk for Veterans (Baltimore)

Follow-Up Study of a National Cohort of Gulf War and Gulf Era Veterans

Survey Goal

Follow-up Study of a National Cohort of Gulf War and Gulf Era Veterans



Overall Health of Veterans

- Comprehensive assessment of health and wellness
- Domains: physical (such as neurologic, immunologic and respiratory), mental, women's health, functional, and social
- Focus is on multiple domains and health conditions, which will provide a population level assessment of overall health

Survey Timeline

- Survey instrument approved by Office of Management and Budget: 2/27/2012
- Mailing of survey began: 5/21/2012
- Last mailing of survey: 12/03/2012
- Data set delivery projected: Spring 2013
- Preliminary results projected: Fall 2013

Survey Contents

- Questions cover a multitude of manifestations of physical and mental health
- Contains 217 questions total
  - 26% physical symptoms
  - 21% mental health symptoms
  - 19% medical diagnoses
  - 12% life events
  - 8% treatment of symptoms
  - 7 % demographics
  - 6% behavioral risk factors (smoking, drinking, etc.)

Some Questions in the Survey are Related to Stress

- There are many physical and emotional responses to stress—physical (e.g., headache, muscle pain), mood (e.g., anxiety, irritability), and behavioral (e.g., angry outburst, tobacco use)*
- Stress in this survey is one factor potentially influencing a whole range of medical outcomes
- Stress is a non-specific term that refers to an array of triggers and processes
- We recognize that stress and the mind/body link is only one of the important dimensions to be examined

* American Psychological Association's "Stress in America" report, 2010

IOM Study of Treatment for Multi-Symptom Illness

IOM Committee on Treatments for Multi-Symptom Illness

- IOM final report due for public release February 2013
- IOM Committee members recognize a comprehensive approach in their study of the treatment of multi-symptom illness in the Veteran population
- IOM has held four public meetings on this study. The committee determines public meeting schedule

Study on Multiple Sclerosis

Study on Multiple Sclerosis
Section 804 of Public Law 110-389

- VA "will contract with IOM to conduct a comprehensive epidemiological study for purposes of identifying any increased risk of developing multiple sclerosis…"
- VA talked with IOM about conducting a comprehensive study; IOM's approach was to first focus on review of current literature as part of ongoing Gulf War and health review
- IOM in its Vol. 8 report (p. 124–126) indicated there was inadequate/insufficient evidence to support an association
- Evidence to date shows no increased incidence of multiple sclerosis in Gulf War Veterans and the studies are continuing
  - Neurological mortality among U.S. Veterans of the Persian Gulf War by Barth, Kang, Bullman & Wallin *(American Journal of Industrial Medicine*, 2009)
  - The Gulf War era multiple sclerosis cohort by Wallin et al *(Brain*, 2012)

Study on Multiple Sclerosis Section 804 of Public Law 110-389 (continued)

- Follow-Up Study of a National Cohort of Gulf War and Gulf Era Veterans
  - Questions on diagnoses of multiple sclerosis and other diagnosed neurological diseases (ALS, brain cancer, Parkinson's)
  - Longitudinal self-reported data includes historical military environmental exposures and medical prophylaxis
- Follow-Up Study of Multiple Sclerosis Cohort
  - Case control study examining entire period with deployed and non-deployed controls
  - Goal is to quantify risk for developing multiple sclerosis among Gulf War Veterans
- Follow-Up Study of Neurological Mortality among U.S. Veterans of the Persian Gulf War
  - Data collection complete on deaths through 2008; pending physician review
  - Continued data collection is ongoing for deaths through 2010
  - Study will add OEF/OIF Veterans who have same neurological causes of death
- Seeking Input from Research Advisory Committee on Gulf War Veterans' Illnesses

Summary

- We are organized and "…designed around the needs of the patient" through population-based health programs
  - Employ stellar multidisciplinary staff credentialed in occupational medicine, clinical public health, toxicology, and epidemiology using multiple tools and means
  - Transitioning from exposure→disease model to health outcome→potential cause model of evaluating military exposures
  - Seeking answers in collaboration with DoD, VA Office of Research and Development, and the Research Advisory Committee on Gulf War Veterans' Illnesses
- Our Work is Relevant to all Veterans including Gulf War Veterans
  - Expertise and knowledge maintains health and safety of Veterans
  - Surveillance and research drives policy decisions about Veteran benefits

Learn More

Visit us
at
www.publichealth.va.gov

Effectiveness of Acupuncture in Treating Gulf War Illness

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New England School of Acupuncture
Principal Investigator
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- Overview of design and methodology
- Preliminary Results
- Next Steps

Methodology

- Objectives: To find a successful treatment for GWI, by gathering data to better understand: 1) the effectiveness of acupuncture in treating GWI; 2) the mechanisms of this disease.
- Specific Aim: In a sample of veterans with GWI, evaluate the effectiveness of an individualized acupuncture treatment protocol on the volunteers' most distressing GWI symptom.

Methodology

- Unblinded randomized controlled trial design with a wait-list-control.
- Individualized treatments
- Active group→6 months of biweekly treatment
- Waitlist group→2 months of waiting then 4 months of weekly treatments

Definition: Symptoms in 3 clusters

Cluster A *Fatigability*	Cluster B *Mood & Cognition*	Cluster C *Musculoskeletal*
persistent fatigue 24 hrs or more after exertion	feeling depressed	joint pain/ muscle pain
	feeling irritable	
	feeling worried, tense, or anxious	
	difficulty thinking	
	difficulty concentrating	
	problems finding words	
	problems sleeping	

How we measure improvement

- Main Outcome: Sf-36
- Fatigability
  - fatigue 24 hours or more after exertion
- Mood and Cognition
  - feeling depressed or
  - feeling irritable or
  - difficulty thinking or concentrating or
  - feeling worried, tense, anxious or
  - problems finding words or
  - problems getting to sleep
- Musculoskeletal
  - joint pain or muscle pain

How we measure improvement

- The SF-36
- Multidimensional Assessment of Fatigue
- The Profile of Mood States
- Pittsburg Sleep Quality Index
- Measure Your Medical Outcomes Profile
- Beck Anxiety Inventory
- McGill Pain Scale
- Carroll Depression Scale
- Social support, Social Networks, and Stress
- Medication use and Expectations for Treatment
- Blood draw to examine levels of selected markers of inflammation, stress, and immune function

Measure improvement according to Traditional Chinese Medicine

- Recording
  - TCM symptoms
  - Diagnosis
  - Prognosis
  - Expectations for treatment
  - Alliance with subject
- Measures
  - OM intake-baseline
  - Health History Questionnaire-baseline
  - Monthly progress TCM (baseline and monthly for 6 months of study)

How TCM Characterizes GWI

- TCM's individualized diagnosis and treatment good for heterogeneous presentation

- Treatment Guided By
  - Literature Review
  - Expert Interviews
  - Exposures to neurotoxicants

- Recommendations
  - TCM Neurology
  - Wei-zhang (Flaccidity Syndrome) – treatment of organophosphate poisoning from TCM perspective
  - Autonomic Nervous System (ANS)
  - Bi Syndrome

TCM Treatments

Veterans with GWI will receive individualized TCM diagnosis and treatment strategy, directed at their most distressing symptom, and at any additional symptoms, as well as at their root condition, 1-2 x/week x 4-6 months. Full intake will include medical history and exposure to known or suspected neurotoxicants during the war.

Treatments provided by senior practitioners in private offices, may include:

- needling with *de qi* sensation
- warming treatments, e.g., moxibustion, heat lamps
- manual therapies, including tui na, cupping, gua sha
- electroacupuncture, known to be helpful for its analgesic and anti-inflammatory effects
- microsystems - auricular and scalp
- press balls

TCM Treatments

Not within the scope of this study, excluded treatments are:

- Chinese Herbal Medicine (CHM)
- Supplements

- This type of Acupuncture is the most commonly used in the US making our results easy to apply. 18,000 practitioners in US.

Patient Safety

- An **adverse event** is any negative health change (or side-effect) that happens to a volunteer while he/she is participating in the study.
- Only two AEs were reported

Practitioner Safety

- Safety issues treating trauma survivors
- Safety Resources
  - **Suicide Prevention Hotline**
    1-800-273-8255 (TALK)
  - **VA Boston**
    24-hour nurse available to provide telephone care for veterans
    1-800-865-3384
  - **National Veterans Helpline**
    1-800-507-4571

www.boston.va.gov/

Preliminary Results

- Recruitment
- Main and secondary complaints
- Usability

Preliminary Results: Recruitment

- Newspaper stories & advertisements, Manpower database (6,000 cards), radio, cable TV, word of mouth (VA, Yellow Ribbon)
- 200 vets started the screening process
- 163 screened
- 101 Enrolled & randomized
- 12 dropouts

- 80% White, 10% Black, 10% Other
- Average age 48 years
- Mostly men/women: 7/1

Preliminary Results

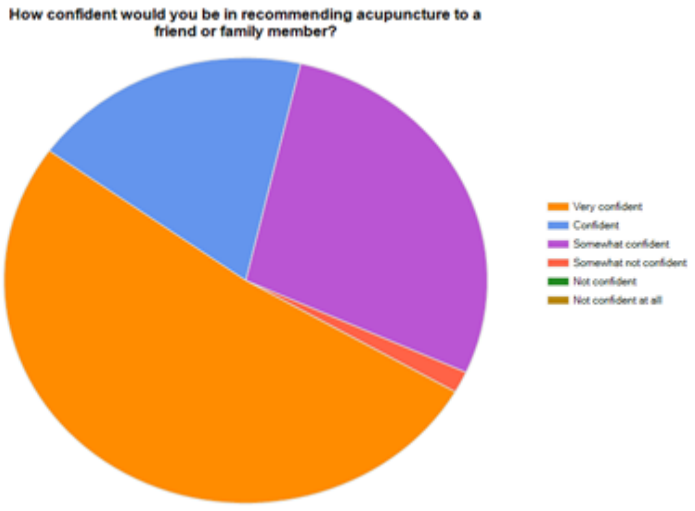
- Recruitment
- Main and secondary complaints
- Usability

Main and secondary complaints

- **MYMOP:**
  Measure Yourself Medical Outcomes Profile Paterson, J. BMJ. 1996 Apr 20;312(7037):1016-20.

- The MYMOP is cross-validated with the SF-36 and thus should offer comparable results.

Usability



Summary

- Almost to target enrollment (might reach n=110)
  - Supplement and Extension to Dec 2012
- Preliminary evidence of treatment effect
  - Primary and secondary symptoms
- Vets are confident recommending acupuncture to loved ones
  - Want to continue with acupuncture

Next Steps

- Applying CDMPR Investigator-Initiated Research Award
  - 1. Which types of acupuncture work best
    - For which symptoms
    - For which individuals (e.g. IBS)
    - Dose
      - 1x week vs 2x week
      - adherence

Next Steps

- Applying CDMPR Investigator-Initiated Research Award
  - 2. Detailed treatment protocols
  - 3. Blood subanalyses
    - Within IBS and compare to normals
  - 4. Self-reported exposures
    - Related to reported symptoms
    - Related to TCM dx

Thank you veterans!

Neural correlates of mindfulness practice

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Bender Institute of Neuroimaging
Universität Gießen

Commonly reported benefits …

- Relaxation and well-being that last beyond the time spent meditating
- Improved mood and ability to deal with difficult / challenging situations
- Improved concentration and memory

Effects of mindfulness practice

- Improved immune function (e.g., Davidson et al., 2003)
- Reduced blood pressure (e.g., Carlson et al., 2007)
- Reduced cortisol levels (e.g., Carlson et al., 2007)

Mindfulness effective in the treatment of …

- Anxiety (Hofmann et al., 2010)
- Depression (Teasdale et al., 2000)
- Substance abuse (Bowen et al., 2010)
- Chronic pain (Grossman et al., 2007)

Mindfulness in the treatment of PTSD

- Preliminary study on mindfulness-based exposure therapy (King et al., 2012)
  - Intervention appeared acceptable and veterans showed compliance
  - PTSD symptoms improved significantly in completers (N=16, p=.03)

Definition

- Non-judgmental awareness of experiences in the present moment
- Attitude of acceptance, curiosity and openness

What are the neural mechanisms that might underlie its beneficial effects?

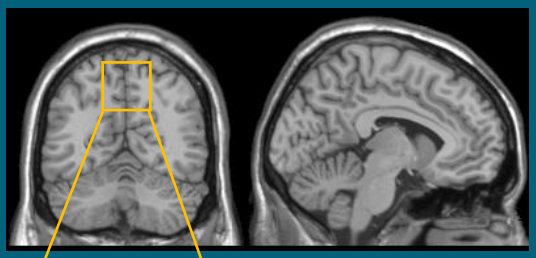
Magnetic resonance imaging (MRI)

Imaging of function and structure of the brain

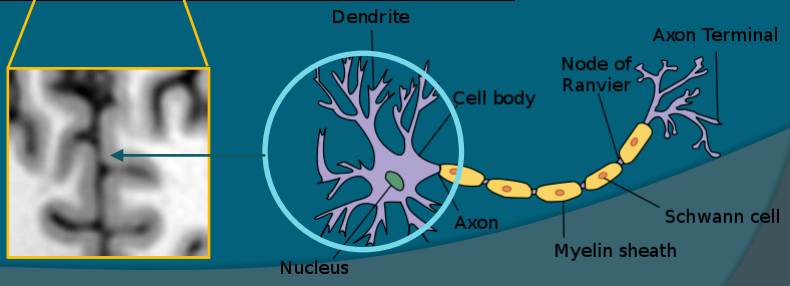
Function: oxygenation of blood
→ activation of brain regions

Structure: morphometry of the brain

Brain gray matter



Surface of both hemispheres
Deeper nuclei
Tissue: **Neuronal cell bodies**



Brain gray matter

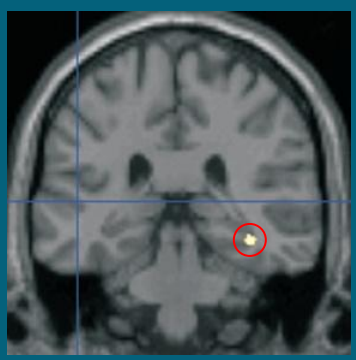
Greater gray matter correlates with better performance of tasks associated with that brain region
(Critchley et al., 2004; Milad et al., 2005; Mechelli et al., 2004)

Difference in brain structure

… between experienced meditators and non-meditators

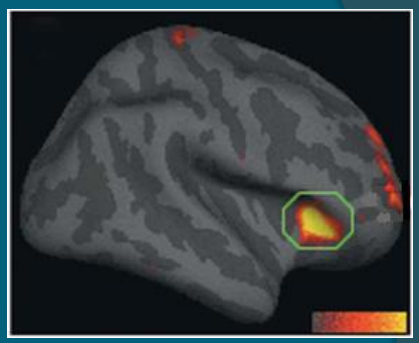
Lazar et al. (2005)
Pagnoni & Cekic (2007)
Hölzel et al. (2008)
Luders et al. (2009)
Vestergaard-Poulsen et al. (2009)
Grant et al. (2010)

Some different and some overlapping findings



Hippocampus

Hölzel et al. (2008);
Luders et al. (2009);
Lazar et al. (unpublished)

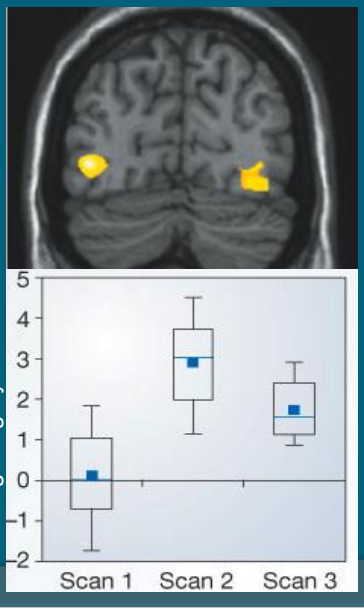


Right insula

Hölzel et al. (2008);
Lazar et al. (2005)

Cross-sectional studies!

Neuroplasticity through training



Draganski et al., 2004, Nature
Reprinted with permission from Macmillan Publishers Ltd.

Study 1

Does gray matter concentration increase following mindfulness practice?

Mindfulness-Based Stress Reduction (MBSR, Jon Kabat-Zinn)

- Body Scan
- Yoga
- Sitting meditation
- Daily homework practice for 8 weeks

Methods

Participants: healthy, meditation-naïve

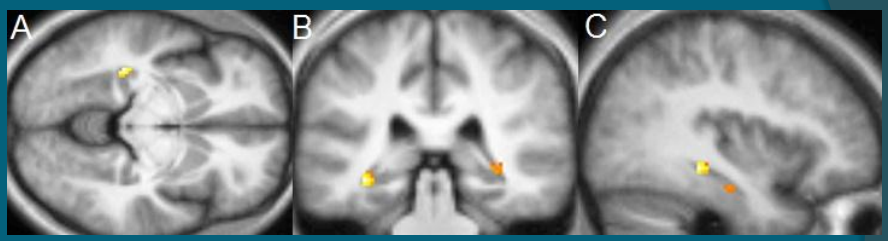
- 16 MBSR
- 17 waitlist control group

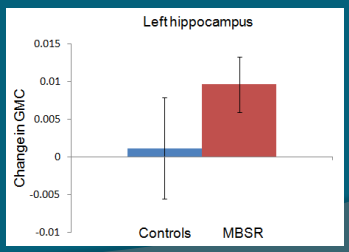
Structural MRIs

- Before and after the course

Increase in gray matter concentration

Left Hippocampus





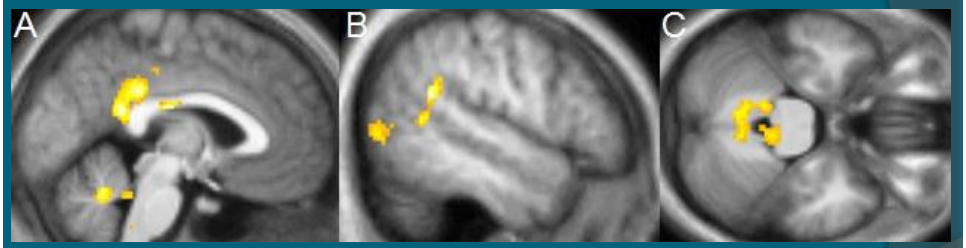
Hölzel et al. (2011). *Psychiatry Research: Neuroimaging.*

Hippocampus

- Susceptible for neurotoxic effect of stress
- Lower gray matter in PTSD, and other disorders (e.g., depression, Alzheimer's)
- Ability to form new synapses and generate new neurons
- Involved in
  - Learning and memory
  - Emotion regulation

Increase in gray matter concentration

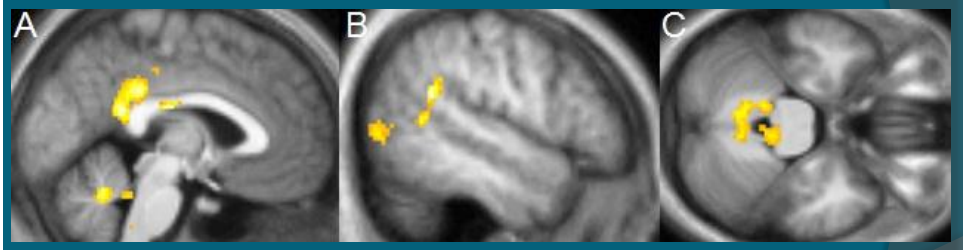
Posterior cingulate cortex | **Temporo-parietal Junction** | **Cerebellum**



Hölzel et al. (2011). *Psychiatry Research: Neuroimaging.*

Increase in gray matter concentration

Posterior cingulate cortex | **Temporo-parietal Junction** | **Cerebellum**



Self

Change in perspective

Coordination of movement & emotion

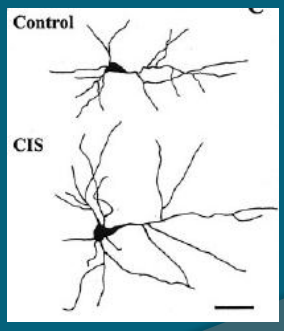
Hölzel et al. (2011). *Psychiatry Research: Neuroimaging.*

Open questions

- Preliminary finding – replication is necessary
- Cellular mechanisms are unknown
- Is meditation the primary cause for the changes?
  (social contacts, movement, diet, etc.)
- How are changes in the brain related to well-being?

Stress

- MBSR reduces stress (Chiesa & Serretti, 2009)
- Amygdala activation in response to stress inducing stimuli
- Rodent studies:
  Stress leads to growth of dendrites
  (Vyas et al., 2002)



Study 2

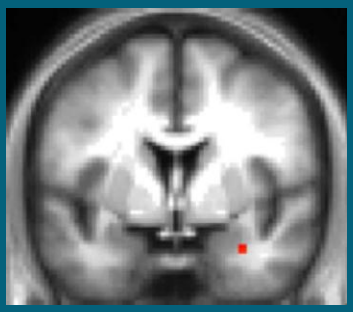
Are changes in perceived stress related to gray matter changes in the amygdala?

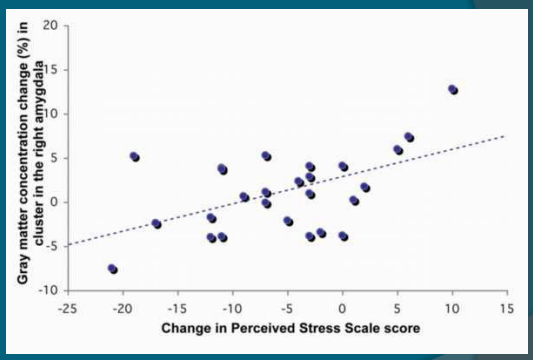
Perceived stress

- 26 healthy, stressed participants
- Perceived stress scale
  (Cohen & Williamson, 1983)
- Before and after MBSR program
- Significant reduction in stress ($p < 0.001$)
- Regression analysis

Hölzel et al. (2010). *Social Cognitive and Affective Neuroscience.*

Decrease in perceived stress correlates with decrease in amygdala gray matter concentration





Hölzel et al. (2010). *Social Cognitive and Affective Neuroscience.*

Summary

- Increase in gray matter concentration, e.g., in hippocampus, following mindfulness training
- Decrease in perceived stress correlates with decrease in amygdala gray matter concentration
- Specific neural mechanisms of mindfulness-induced pain analgesia

Acknowledgement

- Lab
  - Sara Lazar
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  - Mind and Life Institute
  - IGPP Freiburg
  - John Templeton Foundation

Thank you for your attention!

Tai Chi: A Mind-body Exercise for Pain Relief and Well-being

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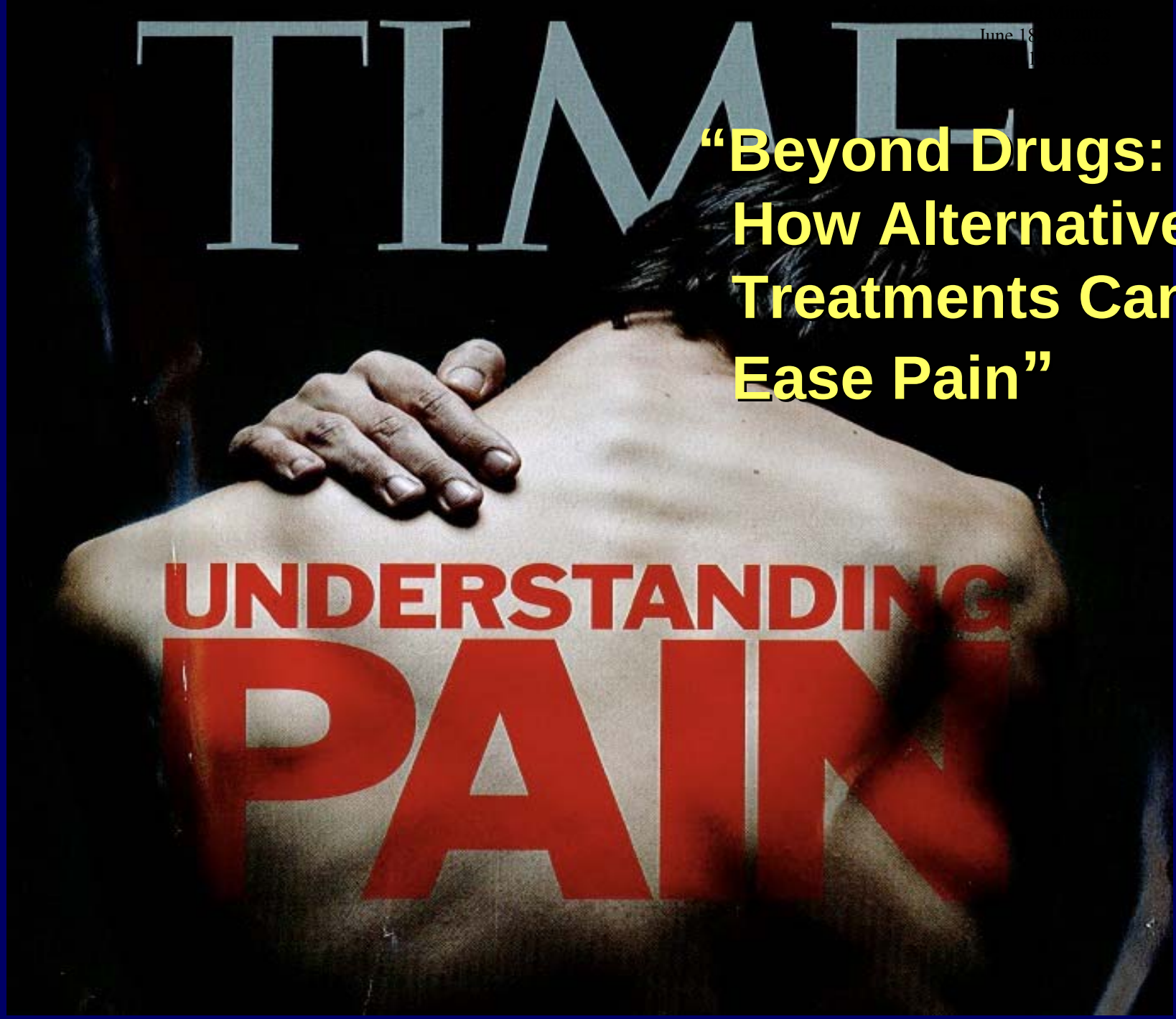
Associate Professor of Medicine

Director, Center for Integrative Medicine
Tufts Medical Center/Tufts University School of Medicine



“Beyond Drugs: How Alternative Treatments Can Ease Pain”

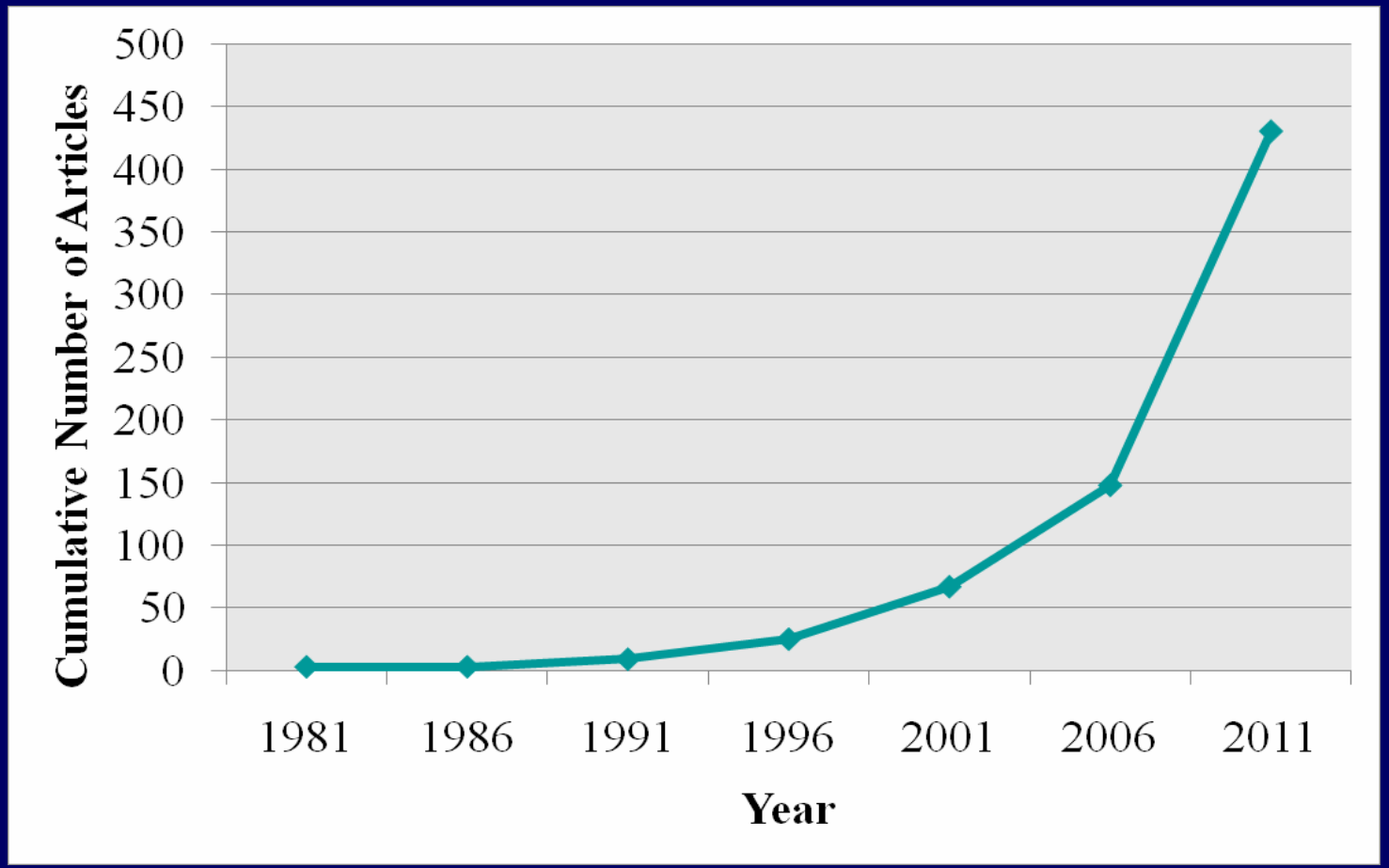
National Health Interview Survey (n = 31,044)
Complementary and Alternative Medicine Use Among Adults and Children: United States, 2007

- Around **2.5 million** Americans practice Tai Chi and the number is rapidly increasing.

- Tai Chi use was associated with higher reports of musculoskeletal conditions (OR 1.43, 95% CI 1.11-1.83).

Birdee et al Journal of Alternative & Complementary Medicine. 2009; 5: 969-73

Growth of Tai Chi Literature



Currently, there are 460 citations for Tai Chi research.

Selected Tai Chi Publications

- 1. Wang C, Schmid C, Kalish R, et al. A Randomized Controlled Trial of Tai Chi for Fibromyalgia. New England Journal of Medicine, 2010; 363: 743-54.
- 2. Wang C, Schmid C, Hibberd P, et al. Tai Chi is Effective in Treating Knee Osteoarthritis: A Randomized Controlled Trial. Arthritis & Rheum. 2009; 61: 1545-1553.
- 3. Wang C, Roubenoff R, Lau J, Effect of Tai Chi in adults with Rheumatoid Arthritis. Rheumatol. 2005; 44: 685-687.
- 4. Wang C. Tai Chi and rheumatic diseases. Rheumatic disease clinics of North America. 2011; 37: 19-32.
- 5. Wang C, Ramel, J, Schmid C. Tai Chi and Psychological wellbeing. BMC Complementary and Alternative Medicine, 2010; 10: 23: 1186-1472.
- 6. Wang C, Collet J, Lau J. The effect of Tai Chi on health outcomes in patients with chronic conditions: a systematic review. Archives of Internal Medicine. 2004; 164: 493-501. PMCID: PMC15006825.
- 7. Yeh GY, Wang, C, Wayne P, Phillips R Tai Chi Exercise for Patients with Cardiovascular Conditions and Risk Factors, A Systematic Review. J Cardiopulm Rehab Prev. 2009, 29:152-60.
- 8. Yeh GY, Wang C, Wayne PM, Phillips RS. The Effect of Tai Chi Exercise on Blood Pressure: A Systematic Review. Prev Cardiology 2008; 11: 82-89.

Outline

- Overview of fibromyalgia and Tai Chi
- A randomized trial of Tai Chi for fibromyalgia
- Conclusion and clinical implications

Case Vignette (the New York Times)

Mary, 59, from Lynn, Mass.

"It hurt me so much just to put my hands over my head."
"Sleeping was difficult".
"I couldn't walk half a mile."
"There was no joy to life."
"I was an entire mess from head to foot."

PE: Multiple tender points; depressed

Mary rejected medication due to side effects.
She tried physical therapy, swimming and other approaches.

Fibromyalgia Syndrome

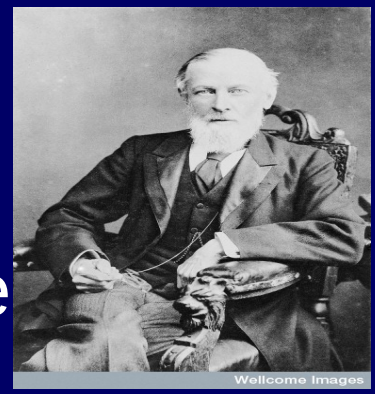
- A common and complex Pain illness
- The second most common condition seen in rheumatologic practice in the US
- Very difficult to treat

Pharmacological Treatment of Fibromyalgia

- Analgesics
- Antidepressants
- Antiseizure drugs

Most of these treatments have modest efficacy when used as stand-alone therapy.

History of Fibromyalgia



Early 20th Century:

- Fibrositis- inflammation of fibrous tissue of muscles

Mid-1970s: termed fibromyalgia

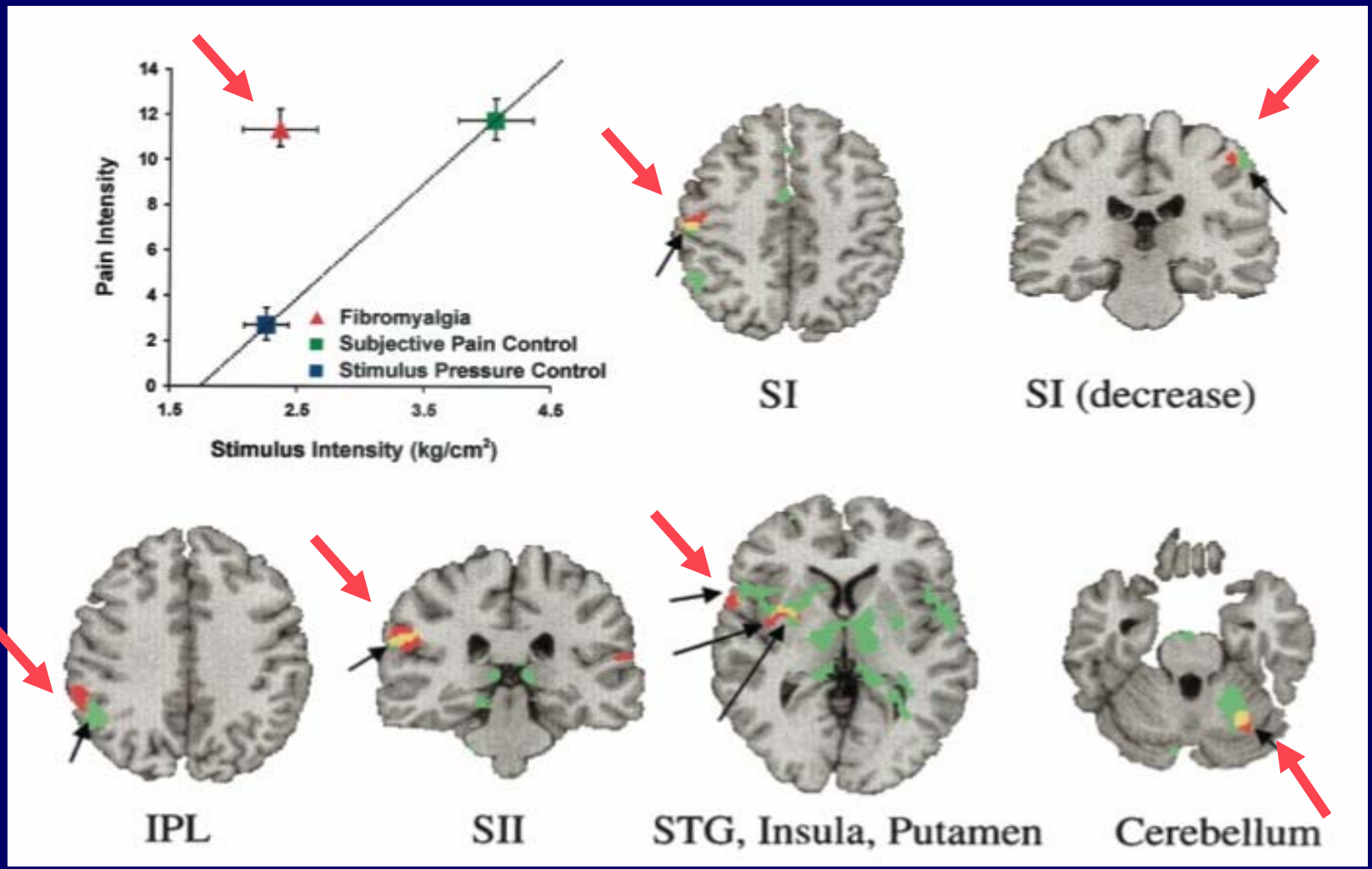
- Muscle biopsy “abnormalities” found no different from deconditioned controls

Mid-1980s: a classified as disorder of the central nervous system

Pathophysiology- Current Theories

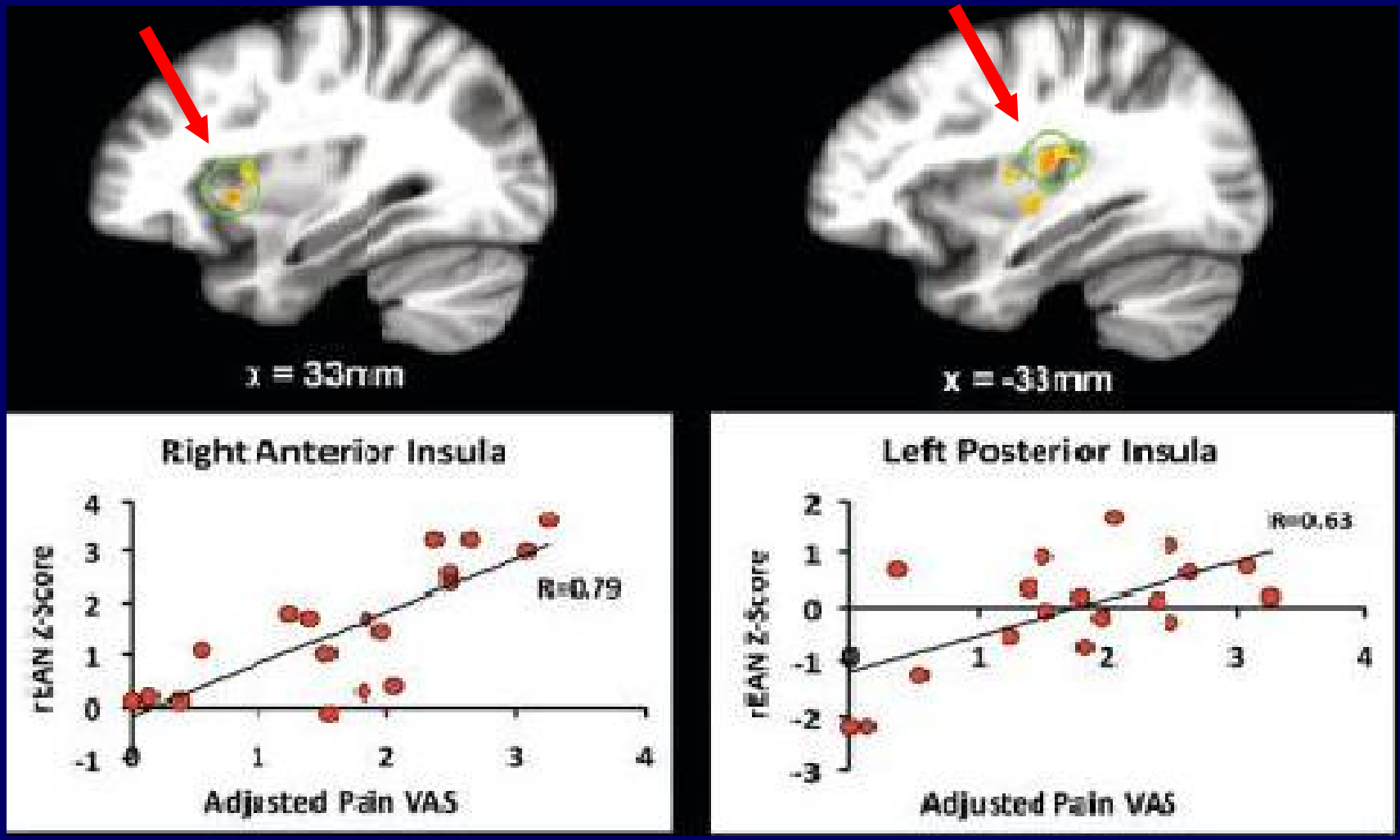
Central Nerve System pain deregulations

Brain Regional Blood Flow Response to Pain in Fibromyalgia vs Controls



Gracely et al, Arthritis & Rheumatism 2002; 46: 1333-1334

Pain Intensity correlated with executive attention network connectivity to the insula

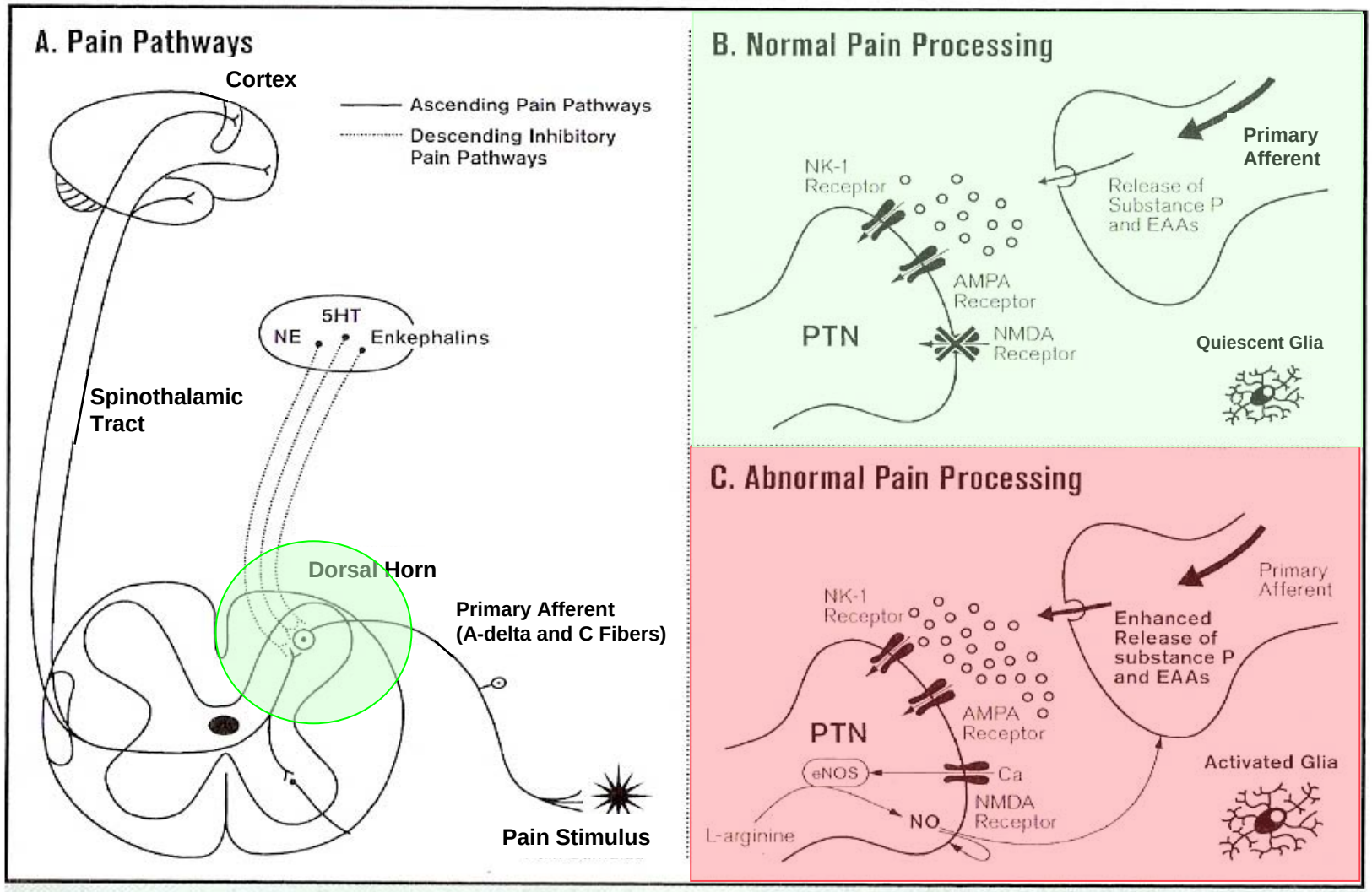


Napadow et al, Arthritis & Rheumatism 2010; 62: 2535-2555

Summary of Brain Imaging Results

- Brain function or activity changes in patients with FM.
- Pain associated with FM may be mediated by central nervous system hyper-excitability.
- Brain activity within multiple networks is associated with spontaneous clinical pain.

Abnormal Pain Processing in Fibromyalgia

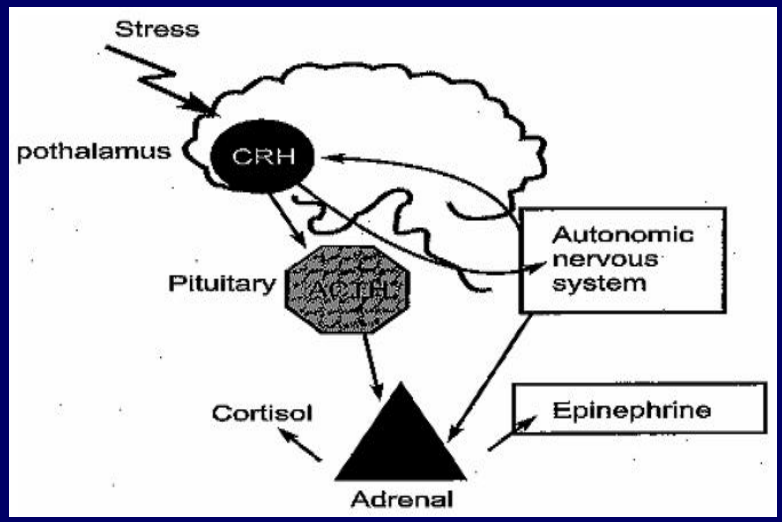


Bradley et al; Am J of Med. 2009

Pathophysiology – Current Theories

Stress-related disorder

- Abnormalities in the Hypothalamic-pituitary-adrenal axis

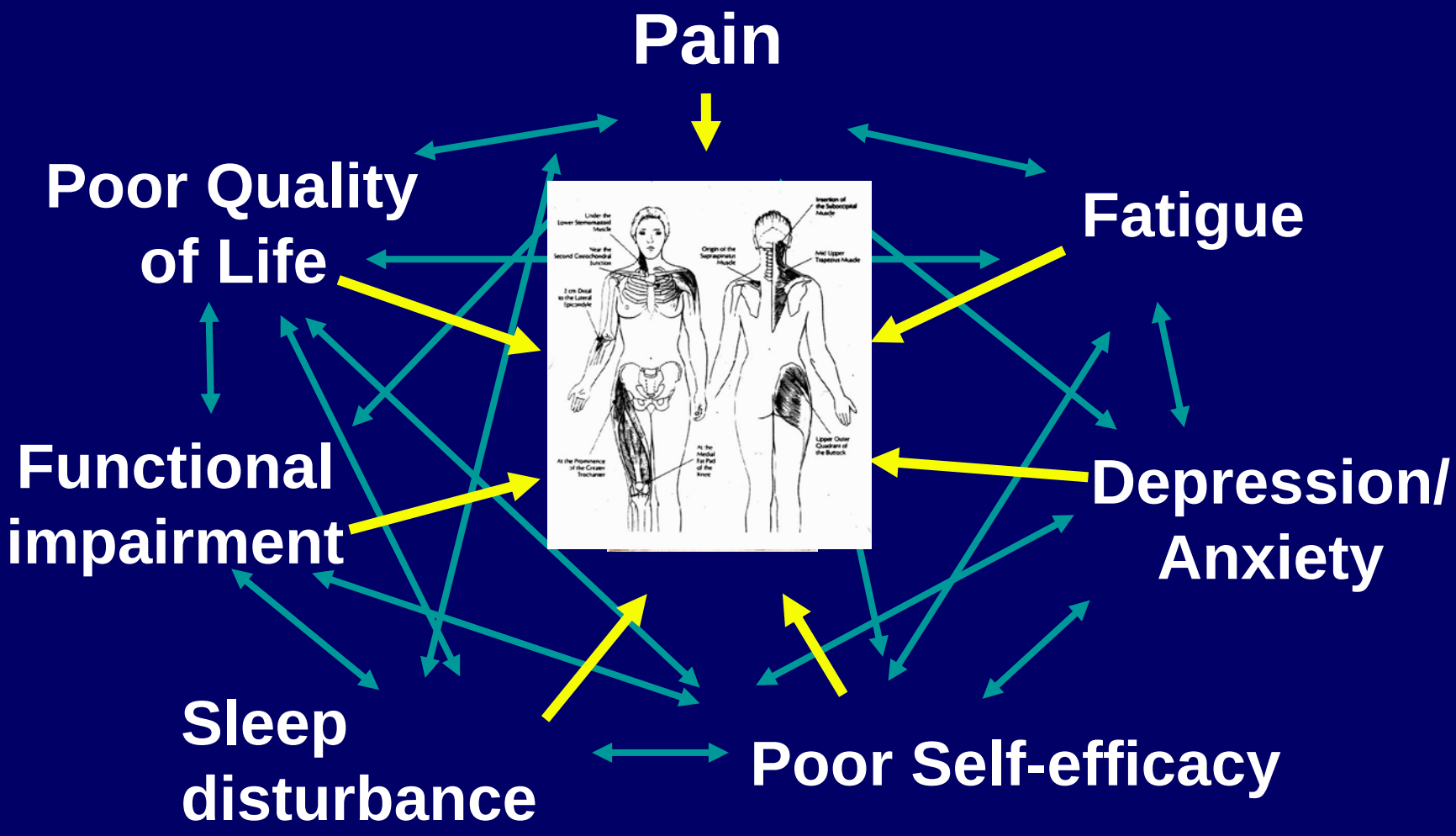


Neurotransmitter deficiency

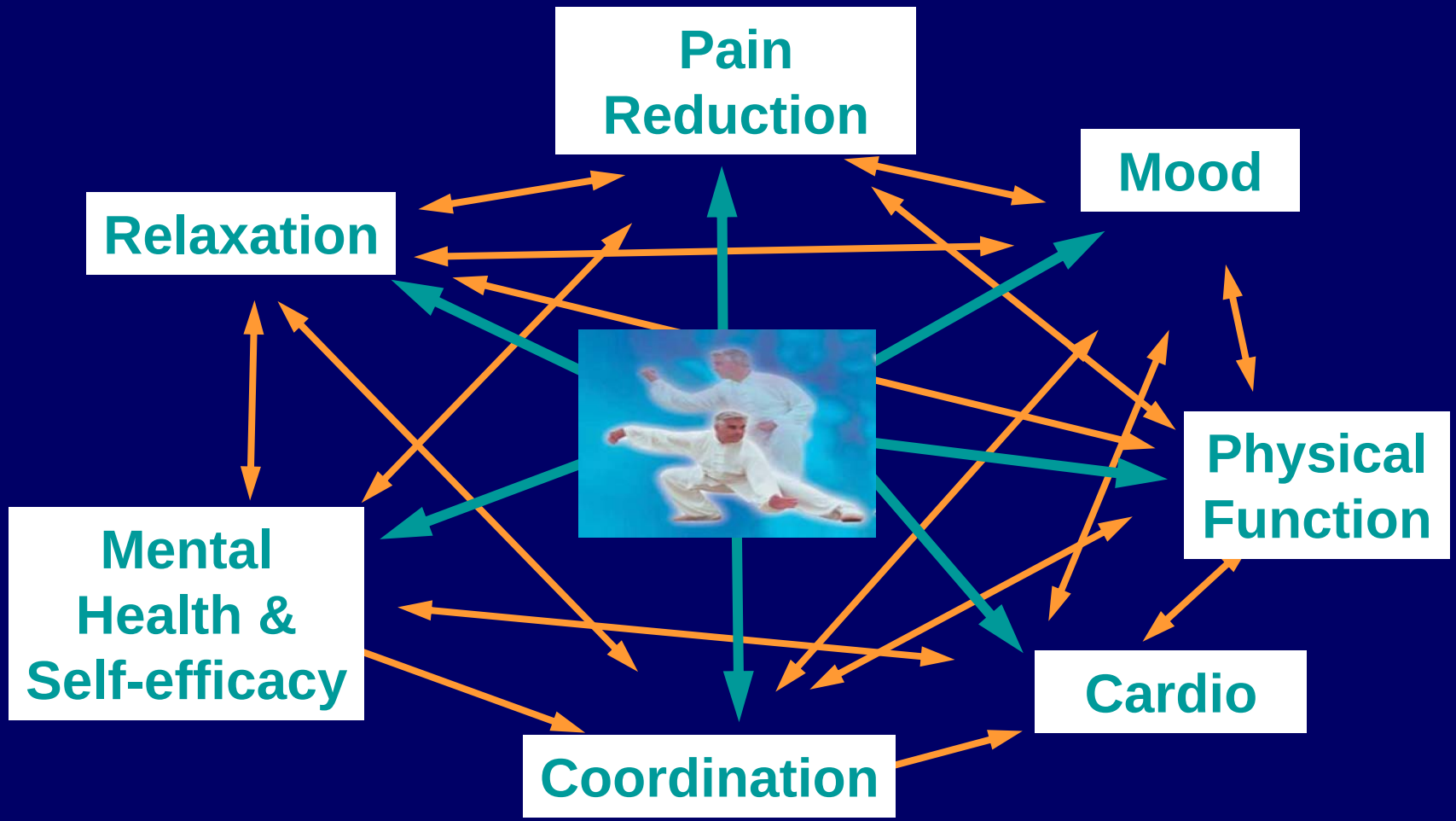
- Low level of serotonin, norepinephrine, and dopamine metabolites in blood and cerebrospinal fluid

Adler GK, et al. Am J Med. 1999; 106; 534-543

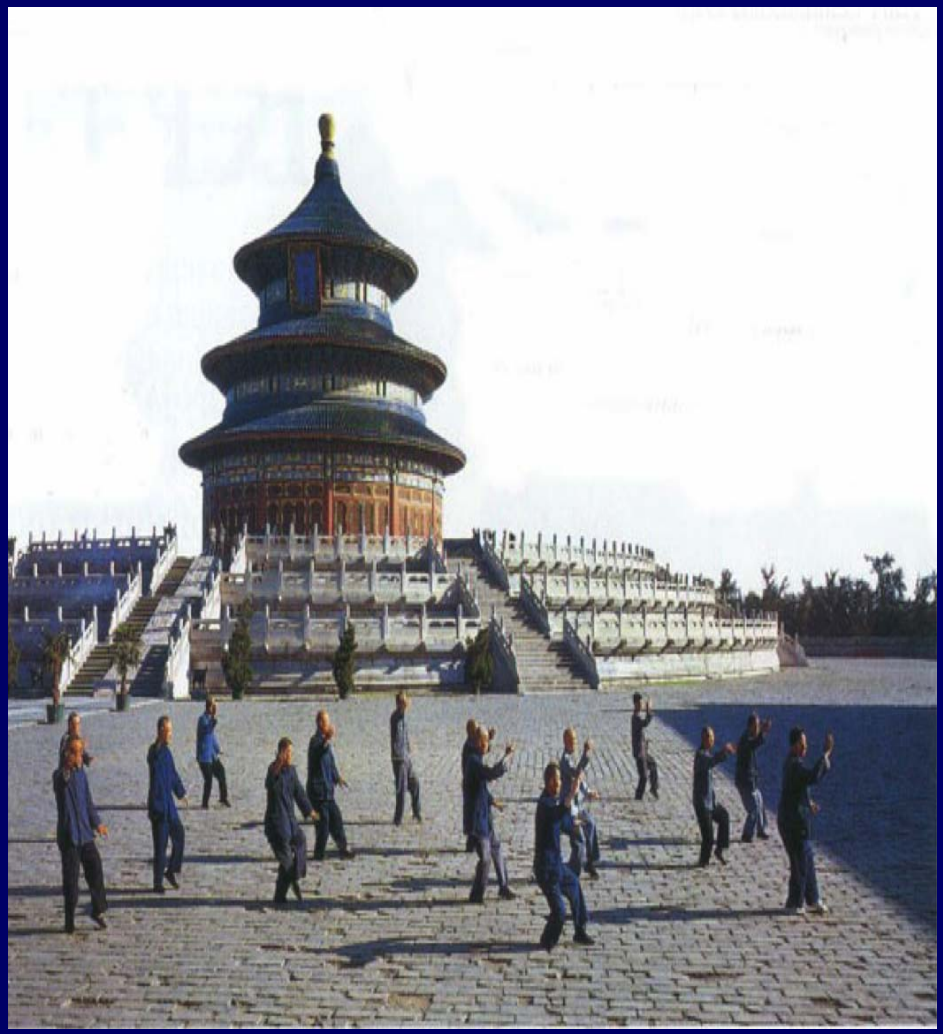
Physical and Psychological Change in Chronic Pain



Tai Chi Mind-body Benefits for Chronic Pain



What is Tai Chi ?



A traditional Chinese martial art. Tai Chi combines meditation with slow, gentle, graceful movements, deep breathing and relaxation[1]

Interactions between the brain, mind, body, and behavior[1]

Physiological and psychosocial benefits for patients with chronic conditions[2]

1. Delza, S. Rev. ed.. State University of New York Press Albany, N.Y., 1985.
2. Wang C et al. Archives of Internal Medicine. 2004;164: 493-501

REVIEW ARTICLE

The Effect of Tai Chi on Health Outcomes in Patients With Chronic Conditions

A Systematic Review

Chenchen Wang, MD, MSc; Jean Paul Collet, MD, PhD; Joseph Lau, MD

(REPRINTED) ARCH INTERN MED/ VOL 164, MAR 8, 2004 WWW.ARCHINTERNMED.COM
493

- **47 studies including randomized controlled trials, non-randomized studies, and observational studies published in English or Chinese.**
- **Benefits were reported for balance and strength, cardiovascular and respiratory function, symptoms of arthritis, muscular strength and psychological well-being.**
- **Additional well-designed studies are needed.**

Wang *et al. BMC Complementary and Alternative Medicine* 2010, **10**:23
http://www.biomedcentral.com/1472-6882/10/23

BMC Complementary & Alternative Medicine

RESEARCH ARTICLE Open Access

Tai Chi on psychological well-being: systematic review and meta-analysis

Chenchen Wang*[1], Raveendhara Bannuru[1], Judith Ramel[1], Bruce Kupelnick[1], Tammy Scott[2] and Christopher H Schmid[2]

- **8 English and 3 Chinese databases were searched through March 2009.**
- **40 studies, totaling 3817 subjects, reported at least 1 psychological health outcome.**
- **The trials in each subcategory were meta-analyzed using a random-effects model.**
- **Tai Chi significantly improved psychological well-being.**

Tai Chi: An Overview

- 35 reviews published between 2002 and 2010 were analyzed.

- The evidence is convincingly positive for fall prevention, improved balance, and improved psychological health.

Lee and Ernst, BJSM, 2011; 1-6

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Tai Chi for Fibromyalgia

Chenchen Wang, M.D., M.P.H., Christopher H. Schmid, Ph.D., Ramel Rones, B.S., Robert Kalish, M.D., Janeth Yinh, M.D., Don L. Goldenberg, M.D., Yoojin Lee, M.S., and Timothy McAlindon, M.D., M.P.H.

Study Aims

Explore the effects of Tai Chi on musculoskeletal pain, sleep quality, psychological distress, functional impairment and health status in patients with fibromyalgia.

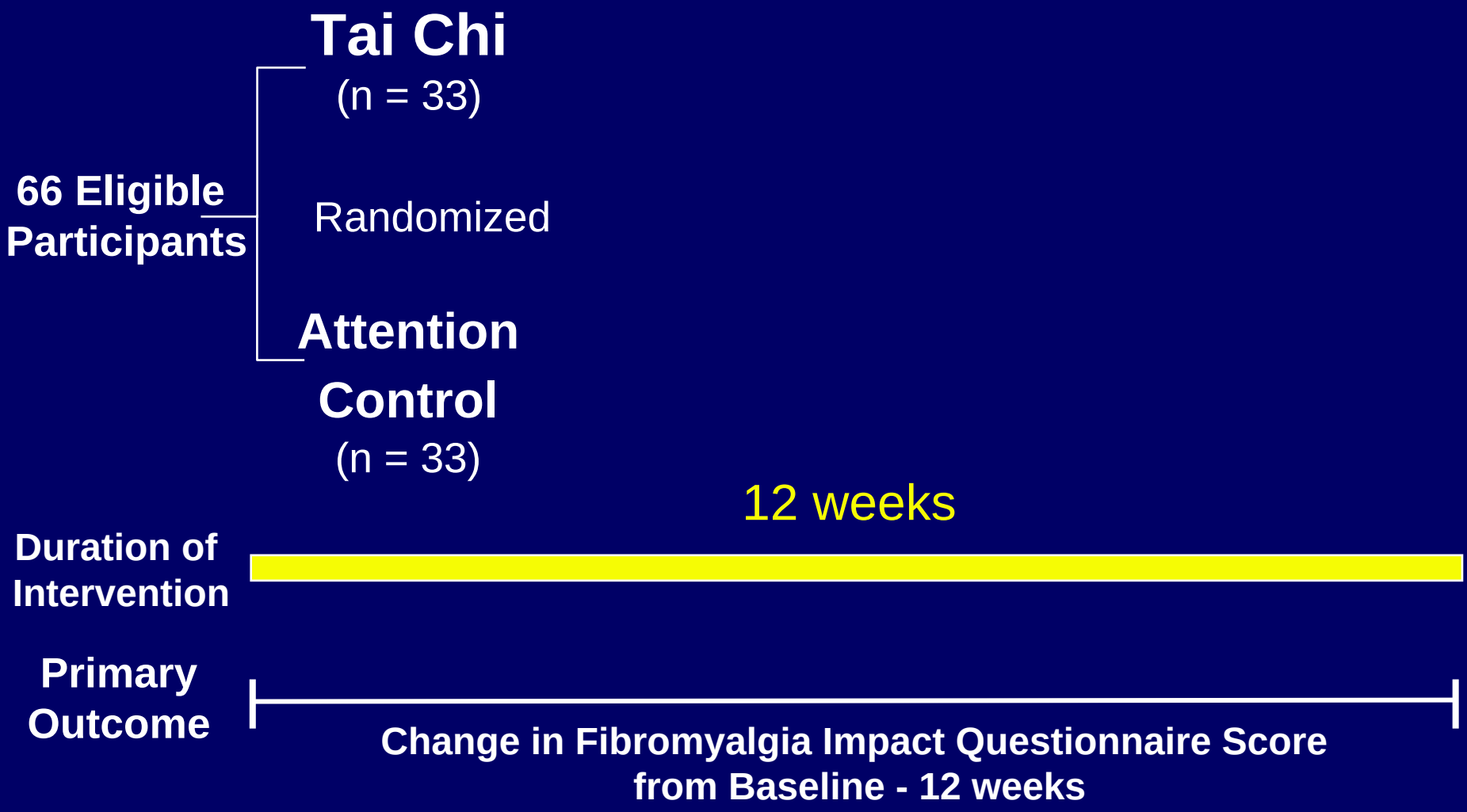
In NEJM **August** 19, 2010

Inclusion Criteria

- **Age 21 or older**

- **American College of Rheumatology criteria for classifying fibromyalgia (1990)**
  - **History of widespread pain >3 months**
  - **Tender point sensitivity**

Study Design



Primary Outcome Measure

Fibromyalgia Impact Questionnaire (**FIQ**)

- a validated multidimensional measure for participant-rated overall severity of Fibromyalgia.

- includes intensity of pain, physical functioning, fatigue, morning tiredness, stiffness, depression, anxiety, job difficulty and overall well-being.

- The total score ranges between 0 and 100 with higher scores indicating more severe symptoms.

Tai Chi - Intervention

- **Classical Yang style Tai Chi**
- **1 hour, 2 x /week (12 weeks)**
- **Every session included:**
  - **1) Warm up and review Tai Chi principles**
  - **2) Meditation with Tai Chi movement**
  - **3) Breathing technique**
  - **4) Relaxation**

Attention Control
(Stretching and Wellness Education)

- **1 hour, 2 x /week (12 weeks)**
- **Sessions include**

Education

- **FM knowledge**
- **Diet and nutrition**
- **Physical and mental heath**

Stretching exercise

Results

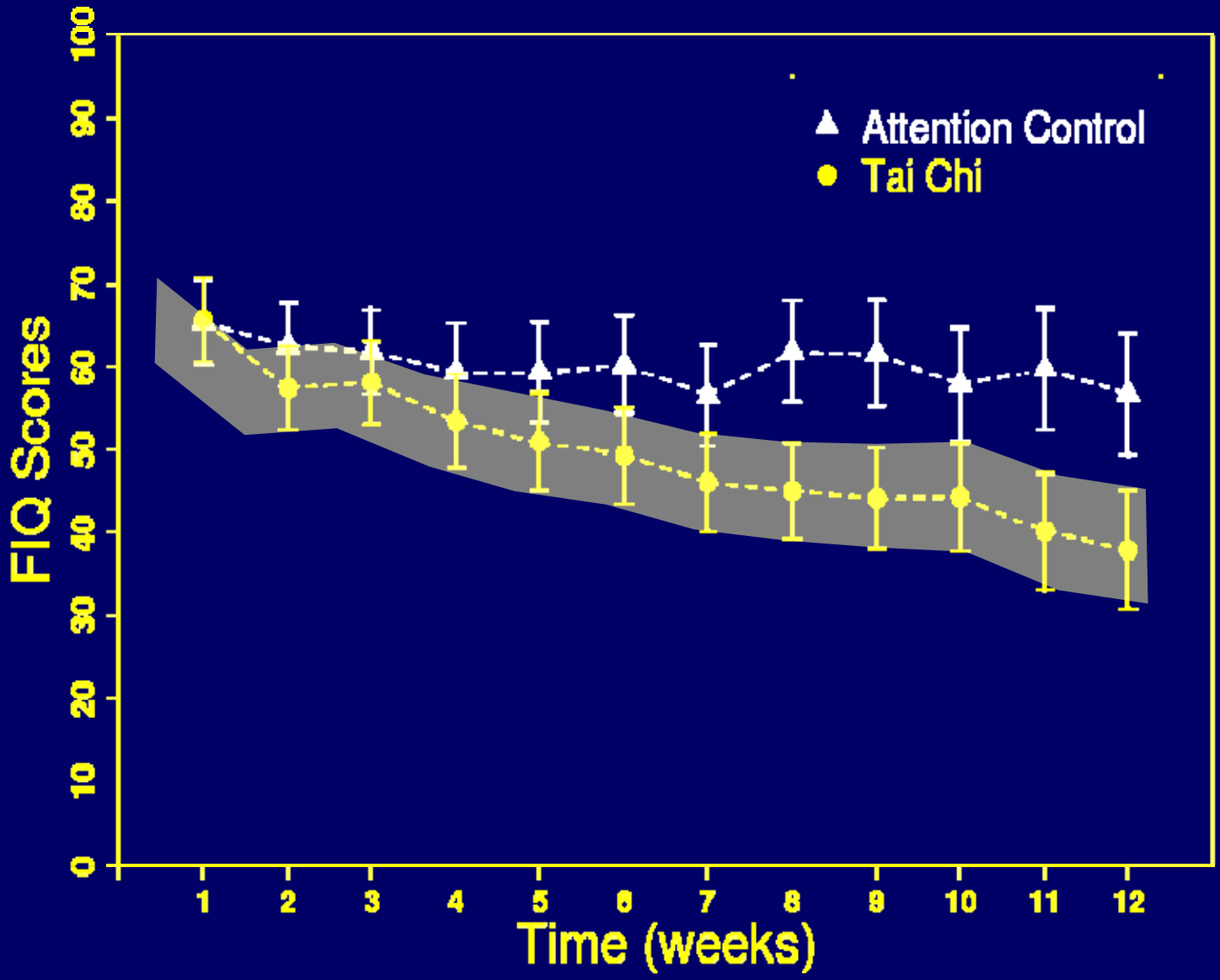
- **92 % of participants completed the study**
- **Attendance:**

  77% (Tai Chi)
  70% (Attention control)

Baseline Characteristics (N=66)

	Tai Chi (n=33)	Control (n=33)
Age (year)	50	51
Female	85%	88%
White	61%	52%
Body Mass Index	34	32
Duration of Pain (yr)	11	10
FIQ, (0-100mm)	63	68
Physician global, (0-10cm)	6	6
Patient global, (0-10cm)	6	6
SF-36, PCS, (0-100)	29	28
Outcome expectation (1-5)	3.7	3.9

Mean weekly Fibromyalgia Impact Questionnaire Scores



Control
-10.2
(-16.6, -3.7)

P = 0.0001

Tai Chi
-28.5
(-34.7, -22.3)

12 Week Changes in Secondary Outcomes

	Tai Chi (n=33)	Control (n=33)	P Value*
Sleep Quality Score (0-21)	3.6	0.7	0.001
Patient Global Assessment Score (0-10 cm)	2.5	0.6	0.002
Physician Global Assessment Score (0-10 cm)	1.0	0.02	0.02
6 Minute Walk Test	60.6	16.3	0.007

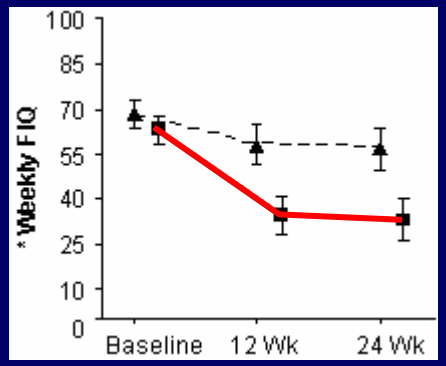
*Adjusted means difference were compared by including interaction of time and group in mixed model

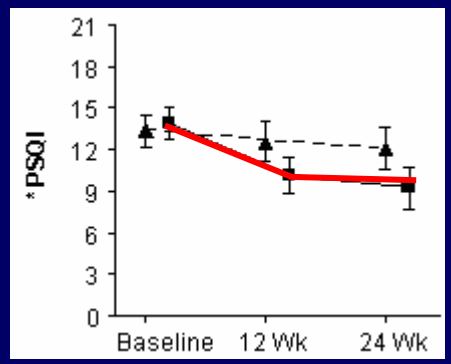
12 Week Changes in Secondary Outcomes

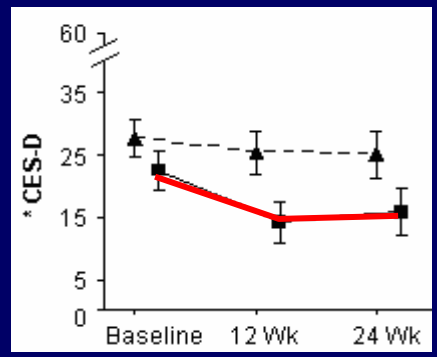
	Tai Chi (n=33)	Control (n=33)	P Value*
SF-36, Physical Component Summary (0-100)	**8.5**	**1.4**	**0.001**
SF-36, Mental Component Summary (0-100)	**7.7**	**1.6**	**0.03**
CES-Depression Score (0-60)	**8.1**	**2.3**	**0.005**
Self-efficacy Score (1-10)	**1.5**	**0.5**	**0.06**

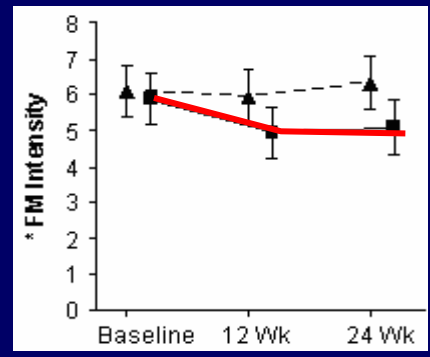
*Adjusted means difference were compared by including interaction of time and group in mixed model

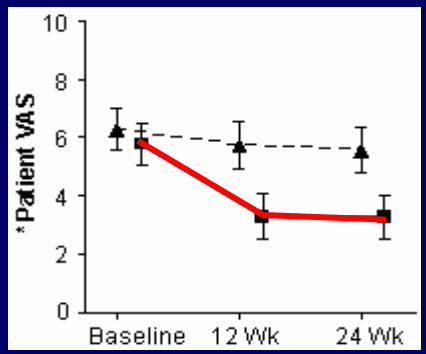
Improvements in Secondary Outcomes

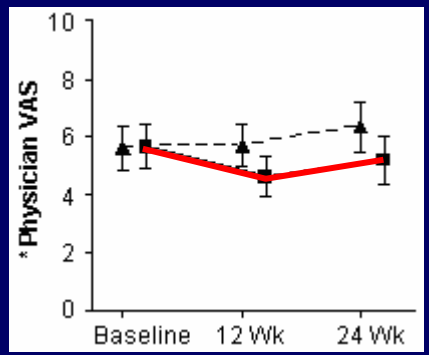


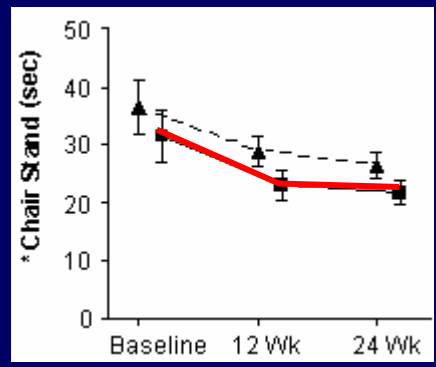


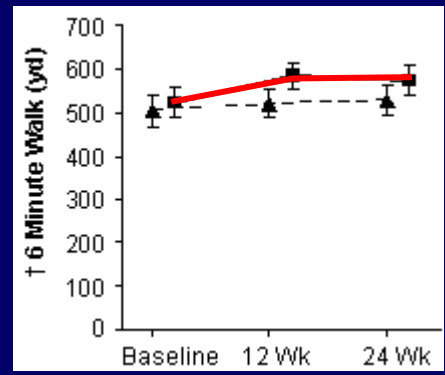


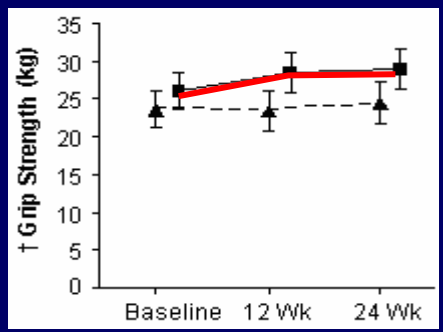


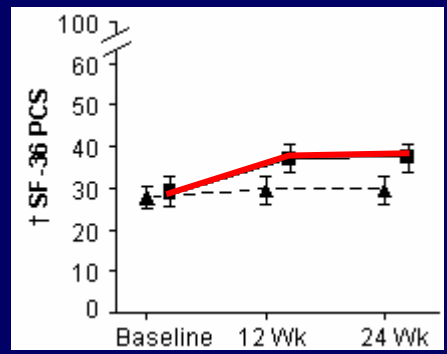


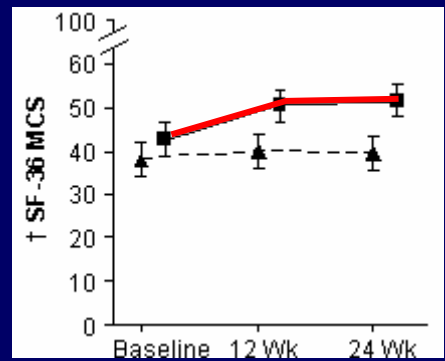


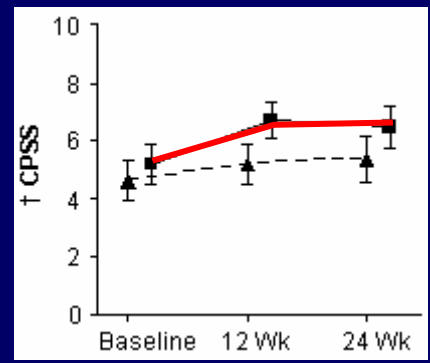












Tai Chi ——— **Control** - - - - - -

*__FIQ__= Fibromyalgia Impact Questionnaire, __PSQI=__ Pittsburgh Sleep Quality Index, __CES-D__= Center for Epidemiology Studies Depression Index, __VAS__= Visual Analogue Scale, SF-36= Short-Form health survey, __PCS__= Physical Component Summary, __MCS__= Mental Component Summary, __CPSS__= Chronic Pain Self-Efficacy Scale.

Medication Use

- More subjects discontinued medication to treat FM in the Tai Chi group than in the control group

[(Tai Chi group 11/31 (35%) vs. controls 4/26 (15%), P=0.09]

Mary (6 months follow up)

- Continues to practice Tai Chi (5 classes/wk, practice at home)
- Pain relief from fibromyalgia related areas
- More flexibility, range of motion, and strength
- Improved energy
- No headaches in last 2 months
- Anxiety is no longer a problem
- Improved and restful sleep (6-7 hours)
- More positive attitude
- Pain medications reduced: Advil (<1/week)

"My PCP at Lahey Clinic for 7+years is so impressed with my improved condition, on all levels, that she asked me to share this Tai Chi experience with her other Fibromyalgia patients. "

Conclusions

Pain Reduction

Quality of Life Improvement

Functional Status Improvement

Self-efficacy Improvement

Sleep Quality Improvement

Depression Reduction

Tai Chi: Clinical Implications

- Safe and enjoyable exercise with high adherence
- Effective for treatment of chronic pain
- Improves physical function, sleep quality, depression, and quality of life in people with chronic pain syndrome
- Qualified instructors with healing experience are essential

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

Kimberly Sullivan, Ph.D.
Maxine Krengel, Ph.D.
June 19, 2012

Collaborators and acknowledgements

- Maxine Krengel, Ph.D. - BUSM
- Ron Killiany, Ph.D. – BUSM
- Timothy Heeren, Ph.D. - BUSPH
- Roberta White, Ph.D. – BUSPH
- DOD Force Health Protections and Readiness office

Funding – DoD Congressionally Directed Medical Research Program

Introduction

Many Gulf War (GW) veterans have reported lasting health symptom complaints since their return from the war in 1991. Reported symptoms include:

- Fatigue
- Memory disturbance
- Concentration difficulties
- Joint and muscle pain
- Sleep disturbance
- Headache
- Respiratory problems
- Gastrointestinal complaints

Introduction- Pesticides

- Acetylcholinesterase inhibitors such as organophosphate (OP) pesticides, anti-nerve gas pills (PB) and nerve agents are known to produce chronic neurological symptoms at sufficient exposures.
- Combinations of exposures to similarly acting pesticides and PB has been suggested as a likely cause of lasting health complaints in GW veterans and some military pest control applicator's exposures likely reached levels of concern for toxicity. Their exposures and unique knowledge of pesticides made them an ideal group to study.

How were pesticides used in Gulf War Theatre?

- Troops used pesticides for personal use on skin and uniforms and as:
  - Insect repellants
  - As area sprays and fogs
  - In pest strips and fly baits
  - As delousing agents for POWs

- Those who applied the pesticides were likely exposed to more pesticide products and at higher doses.
- They were also much more knowledgeable about pesticide types and usages therefore making them an ideally suited group to study.

How many pesticides were in Gulf War Theatre?

- Pesticides were used widely in the Gulf War to protect the troops from pests such as sand flies, mosquitoes and fleas that can carry infectious diseases.
- US forces used pesticides in areas where they worked, slept and ate. In fact, on any given day during their deployment GW veterans could have been exposed to at least 15 pesticide products of concern with 12 different active ingredients.
- A Health Risk Assessment conducted by DOD estimated that 41,000 GW veterans could have been overexposed to pesticides during the war.

Pesticides of Potential Concern

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

*Current use restricted or banned by EPA as part of the Food Quality Protection Act pesticides review.
Source: DOD Environmental Exposure Report - pesticides

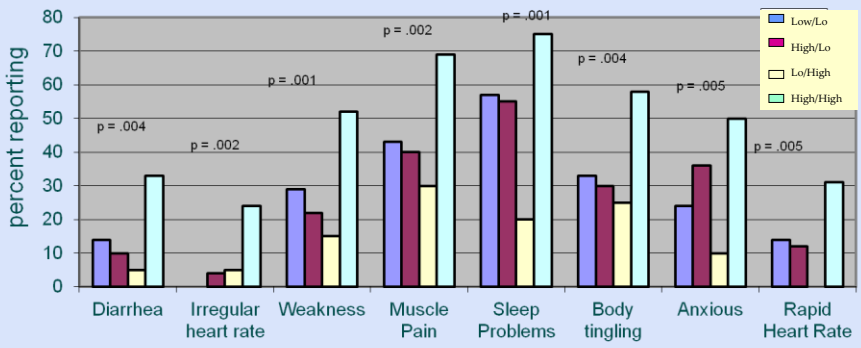
Pesticide Use and Application Overview

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

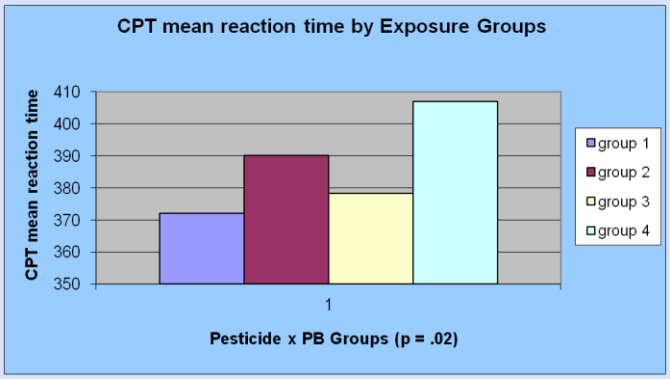
Pesticide Cognition study

- In a prior study, the Pesticide Cognition Study (PCS), a group of 159 pesticide controllers from the GW were assessed for cognitive functioning.
- Those in the high pesticide and high anti-nerve gas (PB) group reported significantly more health symptoms and performed less well on cognitive functioning measures.

Health Symptom Results



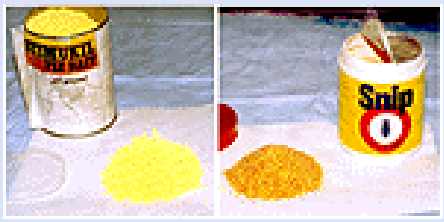
Continuous Performance Test by Pesticide Exposure Groups



Individual comparisons among the groups showed a significant difference between exposure Group 1 (low/low) and Group 4 (high/high) at p=.007.

Pesticide Cognition Study

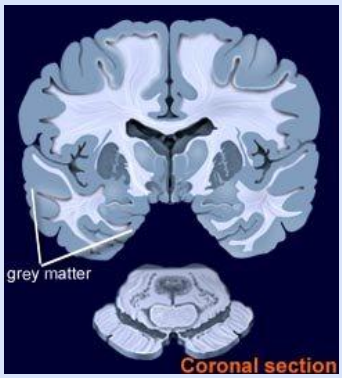
Individual pesticides including pest-strips, delousers, flybait were also found to be independently related to mood and information processing speed.



Pesticide MRI Study

The current study utilized structural MRI and neuropsychological testing to investigate brain-behavior patterns in pest-control personnel from the Gulf War.

These GW veterans had known high or low pesticide exposures based on their military occupational specialty. This sample included physicians, environmental science officers, entomologists, preventive medicine specialists, military police, field sanitation members and other pest controllers.



Hypothesis

- It was hypothesized that the pattern of neuropsychological function between the exposure groups would correlate with structural brain volumes and with reported health symptoms.
- Specifically, it was hypothesized that GW veterans with higher levels and more exposures to pesticides and low level nerve agents would show lower white matter volumes, report more health symptoms, and perform less well on cognitive testing.

Study Participants

- Study participants included a uniquely knowledgeable group of 24 GW veterans drawn from a larger group of 159 pest-control personnel who have been well characterized in terms of demographics and pesticide and PB exposure histories by a previous study.
- Subjects were 87% male with a mean age of 54 years and a mean education of 16 years.

Study Procedures

- Structural brain MRI
- Neuropsychological Assessment
- Health Symptom report

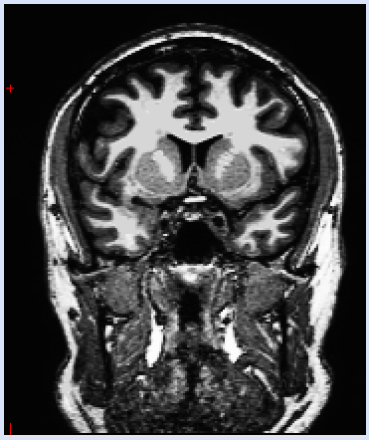
Structural MRI Methods

Neuroimaging

- Each imaging session acquired a MPRAGE sequence which is a T1 weighted image used as a standard for structural brain investigation.
- The MPRAGE acquisition had a FOV of 256 with a matrix of 256, 170 slices with a thickness of 1.2mm, and a TR of 3000ms for each subject.
- Each of the MPRAGE images were post processed using FreeSurfer software.
- Each brain was processed through an automated Talaraich based analysis, with skull removed, then checked for errors of grey and white matter borders, segmented, and statistically corrected for intracranial cavity volume.

MRI Post-Processing Methods

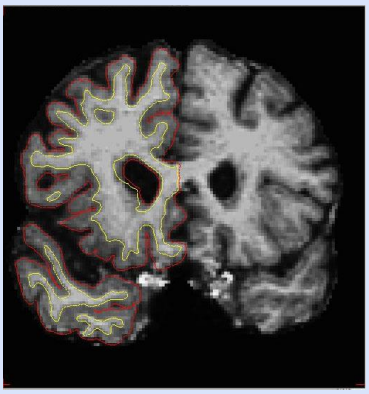
The first step in post-processing involved motion correction, intensity normalization and skull and neck removal so that only the brain remained for further analysis.



MRI Post-Processing Methods

The second step was determining white and gray matter borders using pixel intensity.

The white/gray matter border was then used to provide information for brain segmentation.



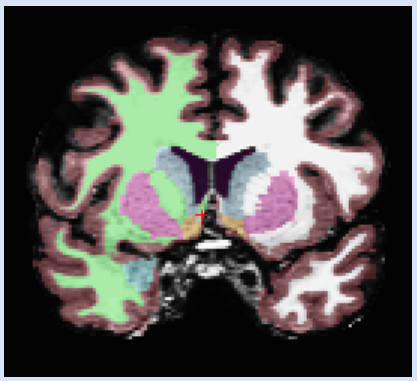
White Matter = yellow border
Gray Matter = red border

MRI Post-Processing Methods

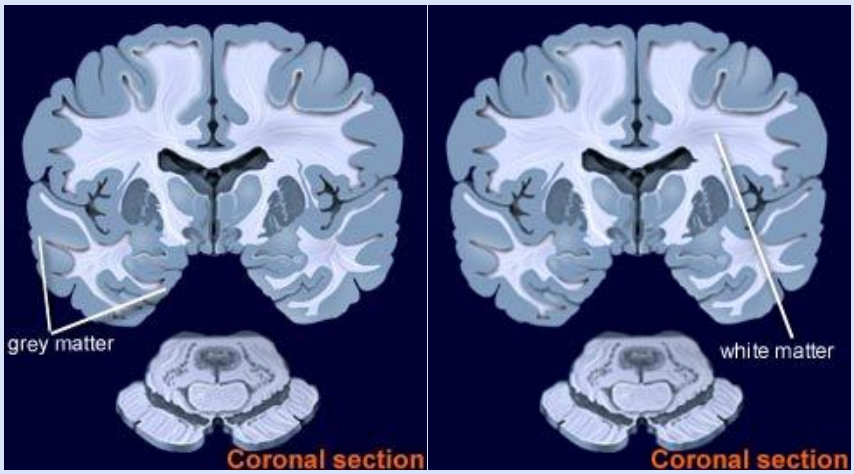
The third step included subcortical segmentation using the FREESURFER program.

This procedure divided the brain into 56 areas per hemisphere including the hippocampus, caudate nucleus and basal ganglia.

FREESURFER was also used to perform cortical parcellation.



Gray and White Matter



Why focus on the White Matter?

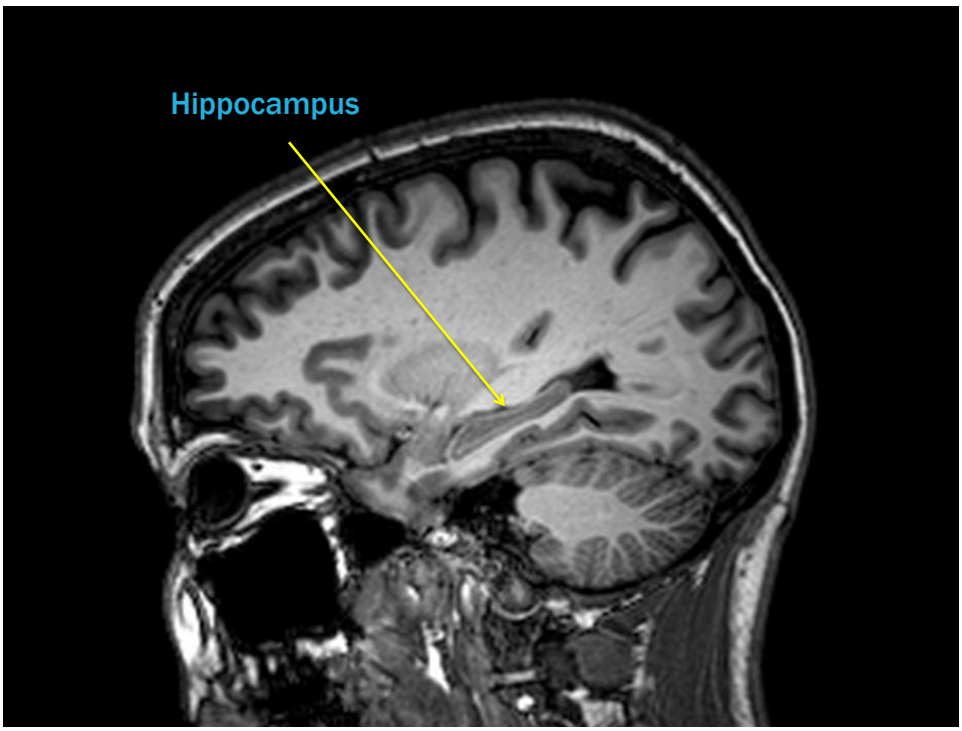
•White matter is highly susceptible to the effects of neurotoxicants.

• GWI symptoms include fatigue, information processing speed and memory retrieval difficulties that are associated with WM disorders.

•Lower white matter volumes were found in two other studies from our group of GW veterans related to exposure to low-level chemical weapons (sarin/cyclosarin) (Heaton et al., 2008) and to higher health symptom report (Powell, 2009; Sullivan, submitted).

Limbic System

- The limbic system is a circuit of highly interconnected midline structures in the brain.
- The major structures in the limbic system are the amygdala, basal forebrain, cingulate gyrus, fornix, hippocampus, mammillary bodies and septum.
- The main functions of the limbic system are to integrate the more primitive survivalistic functions of the brainstem with the higher order cognitive functions of the cerebral cortex.



Neuropsychological Test Methods

Battery of neuropsychological tests included cognitive domains of:

- **Attention/executive** – Continuous Performance Test (CPT), Trail Making Test, COWAT, multiple loops, recurrent series writing.
- **Memory** – Rey-Osterrieth Complex figure Test (ROCFT), California Verbal Learning Test
- **visuospatial** – Hooper Visual Organization Test, Grooved Pegboard, ROCFT copy
- **Motor** – Grip Strength, Finger Tap Test
- **mood** – Profile of Mood States

California Verbal Learning Test

List A Immediate Free-Recall Trials (number correct)	List B Trial	List A Delayed Recall
Trial 1 _____	_____	Short-Delay Free Recall ____
Trial 2 _____		Long-Delay Free Recall ____
Trial 3 _____		Short-Delay Cued Recall ____
Trial 4 _____		Long-Delay Cued Recall ____
Trial 5 _____		Long-Delay Recognition ____

Grooved Pegboard

Data Analysis

- Multivariate analyses of Variance were performed to assess group differences between the high and low exposed groups with respect to brain volumetrics, cognitive test performance and health symptoms.
- Regression and correlation analyses were also performed with continuous variables.

Results – Subject Demographics

- Study participants were 87% male (3 females)
- Mean age for study participants was 54 years.
- Mean education for study participants was 16 years.

Results – White Matter and Health Symptoms

Correlation of White Matter Volume with Health Symptoms in 24 Gulf War Veterans		
	Total white matter volume	p value (2 tailed)
Health symptoms	-.505*	0.012
*Pearson correlation coefficient		

Results: Brain Volumes and Combined Exposures (1)

Brain Volume	Unexposed group mean	Pest-strip x delouser exposed mean	Signif.
WM	34	33	.03
GM	33	27	.008
WM cerebellum	1.9	1.75	.03

Mean white matter, gray matter and cerebellar volumes adjusted for age and presented as percent of intracranial volume.

Results: Brain Volumes and Combined Exposures (2)

Brain Volume	DEET Mean	DEET Signif.	PB Mean	PB Signif.	DEET x PB Mean	DEET x PB Signif.
Right hippocampus	.30	Ns	.31	Ns	.25	.004
Left hippocampus	.30	Ns	.30	Ns	.25	.005
Total hippocampus	.60	ns	.61	Ns	.50	.004

Hippocampal volumes were adjusted for age and presented as percent of intracranial volume.

Results: Cognitive Domains and Combined Exposures (3)

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

Overall Results (1)

- Brain white matter volumes were significantly correlated with total health symptoms reported (p=.01).
- Brain white matter volumes were significantly correlated with attention/executive system domain (p=.001)

Overall Results (2)

- Cerebral and cerebellar white matter and gray matter volumes were significantly lower in veterans over-exposed to pest-strips (dichlorvos) and the delouser (lindane).
- Hippocampal volumes were significantly lower in veterans exposed to DEET and PB. This group also performed significantly worse on visual memory tests.

Structure-function Relationships?

- DEET x PB exposed = lower hippocampal volumes and worse visual memory performance.
- Higher number health symptoms = lower white matter volumes.
- Lower attention/executive system scores = Lower white matter volumes.

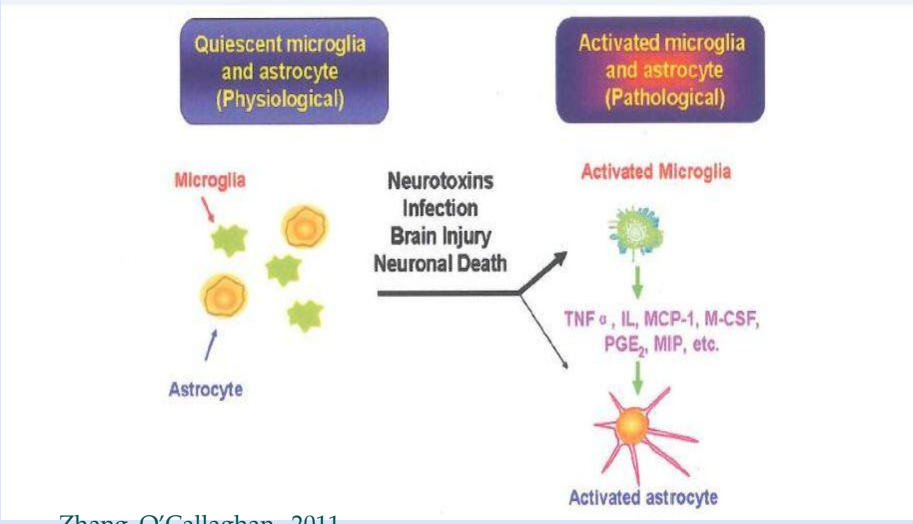
Conclusion

- Although this was a small pilot study and needs to be replicated in a larger study sample, brain-behavior relationships appeared present in this study that correlated with our prior studies (white matter and health symptoms) and with animal models of exposures (hippocampal volumes and DEET x PB interactions).
- These emerging brain-behavior relationships among brain imaging, neuropsychological functioning, health symptoms and environmental exposures suggest biomarkers may be present for GWI that can be targeted for future therapeutics.

Conclusion

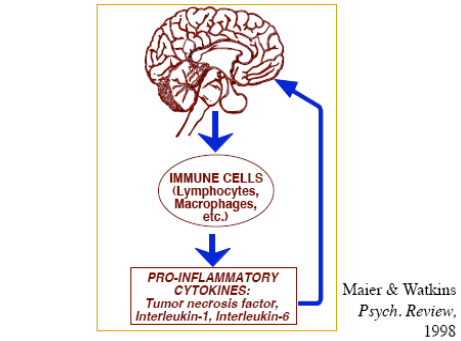
- GW veterans with known pesticide exposures and high numbers of health symptoms showed structural (MRI) differences in lower white matter volumes.
- Correspondingly, glial overactivation (including microglia and astrocytes) has recently been found to be associated with chronic pain syndromes suggesting a potential mechanism for increased health symptom report and altered white matter or glial functioning in exposed groups through chronic neuroinflammation.

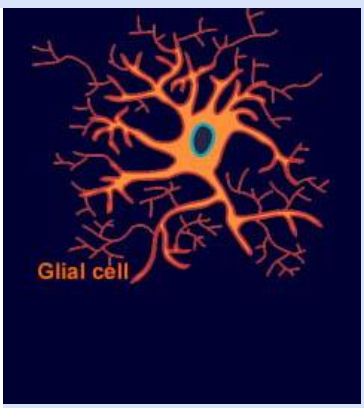
Glial Activation and Priming



Zhang, O'Callaghan , 2011

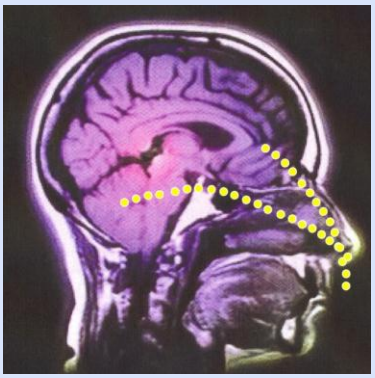
Future Directions –Treatments and Mechanisms





Glial modulators, immune modulators, intranasal insulin and other cognitive enhancers

Treatments – Intranasal Insulin



Insulin - important modulator of brain function.

Brain insulin receptors are located in the hippocampus and frontal cortex. Thought to enhance synapse formation and long-term potentiation (LTP) to improve memory functioning in AD and others (Craft, 2012).

Intranasal insulin also increases levels of neurotransmitters including acetylcholine, dopamine and neuroepinephrine (Figlewicz et al., 1993) and is thought to decrease inflammation by altering proinflammatory cytokines (IL-1, IL-6, TNF) (Fishel et al., 2005).

Intranasal insulin does not alter peripheral glucose levels (Reger et al., 2007; Craft et al., 2009) suggesting that it is safe, can be self-administered and does not change plasma glucose or insulin levels (Benedict et al., 2004).

Thank You

NEW DRAFT

GULF WAR RESEARCH STRATEGIC PLAN

2012-2016

Highlights indicate material that has been edited or added since the January 23, 2012 version

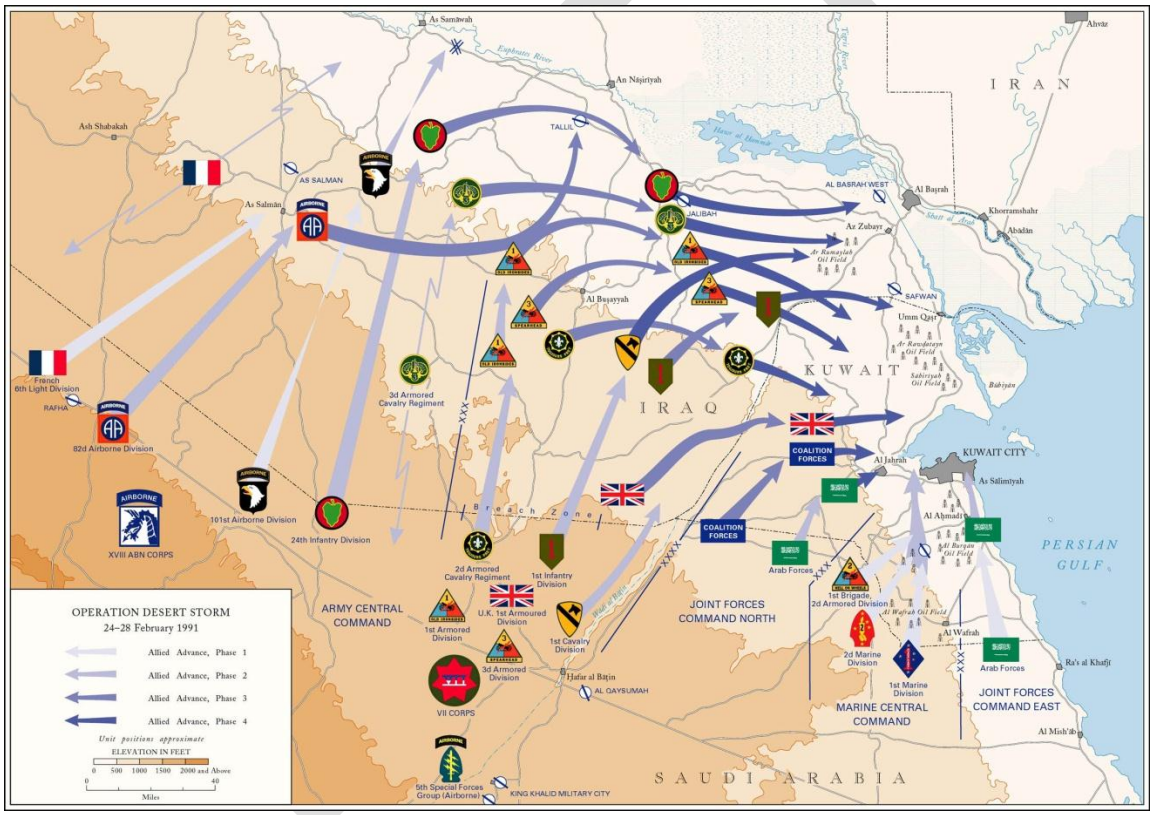


Table of Contents

1.0 EXECUTIVE SUMMARY

After Iraq's occupation of Kuwait in August 1990, the United States deployed military personnel to Southwest Asia in support of Operations Desert Shield and Desert Storm. At the conclusion of the first year of operations on July 31, 1991, the United States had deployed 696,841 military personnel from all five services and National Guard to the Kuwaiti Theater of Operations (KTO).

During and after their return from the KTO, a significant proportion of Gulf War Veterans reported a range of chronic symptoms and health problems at rates that exceeded the rates for non-deployed era Veterans. These symptoms included: persistent headaches, joint and muscle pain, fatigue and sleep disturbances, attention and memory (cognitive) problems, gastrointestinal symptoms, and skin abnormalities. While some of the ill Veterans meet case definition(s) for other chronic multisymptom illnesses such as chronic fatigue syndrome or fibromyalgia, the majority have defied exact diagnosis.

Recent studies by the Department of Veterans Affairs (VA) and others indicate that as many as 250,000 Gulf War veterans are affected. VA, the Department of Defense (DoD), and the Department of Health and Human Services (HHS) have funded more than 390 research projects related to the consequence of military service in the Gulf War. These studies have yielded substantial insight into the health problems of Gulf War Veterans, including physiological differences between Veterans with multisymptom illness and Veterans of the same era who were not deployed. However, neither diagnostic biomarkers nor broadly effective treatments have been identified to date. The VA and CDMRP Gulf War Research programs continue to solicit proposals aimed at identifying new treatments for ill Gulf War Veterans. The health and well-being of Veterans is the main focus of the Gulf War Research Strategic Plan. VA is committed to studying and treating chronic multisymptom illness and any other conditions affecting Gulf War Veterans. No Veteran should feel that his/her particular ailment is less important to VA than any other.

In 2010, an Institute of Medicine (IOM) report, *Gulf War and Health, Vol. 8*, reviewed the literature and accepted that this multisymptom illness is a diagnostic entity, which it found to be associated with Gulf War service [56]. It further found that the symptoms "cannot be ascribed to any known psychological disorder." Rather, "it is likely that Gulf War illness results from an interplay of genetic and environmental factors."

The *Gulf War Research Strategic Plan 2012-2016* is VA's response to the IOM report. **Its overall goals are to:**

- **Improve the health and well-being of Gulf War veterans.**

- **Utilize emerging knowledge to prevent similar war-related illnesses in the future.**

As recommended by the IOM, the Plan has two branches that:

- Monitor the health of Gulf War veterans.
- Identify diagnostic biomarkers and treatments for ill Gulf War Veterans.

Recognizing the need, articulated by the IOM, to accomplish this mission *rapidly*, the Plan establishes a program to identify biomarkers and treatments within the time frame of the Plan -- five years. VA's ability to process RFA's frequently and to establish other research projects through executive action give it the flexibility to move at this accelerated pace. In view of the magnitude of the need and the opportunity for success, VA is committed to the five-year timetable.

The Plan has six major sections:

1.0 Executive Summary

2.0 Introduction and Background

3.0 Evolution of the Gulf War Strategic Plan

4.0 Summary of Gulf War Research Results and Past Federal Research Support

5.0 Gulf War Research Strategic Objectives 2012-2016

6.0 Conclusions

The eight strategic goals that the *Gulf War Research Strategic Plan 2012-2016* advances are presented in detail in Section 5 of the Plan:

5.1. Symptomatic and Specific Treatments

5.2. Databases and Continued Surveillance

5.3. Establish a Case Definition of Chronic Multisymptom Illness

5.4. Genetics/Genomics/Systems Biology

5.5. Biomarkers

5.6. Animal Models

5.7. Coordination and Communication with Federal Partners, Researchers, and

the Private Sector

5.8. Translation of Research into Practice

Since the overall goals of the Strategic Plan are improved health and prevention, the first specific goal presented focuses on symptomatic and specific treatments. The Strategic Plan then presents scientific approaches that are most likely to yield improvements in treatment, health and prevention. These sections are followed by approaches to enhance coordination and communication between partners and researchers. The Strategic Plan then ends with approaches to translate research into practice to yield improved treatments, health and prevention.

Although progress has been made in Gulf War Research, much work remains to be done. This *Gulf War Research Strategic Plan 2012-2016* has been formulated to accelerate this progress. The Plan will be reviewed annually by the Gulf War Steering Committee, the National Research Advisory Council, and the Research Advisory Committee on Gulf War Veterans' Illnesses, and updated as needed.

2.0 INTRODUCTION AND BACKGROUND

2.1 The 1990-1991 Gulf War and the Nation's Response to the Need for Research

After Iraq's occupation of Kuwait in August 1990, the United States deployed military personnel to Southwest Asia in support of Operations Desert Shield and Desert Storm. At the conclusion of the first year of operations on July 31, 1991, the United States had deployed 696,841 military personnel from all five services and National Guard to the Kuwaiti Theater of Operations (KTO).

During and after their return from the KTO, a significant proportion of Gulf War Veterans reported a range of chronic symptoms and health problems at rates that exceeded the rates for non-deployed era Veterans. These symptoms included: persistent headaches, joint and muscle pain, fatigue and sleep disturbances, attention and memory (cognitive) problems, gastrointestinal symptoms, and skin abnormalities. While some of the ill Veterans meet case definition(s) for other chronic multisymptom illnesses such as chronic fatigue syndrome or fibromyalgia, the majority have defied exact diagnosis.

On August 31, 1993, pursuant to Public Law 102-585, President Clinton named the Secretary of Veterans Affairs to coordinate research on the health consequences of service in the Gulf War. VA initially carried out its coordinating role through the auspices of the Persian Gulf Interagency Research Coordinating Council (PGIRCC). On January 21, 1994, the Secretaries of Defense, Health and Human Services, and VA announced the establishment of the Persian Gulf Veterans Coordinating Board (PGVCB) to coordinate efforts to resolve the health concerns of Gulf War Veterans. PGVCB developed three mission objectives, and assigned each to a separate working group: the Clinical Working Group, the Research Working Group, and the Disability and Benefits Working Group. The Research Working Group (RWG) subsumed PGIRCC responsibilities.

In 1995, the PGVCB developed a contextual framework for evaluating research related to military service in the 1990-1991 Gulf War [83]. To that end, the PGVCB identified 19 major epidemiological research questions and subsequently added two additional questions in 1996 [84]. This framework was published as the "Working Plan for Research on Persian Gulf War Veterans' Illnesses" and has served as the guiding principles for Gulf War Research up to the present day. To date, VA, the Department of Defense (DoD), and the Department of Health and Human Services (HHS) have funded 390 research projects pertaining to the health consequences of military service in the 1990-1991 Gulf War, as reported annually to Congress.

These studies have yielded substantial insight into the health problems of Gulf War veterans, including physiological differences between veterans with multisymptom illness and veterans of the same era who were not deployed. However, neither diagnostic biomarkers nor effective treatments have been identified. Studies by the Department of Veterans Affairs (VA) and others indicate that as many as 250,000 Gulf War veterans are affected.

In 2010, an Institute of Medicine (IOM) report, Gulf War and Health, Vol. 8, reviewed this literature and accepted that this multisymptom illness is a diagnostic entity, which it found to be associated with Gulf War service[56]. It further found that the symptoms "cannot be ascribed to any known psychological disorder." Rather, "it is likely that Gulf War illness results from an interplay of genetic and environmental factors."

2.2 Gulf War Research Strategic Plan 2012-2016

The *Gulf War Research Strategic Plan 2012-2016* is the most recent and substantial revision of the original "Working Plan" put forth in 1995-96 [83, 84]. It is VA's response to the need and opportunity identified by the 2010 IOM report.

In the process of developing the Gulf War Research Strategic Plan, ORD has utilized two federal advisory committees, the Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) and the National Research Advisory Council (NRAC), as well as ORD's Gulf War Steering Committee (GWSC). An outline of a draft strategic plan was discussed at the GWSC meeting in April, 2011. In June, 2011, a draft prepared by ORD was presented to the RACGWVI by the chairman of the GWSC. Based on the ensuing discussion, the GWSC chairman suggested the formation of ten working groups to recommend modifications and improvements to the draft plan.

The working groups generally consisted of six or more individuals who were either RACGWVI members, NRAC members, GWSC members, VA employees, or scientists/physicians recommended by RACGWVI or VA. More than 45 individuals participated, and nine of the working groups held meetings between September and November, 2011. These groups were responsible for reviewing the sections of the draft strategic plan which dealt with introductory and background material, symptomatic and specific treatments, databases and surveillance, case definitions, genetics and genomics, biomarkers, animal models, coordination among stakeholders, and translation of research into practice.

The recommendations of these groups were submitted for consideration at a GWSC meeting in December, 2011. The GWSC provided guidance to the final working group whose task it was to combine the recommendations of the other nine working groups.

This group held meetings in December, 2011, and January, 2102, in preparation for the upcoming RACGWVI meeting.

In late January, 2012, at a meeting of the RACGWVI, which was also attended by some members of the NRAC and GWSC, the revised draft Gulf War Research Strategic Plan was discussed at length. After the meeting, additional revisions were made based on the recommendations of the RACGWVI and the mission of VA, and the newly revised Gulf War Research Strategic Plan was presented to the entire NRAC at their meeting in late February, 2012. With NRAC recommendations, the draft Gulf War Research Strategic Plan was ready for final review by the RACGWVI and NRAC at their respective meetings in June, 2012.

The *Gulf War Research Strategic Plan 2012-2016* will be reviewed annually by the Gulf War Steering Committee, the National Research Advisory Council, and the Research Advisory Committee on Gulf War Veterans' Illnesses to recommend modifications as needed.

2.3 VA Research and Development Strategic Plan: 2009-2014

The *VA Research and Development Strategic Plan: 2009-2014* is the strategic plan for all research in the VA Office of Research and Development (ORD) [80]. It sets four over-arching goals that apply to all VA Research, including Gulf War Research. These are:

- Advance knowledge toward improving each Veteran's health and well-being, relying on a spectrum of research including basic, translational, clinical, health services, and rehabilitative science.
- Apply advances in scientific knowledge to create, test, compare, and implement new treatments, technologies, education modules, and models of care so that Veterans receive the most effective individualized care solutions.
- Attract, train, and retain the highest-caliber investigators and staff, and nurture their continuous development as leaders in their fields.
- Assure a state-of-the-art research enterprise with a culture of professionalism, collaboration, accountability and the highest regard for research volunteers' safety and privacy.

The *Gulf War Research Strategic Plan 2012-2016* complements the existing *VA Research and Development Strategic Plan: 2009-2014*. This larger strategic plan also articulates the need for continuing targeted Gulf War Research. For example, the "Deployment-related exposure to hazardous environmental agents" is listed as one of the 10 priority areas for VA's ORD.

3.0 EVOLUTION OF THE GULF WAR RESEARCH STRATEGIC PLAN

During deployment to the Gulf, and as Service members began returning from the Gulf, it became apparent that some Service members and Veterans were showing symptoms that were difficult to explain using current diagnostic criteria for illnesses. In January 1994, the Secretaries of DoD, HHS and VA announced the establishment of the Persian Gulf Veterans Coordinating Board (PGVCB) to coordinate efforts to resolve the health concerns of Gulf War Veterans.

A critical unresolved issue was whether deployed Service members were experiencing these symptoms at a higher rate than comparable non-Gulf War Service members and Veterans. In addition, many Service members and Veterans were questioning whether the illnesses that are common and diagnosable were etiologically linked to their service in the Gulf War. It became apparent to both DoD and VA that scientific and medical research would be required to address this complex issue. The question then had to be answered: "What research needs to be undertaken?" [83, 84]. The PGVCB established three primary mission objectives to achieve through interagency coordination:

- Ensure all Veterans receive the complete range of healthcare services necessary to evaluate and treat Gulf War-related health problems.
- Develop a research program that produces a complete and accurate understanding of Gulf War-related health problems.
- Develop clear, consistent guidelines for evaluating disabilities related to Persian Gulf service.

Three broad research goals were presented in the original 1995-6 Working Plan:

- Establish the nature and prevalence of symptoms, diagnosable illnesses, and unexplained conditions among Persian Gulf Veterans in comparison to appropriate control groups.
- Identify the possible risk factors for any illnesses, beyond those expected to occur, among Persian Gulf Veterans.
- Identify appropriate diagnostic tools, treatment methods, and prevention strategies for any excess illness conditions found among Persian Gulf Veterans.

The plan also identified a number of areas for which significant gaps in knowledge existed at that time:

- Information on the prevalence of symptoms, illnesses, and/or diseases within other coalition forces.

- Information on the prevalence of symptoms, illnesses, and/or diseases within indigenous populations within the Persian Gulf area including Saudi Arabia and Kuwait.
- Information on the prevalence of adverse reproductive outcomes among Persian Gulf Veterans and their spouses.
- Simple and sensitive tests for *Leishmania tropica* infection that could lead to quantification of the prevalence of *L. tropica* infection among Persian Gulf Veterans.
- Information on the long-term, cause-specific mortality among Persian Gulf Veterans.

In the revised 1996 Working Plan, 21 epidemiological research questions were formulated [84]. These research questions have served as the guiding principles for federally-funded Gulf War Research up to the present day. The strategic elements described below in Section 5.0 have been formulated to accelerate progress in improving the health and well-being of Gulf War Veterans.

4.0 SUMMARY OF GULF WAR RESEARCH RESULTS AND PAST FEDERAL RESEARCH SUPPORT

The most recent evaluation of the results of Gulf War Research was published in the 2010 IOM report entitled *Gulf War and Health: Volume 8: Update of Health Effects of Serving in the Gulf War* [56]. The IOM is generally regarded as the "Gold Standard" with respect to evaluating the results of research programs that are published in the peer-reviewed literature, including publications resulting from federally-funded research programs across agencies. The VA first contracted with the IOM to review Gulf War research and produce such reports in 2000 [48-61].

These IOM assessments are used by the VA and other federal agencies to help determine and reassess the extent to which the collective findings of completed Gulf War Illnesses research projects have in fact addressed key Gulf War Research questions, and whether research questions being investigated remain relevant. The IOM report of 2010 is an independent, thorough and comprehensive analysis of past Gulf War Research results across the VA and all federal agencies [56].

In addition, the most recent report of the Research Advisory Committee for Gulf War Veterans' Illnesses (RACGWVI), *Gulf War Illness and the Health of Gulf War Veterans* was also comprehensive and provided specific research recommendations [91].

By carefully comparing the RACGWVI and IOM reports, as well as other information [62, 88, 94, 98], the present *Gulf War Research Strategic Plan 2012-2016* identifies the areas of research that appear most likely to succeed in providing new information that will help Gulf War Veterans.

For the findings that have emerged from past research, readers are referred to these reports. The findings most relevant to future research are summarized in Section 5 below. Additional information is available in the Annual Reports to Congress on Federally Funded Research on Gulf War Veterans' Illnesses prepared by the interagency Deployment Health Working Group [18-25, 75, 76, 85-87].

4.1 Summary of Federal Funding of Gulf War Research 1994-2011

Fiscal Year	VA*	UTSW Contract**	DoD*	HHS*	FY Total
1994	$ 1,157,879	$ 0	$ 6,492,882	$ 0	$ 7,650,761
1995	$ 2,334,083	$ 0	$ 10,973,000	$ 2,514,762	$ 15,821,845
1996	$ 3,853,095	$ 0	$ 11,905,214	$ 1,616,755	$ 17,375,064
1997	$ 2,834,790	$ 0	$ 28,880,536	$ 0	$ 31,715,326
1998	$ 4,722,820	$ 0	$ 13,213,232	$ 1,634,347	$ 19,570,399
1999	$ 9,006,155	$ 0	$ 22,674,338	$ 1,640,378	$ 33,320,871
2000	$ 12,020,519	$ 0	$ 23,847,679	$ 1,567,439	$ 37,435,637
2001	$ 8,576,675	$ 0	$ 31,587,006	$ 998,870	$ 41,162,551
2002	$ 4,512,676	$ 0	$ 18,827,819	$ 799,814	$ 24,140,309
2003	$ 5,746,467	$ 0	$ 16,419,497	$ 964,105	$ 23,130,069
2004	$ 7,644,560	$ 0	$ 11,096,063	$ 466,126	$ 19,206,749
2005	$ 9,484,679	$ 0	$ 10,091,848	$ 466,481	$ 20,043,008
2006	$ 13,013,552	$ 0	$ 10,128,261	$ 455,587	$ 23,597,400
2007	$ 7,059,061	$ 15,000,000	$ 3,417,570	$ 441,974	$ 25,918,605
2008	$ 6,934,214	$ 15,000,000	$ 11,672,967	$ 433,467	$ 34,040,648
2009	$ 9,628,318	$ 6,972,481	$ 10,380,423	$ 0	$ 26,981,222
2010	$ 11,567,997	$ 2,288,755	$ 10,223,231	$ 0	$ 24,079,983
2011§	$ 5,591,875	$ 34,720	$ 3,145,000	$ 0	$ 8,771,595
Total 1994-2011	$ 125,689,415	$ 39,295,956	$ 254,976,566	$ 14,000,105	$ 433,962,042

* Funds expended to support Gulf War research projects
** Funds obligated for reimbursement to UTSW at completion of contracted work on individual task orders
§ Current estimate of VA, DoD, and HHS funds allocated for GW research in FY2011. DoD estimate does not include CDMRP funds.

The VA estimate for FY2010 includes 40% of MRI imaging equipment upgrade at San Francisco for Gulf War research.

This estimate does not include expenditures from the VA Medical Care appropriation of $3.7 million for the Veterans Equitable Resource Allocation (VERA) System to support funded Gulf War research projects. Historically, these costs have not been included in the FY expenditures reported above.

5.0 GULF WAR RESEARCH STRATEGIC OBJECTIVES 2012-2016

5.1 Symptomatic and Specific Treatments

5.1.1 Goal

To develop symptomatic and specific treatments for ill Gulf War Veterans. The most urgently needed Gulf War research studies are those that advance identification of effective treatments that can substantially improve veterans' health and quality of life, and this is the focus of the Gulf War research portfolio. To address this important objective, both DoD and VA have funded a growing number of treatment-related studies in recent years. These include clinical studies to evaluate treatments for chronic multisymptom illness in affected veterans, as well as preclinical studies to evaluate treatments to improve neurobiological parameters. Even if the molecular mechanisms behind Gulf War Illnesses are not fully understood, it is possible to study and develop treatments that may improve a Veteran's medical condition. As the molecular mechanisms which may explain the causal relationship of toxic insults and observed symptoms are continuing to be discovered – using information revealed in genetic/genomic, biomarker and model organism research – systematic approaches to the development of specific or causative treatments for GWVI will be pursued. This will initially involve mechanistic proof-of-concept studies in both animals and humans and can be scaled up to larger programs using the cooperative studies clinical trials resources of the VA.

5.1.2 IOM Recommendations

The IOM noted that: "There is a dearth of organized clinical trials to examine potential treatments for the observed symptoms experienced by Gulf War Veterans. Aligned with the effort to improve care pathways for Gulf War illness sufferers, there should be a focused effort to consider the development of clinical trials informed by the best biological data related to the cause of Gulf War illness." [53].

Also in the IOM report briefing for the April 2010 report, it was recommended that there was a need to, "Expand the number of clinical trials to examine potential treatments for symptoms of Gulf War veterans and improve care pathways for Gulf War illness sufferers." [56].

5.1.3 RACGWVI Recommendations

"Gulf War illness is a serious condition that affects at least one fourth of the 697,000 U.S. Veterans who served in the 1990-1991 Gulf War. This complex of multiple concurrent symptoms typically includes persistent memory and concentration problems, chronic headaches, widespread pain, gastrointestinal problems, and other chronic abnormalities not explained by well-established diagnoses. No effective treatments have been identified for Gulf War illness and studies indicate that few Veterans have recovered over time." [91].
The 2008 RAC Report (Chapter 5, Research Priorities and Recommendations) states that "the highest priority should be given to research conducted to identify beneficial treatments for Gulf War Illness. The primary objective is the conduct of well-designed clinical trials of treatment that hold promise for providing substantial benefit for veterans with Gulf War illness or identifiable subgroups." [91].

Specific RAC recommendations stated that this research should include:

- Studies that identify and systematically evaluate the effectiveness of currently available treatments used for Gulf War illness or conditions with similarities to Gulf War illness. Preliminary research should include pilot studies and/or observational studies capable of identifying promising treatments suitable for evaluation in larger clinical trials.
- Research to identify specific pathophysiological mechanisms underlying Gulf War Illness that are potentially amenable to treatment interventions.
- Research to evaluate novel therapies based on scientific findings as they emerge.

5.1.4 ORD Research

Examples of past ORD research in this area are given below.

As part of an ORD-funded Career Development Award, a pilot clinical trial was conducted to determine whether nasal continuous positive airway pressure (CPAP) alleviates the symptoms of veterans with Gulf War illnesses and sleep disordered breathing (SDB). Compared to the nine sham nasal CPAP recipients, the eight participants receiving therapeutic nasal CPAP experienced significant improvements in pain (34%), fatigue (38%), cognitive function (33%), sleep quality (41%), physical health (34%), and mental health (16%) [2].

In a study of potential new treatments for IBS, the expression of glutamine synthetase and its complementary miRNA in blood microvesicles and gut tissues of IBS patients were studied. Data from 19 diarrhea-predominant IBS subjects and 10 controls supported the conclusion that GLUL regulates intestinal membrane permeability and

miR-29a regulates both GLUL and intestinal membrane permeability. Targeting this signaling pathway could lead to a new therapeutic approach to the treatment of patients with IBS, especially because small molecules that mimic or inhibit miRNA-based mechanisms are readily available [117].

A randomized controlled multi-site clinical trial was developed through the Cooperative Studies Program to compare the effectiveness of cognitive behavioral therapy (CBT), exercise and the combination of both for improving physical functioning and reducing the symptoms of Gulf War Veterans Illnesses (GWVI). The results suggested that CBT and/or exercise can provide modest relief for some of the symptoms of chronic multisymptom illnesses such as GWVI [26].

The state of the cardiopulmonary system is important for planning treatments that involve exercise. A study of metabolic responses to maximal exercise in Gulf War Veterans with chronic fatigue syndrome (CFS) was compared with a control group who did not have CFS. Compared with healthy controls, Veterans who report multiple medically unexplained symptoms and meet criteria for CFS do not show a decreased exercise capacity. Thus, it does not appear that the pathology of the GWVs with CFS includes a deficiency with mobilizing the cardiopulmonary system for strenuous physical effort [77].

5.1.5 Research Plans and Funding Mechanisms

VA has an established research infrastructure to support research projects of various sizes and complexity. Current pilot studies will be evaluated for expansion to larger trials. VA Researchers will investigate new treatments including:

- A goal to expand the number of treatment trials within the 5-year strategic planning period will be established in order to increase the chance of obtaining more viable and effective treatments for GWVI. The goal is dependent on successful identification of potential treatment targets and completion of preclinical development. A more focused effort to identify mechanistic-based treatments for GWVI will be a priority. Examples of studies targeted to reported biomarkers of GWVI will include but not be limited to treatments to regulate neuroendocrine function, coagulation, immune and inflammatory alterations, and neuropsychological and neuroimaging differences reported in ill GW Veterans. Detailed studies of the gastrointestinal microbiome in Gulf War Veterans and controls could be performed and may lead to probiotic or antibiotic treatments. Specific therapies from this research could include antioxidants, anticoagulants,

immune modulators, IL1 antagonists, and other inflammatory modulators, neuroendocrine modulators, intranasal insulin and other cognitive enhancers.

- Expand the number of "small projects" (pilot trials) in the area of new treatments that could lead to larger studies (individual pilot projects, single-site pilot clinical trials).

- Establish a virtual Gulf War Treatment Research Coordinating Activity to identify potential pilot study hypotheses and track their results as appropriate.

- In order to identify at-risk Veterans who could benefit from enhanced preventive medical care including obesity prevention, smoking cessation, and other programs, ORD will work with the Office of Health Information to develop a mechanism to identify GWVs in the computerized patient record system. This could assist primary care and specialty providers in their attempts to provide optimal care.

- More complementary and alternative or integrative medicine therapies should also be studied for GWVI. Such treatments could include mindfulness based therapies as well as acupuncture, laser acupuncture, Tai-Chi, Qi gong, meditation, nutritional therapies, and probiotics.

- Cognitive rehabilitation therapy should be studied for the management of cognitive difficulties associated with GWVI.

- Explicit criteria (case definition) for chronic multisymptom illness will be adopted and used as uniformly as practical in clinical research on proposed therapies.

The VA funding mechanisms for Symptomatic and Specific Treatments will initially be through RFAs, then followed by CSP development of multisite trials as warranted by preliminary data and as funding allows.

5.2 Databases and Continued Surveillance

5.2.1 Goal

To enhance ongoing surveillance efforts of Gulf War and Gulf War Era Veterans, to improve the usefulness of existing databases, and to develop new databases to address specific research questions. Although the 1990-1991 Gulf War was brief, a substantial proportion of Veterans who served in that conflict have reported difficult-to-diagnose health problems since their return from that theater. In addition to considering the chronic undiagnosed symptoms associated with Gulf War service, research studies have provided preliminary indications that a number of diagnosed medical conditions may affect 1991 Gulf War Veterans at excess rates. In the years since the Gulf War, federal committees and scientific advisory panels have regularly identified the importance of coordinating federal data-collection efforts and resources to provide a clearer picture of the health status of 1991 Gulf War Veterans. In particular, these panels have pointed to the importance of monitoring the health of Gulf War Veterans over time to identify the occurrence and prognoses of undiagnosed and diagnosed health conditions affecting this population.

Literature reviews conducted by the Institute of Medicine (IOM), however, continue to indicate there is insufficient information to determine whether or not Gulf War Veterans have been affected by diagnosed medical conditions at excess rates. In addition, studies in recent years have increasingly identified differences in the health and mortality experience of Gulf War personnel who served in different locations and/or had different experiences and exposures during deployment. Findings of this nature highlight the importance of assessing Gulf War data and monitoring health outcomes in identifiable Gulf War Veteran subgroups, including women who served in this deployment. Overall, important questions remain concerning the impact of the 1990-1991 Gulf War on the health and lives of the Veterans who served there.

Currently, multiple large population-based databases, an extensive number of administrative datasets, and a large number of smaller databases provide important information on the health of Gulf War Veterans. However, existing databases are usually stand-alone with limited ability to link to other databases and to other information on Gulf War Veterans. Establishing linkages across databases will facilitate improved understanding of the health status of Gulf War Veterans. Existing databases should be combined with newly-developed databases as necessary to address specific projects when it is clear that doing so will address a specific problem. This will require breaking down institutional barriers within VA and between VA, the Department of Defense, and academic research centers. Human subject protections will also need to be addressed since informed consent forms signed by Veterans for previous research projects likely

did not address the potential to link their data to other data sources. In addition, it would be useful to have a data warehouse to serve as a repository for these data as well as an access point for researchers seeking to use data to address research questions on the health of Gulf War Veterans. This warehouse could include the protocols under which the data were collected and information on the structure and content of each database to facilitate usage of these data.

Although some existing databases are longitudinal in nature, most were not conceived to address surveillance of the health of Gulf War Veterans over time. Increased and improved surveillance efforts are essential to understanding the long-term health consequences of having served in the Gulf War.

Two previous studies collected data on treatments used for Gulf War Veterans with multisymptom illness to determine which of these treatments may be effective. The continuing paucity of effective treatments for Veterans suffering from chronic multisymptom illness needs to be addressed. Improved data linkages and surveillance techniques—coupled with emerging data-discovery methods to identify patterns in unstructured data, such as the electronic medical record—will enhance the ability to identify potentially effective treatments, move them into controlled trials to validate their effectiveness, and institute treatment programs using those treatments found to be effective.

Some population-based research related to Gulf War Veterans has been limited by relatively low participation rates. In addition, studies of Gulf War Veterans who receive VA healthcare services do not take into account the health concerns of Veterans who do not seek VA healthcare services. Other data-collection approaches and database designs—such as disease case registries and a twin registry—may offer advantages over population-based studies in addressing other sections of this strategic plan.

In that regard, twin studies can enable investigators to answer questions about combat-related illness and injury, health outcomes, aging and other issues that are not easily answered with other designs. The classical twin method, which capitalizes on the fact that monozygotic (MZ) twins share 100 percent of their genes and dizygotic (DZ) twins share on average 50 percent of their genes, enables investigators to examine the genetic and shared environmental contributions to any characteristic or health condition, such as those related to Gulf War exposure.

Alternatively, the co-twin control design with MZ twins who are discordant for the characteristic of interest is ideal for assessing long-term effects of conditions such as chronic multisymptom illness that may be linked to environmental exposures. The co-twin control design can be especially powerful if the twin pairs are examined

longitudinally to distinguish emerging health conditions related to Gulf War service from general health conditions that arise in a population as it ages.

In addition to the efforts already described, a repository of research results should be developed to keep stakeholders and researchers informed of emerging results. A group also should be formed to regularly review this repository to identify promising directions where additional research should be directed and where treatments indicate potential benefit.

Based on this background and review of previous recommendations and research, the following goals and objectives are put forward and discussed in detail later in this section:

- Promote ongoing surveillance efforts of Gulf War and Gulf War Era Veterans.
- Work to improve the usefulness of existing databases by linking them and then integrating them into a data warehouse and making them available for use by researchers.
- Develop new databases optimized to address specific research questions.

These objectives are intended to support the other initiatives in the strategic plan, specifically: assessment of specific treatments; ongoing detection of increased incidence and prevalence of health conditions; and improved case definitions, genetics/genomics, and biomarkers.

5.2.2 IOM Recommendations

In its 2010 report, *Update of Health Effects of Serving in the Gulf War*, the Institute of Medicine (IOM) noted that the path forward for research should include continued health surveillance of Gulf War Veterans over time. The IOM panel recommended longitudinal evaluation of mortality, cancer, psychiatric outcomes and neurologic disorders in deployed and non-deployed Gulf War Era Veterans including, in particular, both amyotrophic lateral sclerosis and multiple sclerosis. Veterans should also be followed over time to assess rates of diseases of aging, such as cardiovascular and neurodegenerative diseases [56].

5.2.3 RACGWVI Recommendations

In its 2004 report, the RAC concluded "the health of Gulf War Veterans must be carefully monitored to determine if Gulf War service is associated with excess rates of specific diseases, disease-specific deaths or overall mortality." The report provided specific recommendations concerning the use of existing databases and development of population-based research to determine disease rates in Gulf War Veterans overall and in relation to specific deployment exposures [90, pp 72-76].

The 2004 report also reported that "progress in understanding Gulf War Veterans' illnesses has been hindered by lack of coordination and availability of data resources maintained by the Department of Defense and the Department of Veterans Affairs." To address this problem, the committee recommended that VA and DoD link Gulf War-associated databases, develop a comprehensive library for these data and make federal data resources available to researchers, while adopting appropriate safeguards for their use [90, pp 84-86].

The RAC added to these recommendations in 2008, calling for epidemiologic research to determine whether Gulf War Veterans, or identifiable subgroups, have excess rates of specific neurological disorders. The report also called for enhanced efforts to determine rates of cancers, respiratory diseases and cause-specific mortality in Gulf War Veterans overall and in Veteran subgroups of interest [91, pp 313-314].

The RAC later provided specific recommendations aimed at enhancing the capacity of VA Office of Public Health's Longitudinal Survey of Gulf War Era Veterans to provide surveillance of diagnosed and undiagnosed conditions affecting Gulf War Veterans [92, http://www.va.gov/RAC-GWVI/docs/Committee_Documents/RACSurveyRecs_Final110210.pdf)].

5.2.4 Existing Databases

5.2.4.1 Existing large population-based datasets from federally sponsored research studies of 1991 Gulf War Era Veterans

- Datasets assembled for VA mortality studies of Gulf War Era Veterans (n = ~ 1.5 million Gulf War Era Veterans).
- 1995 National Survey of Gulf War Era Veterans and Their Families (n=30,000 Veterans) (Phases I, II and III) and the 2005 follow-up Longitudinal Health Study of Persian Gulf War Era Veterans and Their Families by the VA Office of Public Health. (Another OPH follow-up study will begin in 2012.).
- Department of Defense study of Navy Seabees (n=12,000).

- Department of Defense-sponsored study of U.K. Gulf War and Bosnia Era Veterans (n=8,000).
- Centers for Disease Control study of Air Force Gulf War Era Veterans (n=4,000).
- CDC and VA study of Iowa Gulf War Era Veterans (n=3,800).
- VA-contracted Military Health Study (n=8,000).
- VA-Portland survey of Gulf War Era Veterans in Pacific Northwest (n= ~1,000).
- VA-Portland Survey of Gulf War Era Veterans in five states (n=1,800).
- Study of Gulf War Veterans returning through Fort Devens, MA (n=3,000).
- VA/CDC datasets on cancers in Gulf War Era Veterans, assembled from multiple large state tumor registries [65, 68, 114].
- Multiple large Department of Defense datasets assembled to assess birth-defect rates and pregnancy outcomes in Gulf War Era Veterans [3, 4, 5, 15, 63, 93, 108, 109].
- Multiple large datasets from Department of Defense-sponsored studies of hospitalization rates in Gulf War Veterans [7, 8, 32, 43, 44, 97].
- Department of Defense's Millennium Cohort Study (original sample > 100,000 Veterans, including at least 9,200 1991 Gulf War Era Veterans).

5.2.4.2 U.S. Federal Gulf War Registries

- VA Gulf War Registry (n=102,000 1991 Gulf War Veterans as of 2007 with ongoing enrollment).
- VA Persian Gulf Spouse and Child Examination Program Registry for spouses and children of Gulf War Veterans (n = ~1,100 in October 2001, discontinued in August 2005).
- Department of Defense Comprehensive Clinical Evaluation Program (CCEP) for 1991 Gulf War Veterans (n = ~32,800, discontinued in 2002).

5.2.4.3 VA Administrative Datasets

- The Corporate Data Warehouse, which contains multiple datasets associated with VHA clinical data (inpatient/outpatient visits, diagnoses, laboratory, pharmacy, mortality files, disability and pension).
- VBA benefits data.

5.2.4.4 Gulf War data resources assembled and maintained as a department-wide VA effort

One outcome of the VA Secretary's Gulf War Veterans' Illnesses Task Force was the formation of an inter-disciplinary team of VA employees charged with developing and producing a recurring series of integrated and comprehensive Departmental reports on the Gulf War Era Veteran population. Known as the Gulf War Integrated Project Team, this body generated a two-part reporting structure consisting of a Pre-9/11 Report (August 2, 1990 through September 10, 2001) and a Post-9/11 Report (September 11, 2001 to present). A supporting data system known as the Southwest Asia Veterans System (SWAVETS) will house the data for these statistical reports.

Both the scalable reports and SWAVETS will statistically link selected VA benefits and healthcare data with Department of Defense data. Collectively, the Pre-9/11 Report, the Post-9/11 Report and SWAVETS form a dynamic reporting mechanism for Gulf War Era data.

Pre-9/11 Report: The report provides comprehensive statistics on the use of VA benefits and healthcare services by Gulf War Era Veterans who served at least one day from August 2, 1990 through September 10, 2001 [78]. The generated statistical tables are bucketed into four major profiles: Service member, VA benefits, VA healthcare services, and integrated VA benefits and healthcare services. A portion of these tables address service-connected undiagnosed illnesses (UDX). By breaking out the Pre-9/11 Period into event-based cohorts and sub-cohorts, it is now possible to conduct in-depth analyses of deployed Gulf War military personnel who participated in events such as Operation Desert Shield and Operation Desert Storm or who may have been in the immediate vicinity of exposure events at Al Jubayl, Saudi Arabia, or Khamisiyah, Iraq. VA released the initial Pre-9/11 Report in February 2011.

Post-9/11 Report: Still under development, the initial Post-9/11 Report will provide VA benefit and healthcare service utilization statistics for Gulf War Era Veterans who served at least one day from September 11, 2001 through September 30, 2010. Because the Persian Gulf War wartime period remains open, each successive report

will extend the previous report's end date until a date prescribed by Presidential proclamation or law. The Post-9/11 Report expands the scope of the Pre-9/11 Report's benefit portfolio by including utilization information for the following six benefits programs: compensation, education, insurance, loan guaranty, pension, and vocational rehabilitation and employment. VA expects to release the first Post-9/11 Report in spring 2012.

SWAVETS: This population-based data mart contains an individual record for each DoD-identified Pre-9/11 or Post-9/11 Gulf War Era Veteran. Operationally, the SWAVETS data mart serves as a standard analysis and reporting system by integrating key data from both VA and non-VA sources. Such data include DoD demographic information; VA benefits-related information to include service connection status, diagnostic codes and disability evaluations; and VA healthcare-related information to include enrollment, inpatient and outpatient care, ICD-9 codes, and costs. By Spring 2012, SWAVETS will have captured key information on most Gulf War Era Veterans.

5.2.4.5 Other large federal datasets that provide data relevant to the health of Gulf War Veterans

- Department of Defense 1991 Gulf War Troop Location Database: Identifies unit locations during 1991 Gulf War deployment.
- Department of Defense datasets that model unit exposure levels to nerve agents associated with 1991 weapons demolitions at Khamisiyah, Iraq.
- Department of Defense datasets that model unit exposures to contaminants from the 1991 Kuwaiti oil-well fires.

5.2.5 Ongoing VA Funded Projects

Several ongoing projects funded by VA have either been designed specifically to facilitate research on Veterans of the Gulf War or may aid such research.

5.2.5.1 Ongoing OPH Funded Projects

- VA mortality study of neurological outcomes.
- VA Follow-up Study of a National Cohort of Gulf War and Gulf Era Veterans.

- Research and datasets developed by the War Related Illness and Injury Research Centers (WRIISCs).

5.2.5.2 ORD Funded Projects

These have been referenced earlier in this report:

- Gulf War Veterans' Illnesses Biorepository (CSP #501B).
- Million Veteran Program (MVP, CSP #G002).
- Gulf War Era Cohort and Biorepository (CSP #585).

5.2.6 Action Plans

Goal 1: Promote ongoing surveillance efforts of Gulf War and Gulf War Era Veterans.

- Work with OPH to expand the surveillance capacity of the OPH longitudinal survey of 30,000 Gulf War Era Veterans to collect detailed and systematic data on symptoms associated with Gulf War service, on Veteran-reported diagnosed diseases, on medical and self-care treatments used by Veterans with multi-symptom illness, and on VA and non-VA hospitalization and healthcare utilization by this population.
- Work with VA's National Center for Veterans Analysis and Statistics (NCVAS) to enhance the statistical reporting capabilities in VA's Pre-9/11 Report [78] by reporting on the following cohorts: (1) Gulf War Veterans who served in the theater between August 1990 and July 1991; (2) Non-theater Gulf War Veteran cohorts that complement existing in-theater cohorts to include those who served between August 1990 and July 1991.
- Investigate the possibility of developing a "pharmacovigilance"-style surveillance system from the VA electronic medical record to identify emerging trends in incident health conditions that may be specific to Gulf War service.
- Investigate the possibility of using the CSP #585 cohort to develop a treatment identification surveillance system from the VA electronic medical record to

identify treatments given to Gulf War Veterans that may be suitable for further research.

Goal 2: Work to improve the usefulness of existing databases by attempting to link them and then integrate them into a data warehouse and make them available for use by researchers.

- Convene a meeting of relevant experts to discuss and recommend possible Gulf War data coordination and linkage efforts at VA.
- Evaluate the issues pertaining to human subjects' protections in order to address the consent and privacy issues impeding the ability to link various data sources.
- Encourage the use of a more flexible consent process, such as currently used in MVP, for future research projects of Gulf War Veterans to facilitate linkage with other data sources.
- Investigate the feasibility of forming a Gulf War Era Veterans' data repository that includes and links federal datasets for this population as necessary and also makes de-identified data available to researchers to address specific questions related to the health of Gulf War Veterans.
- Investigate the feasibility of developing an inventory as part of a data repository that includes protocols for the studies and the structure and content of the databases, including an inventory of data elements in each.
- Promote methods for research data-sharing between VA and DoD in support of the DHWG so that DoD data can be used by VA researchers and vice versa.
- Investigate the feasibility of linking existing earlier databases with MVP and CSP #585 if warranted by specific research projects.
- Work with the OHI to develop a mechanism to identify GWVs in the VA medical record to facilitate identification of potential subjects for research studies and to enable linkage with other databases.
- Encourage VA researchers to provide results in a way that identifies Gulf War Veterans as a group so that meta-analyses and similar comparisons can be conducted and to submit data pertaining to Gulf War Veterans that can be shared appropriately.
- Enhance MVP as a resource for research on Gulf War Veterans to:
    - Co-enroll Gulf War Veterans in MVP and CSP #585.

- Incorporate targeted recruitment of Veterans who were deployed to the Gulf during the conflict.

Note: *Appendix 1 outlines those major activities involved in linking multiple datasets and integrating data into a usable database, based on the experiences of the VA Gulf War Integrated Project Team in developing the Pre-9/11 Report, the Post-9/11 Report and their supporting data system, SWAVETS.*

Goal 3: Develop new databases optimized to address specific research questions.

- Support projects to compile retrospective and prospective longitudinal data from medical records of Gulf War Veterans with multi-symptom illness who are treated in the VA system to: (a) provide preliminary information on treatments that appear to be useful for some Veterans or for some symptoms, (b) assess co-morbid conditions and (c) monitor for additional problems that may develop in this cohort.
- Promote the development of a separate database focused on the women deployed to the Gulf and their specific health issues.
- Promote the use of existing databases to develop case registries and design case-control studies as appropriate.

5.3 Establish An Evidence-Based Case Definition of Chronic Multisymptom Illness in Gulf War Veterans

5.3.1 Goal

To establish a consensus case definition for chronic multisymptom illness in GWVs, and guidelines for its use.

Overview. Since returning from military service in the 1990-1991 Gulf War, studies indicate that at least one in four veterans have suffered from a complex of multiple concurrent symptoms not readily explained by established medical or psychological diagnoses. Studies of diverse veteran populations have identified the same general types of symptoms, co-occurring as a "multisymptom illness," that affect deployed Gulf War Veterans at significantly higher rates than veteran comparison groups, and have indicated that few veterans have recovered over time. In the absence of an objective diagnostic test, this multisymptom illness has been defined in research studies on the basis of veterans' symptoms, with different research groups defining the illness in different ways. Multiple large population studies [9, 13, 27, 28, 47, 64, 101] have identified similar statistically-defined symptom domains that affect Gulf War veterans at

significantly excess rates relative to veteran comparison groups. The manner in which these symptoms have been assessed, counted, and combined by different research groups in order to define a multisymptom illness complex has been highly variable, however, resulting in substantially different case definitions used by different studies. At least 10 different approaches for characterizing symptomatic illness in Gulf War veterans have been described.[91] Examples include requiring that veterans endorse at least one symptom, [100] or two symptoms out of three types, [28] or five symptoms from a general list,[111] or obtain certain scores on factors defined by principle components analysis of symptoms, [36, 64] or meet chronic fatigue syndrome criteria [115] or have been diagnosed with any of a number of medical and psychiatric conditions.[33] In the 20 years since the war, however, no single case definition has been generally accepted or widely used. Various terms have been used to refer to this health problem. "Chronic multisymptom illness" is used here as an umbrella term, referring to the excess burden of symptoms such as gastrointestinal problems, fatigue, joint and muscle pain, and cognitive problems associated with military service in the 1990-1991 Gulf War.

The lack of a consensus, evidence-based case definition for chronic multisymptom illness has negatively affected the quality of research and impeded progress in addressing this serious health problem. Studies have used diverse approaches for defining symptomatic cases, or have used no case definition at all. Overall, the case definitions put forward have not been systematically assessed to determine if they provide an adequate characterization of the profile of symptoms associated with Gulf War service. Case definitions that miss the mark, are too broad, or too narrow, can potentially obscure or misrepresent findings that are important for better understanding chronic multisymptom illness. Furthermore, results from different studies cannot be directly compared with one another, and it is not known the extent to which results from individual studies differ as a function of the case definitions used.

It is therefore important that an evidence-based, consensus case definition for use in studies of ill Gulf War Veterans be developed. Consistent use of a case definition, which is optimized to identify case subjects that are precisely and rigorously defined, is necessary for advancing better quality and more sharply-focused research. It is essential for successful application of powerful new scientific capabilities such as biomarker identification and genome-wide association studies (GWAS) that could potentially significantly advance understanding of this challenging condition.

This plan outlines a process that can establish a research case definition for chronic multisymptom illness. The case definition should be developed by a consensus panel of experts in the field, utilizing analytic results from a comprehensive evaluation of available data resources.

This evidence-based process would prioritize characteristics of specificity, sensitivity, and standardization of symptom assessment in order to identify more homogeneous groups, and subgroups, of symptomatic veterans for research studies. Once completed, the plan recognizes the need to revisit the consensus case definition over time, as additional data and new insights related to chronic multisymptom illness in GWVs, and illness subgroups, become available.

The case definition process should be completed as efficiently as possible, within a targeted time period, recognizing the need to make available an evidence-based, consensus case definition for other studies conducted as part of the strategic plan. It is hoped that use of a consistent, "optimized" case definition will be instrumental in hastening progress made by the broader research effort focused on deepening understanding of chronic multisymptom illness and improving the health and lives of affected Veterans. In the meantime, while a consensus case definition is being developed, researchers should identify and justify the choice of case definition in their studies.

5.3.2. IOM Recommendations

The Institute of Medicine (IOM) has determined there is sufficient evidence indicating an association between deployment to the 1991 Gulf War and chronic multisymptom illness, [56, p.210] but has not provided recommendations concerning case definitions for this condition.

5.3.3. RACGWVI Recommendations

The Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) summarized six case definitions that have been developed by different research groups, the differing prevalence estimates associated with various adaptations of those case definitions, and four additional approaches that have been used for characterizing multisymptom illness in Gulf War veterans [91, pp.25-30]. The Committee did not recommend a specific case definition, but its formal recommendations include:

"Studies of Gulf War veterans should use well-constructed and clearly-described case definitions for Gulf War illness and illness subgroups. Pending more widespread acceptance of an established case definition, preferred case definitions are those that most clearly distinguish the pattern of symptoms in Gulf War veterans from those in nondeployed era veterans, such as the Kansas Gulf War illness case definition." [91, p.315].

5.3.4. VA ORD Previous Research Activities Related to Case Definitions

The Department of Veterans Affairs (VA) Office of Research and Development (ORD) has not previously sponsored research specifically aimed at identifying case definitions for chronic multisymptom illness, but did fund a recent study that validated the factor structure for a set of three syndromes previously identified [46]. Previously, VA's Office of Public Health and Environmental Hazards, as well as the Department of Defense (DoD), have sponsored projects conducted by VA investigators that have developed different approaches for identifying "cases" of symptomatic illness in Gulf War veterans [28, 35-37, 40, 64, 100, 112]. These include a case definition for "Gulf War Unexplained Illness" developed at VA's Portland Environmental Hazards Research Center [100], identification of a unique "Gulf War Syndrome" using factor analysis of symptom data in VA's 1995 national survey of Gulf War era veterans [64], and a statistically-characterized "high symptom" subgroup identified by investigators at VA's New Jersey Center for Environmental Hazards Research, utilizing symptom data from VA's Gulf War Registry [40].

5.3.5. Plan for Establishing a Consensus Case Definition for Chronic Multisymptom Illness in Gulf War Veterans

The lack of objective diagnostic markers for chronic multisymptom illness presents a serious challenge for researchers and clinicians. This challenge is not unique, however. Many familiar medical conditions (e.g. migraines, Alzheimer's disease, fibromyalgia) currently or historically have lacked objective diagnostic tests and so have necessarily been defined on the basis of patients' presenting symptoms. Symptoms for such conditions can also vary to some extent between patient subgroups, necessitating a general, "umbrella" case definition that allows for identification of subgroups of potential importance. Rigorous scientific research can advance progress in addressing conditions initially recognized primarily by their symptoms. We note the significant new insights into Alzheimer's disease and novel therapeutic approaches that have been afforded by identification of the predictive utility of ApoE genotypes, by new insights into the molecular mechanisms of amyloid plaque deposition, and by the capability of identifying amyloid plaques by advanced imaging technologies even before symptoms are recognized.

The consensus case definition for chronic multisymptom illness should be developed in close coordination with VA clinical units to provide the most accurate symptom-based criteria possible for characterizing the excess pattern of undiagnosed chronic symptoms associated with military service in the 1991 Gulf War. This characterization should be

conducted in close coordination with VA clinical units. It is recognized, however, that no symptom-based case definition is likely to be perfectly accurate or ideal, given the non-specific nature of individual symptoms reported by any population group, including Gulf War era Veterans. Rather, it is important that the consensus case definition be "optimized" to the extent possible using currently available data, according to standards identified by the consensus panel assembled for this purpose. It is also important that the consensus case definition be revisited as appropriate over time, as additional data become available on veterans' symptoms and diagnosed conditions, and as objective biological markers are identified in relation to chronic multisymptom illness and/or illness subgroups.

The plan for establishing a consensus case definition for chronic multisymptom illness includes two central components, carried out in parallel, to ensure that an evidence-based, consensus case definition is developed in a timely manner.

- **Expert Consensus Panel.** The case definition effort will convene an expert chronic multisymptom illness Case Definition Consensus Panel to:
  - review existing resources and identify considerations for evaluating chronic multisymptom illness case definitions and
  - establish criteria for a consensus case definition, to be published along with guidelines for its use.

  The panel will include scientists with the expertise required to achieve case definition objectives.

- **Data Assessment.** Development of the case definition will involve a comprehensive analytic effort to evaluate existing case definitions in relation to priorities identified by the expert panel and develop algorithms for revising existing case definitions or establishing new case definition criteria. Analytic results will be provided to the expert panel for their consideration in arriving at a consensus case definition.

The Chronic Multisymptom Illness Case Definition Consensus Panel should initially review information related to existing case definitions and available data resources, consider additional approaches that might be useful for defining cases, and outline priorities to be weighed in evaluating case definitions. This process will necessarily require consideration of diverse issues, including the pros and cons of emphasizing different characteristics (e.g., specificity, sensitivity, homogeneity, subgroup identification) of the case definition to be established. For example, defining an illness in a highly restrictive way might provide some advantages for specific studies (e.g., biomarker and GWAS studies), but can potentially provide cases that are too narrowly-defined for other research purposes. In contrast, case definitions designed to include a

broader range of cases can be overly sensitive, leading to spurious or ambiguous results, e.g., by including veteran "cases" whose chronic symptoms are unrelated to their Gulf War service. The consensus panel will be responsible for weighing different features and approaches to arrive at the "best" case definition possible.

These determinations will be informed by analytic assessments of different case definitions, and specific features of case definitions, using existing population-based datasets, to evaluate strengths and weaknesses in relation to priorities of interest. Case definition algorithms and features can be assessed and compared in Gulf War veterans and nondeployed era veterans to determine, for example, the extent to which they distinguish between the two groups. This might include comparing the impact of different strategies for describing veterans' overall burden of symptoms, for including/excluding specific symptom types, or for assessing the severity level of qualifying symptoms. Criteria that are "optimized" in one population can be further assessed in other datasets to determine the degree to which they effectively characterize the excess symptomatology affecting Gulf War veterans and reliably identify homogeneous groups of cases. Results of these analyses will provide the expert panel with insights that are essential for establishing an evidence-based, consensus case definition.

5.3.5.1 "Optimizing" a Case Definition for Chronic Multisymptom Illness in Gulf War Veterans: Priorities to be Considered by the Consensus Panel

Overall, the consensus case definition should provide clear inclusionary and exclusionary criteria, which precisely and consistently characterize chronic multisymptom illness cases in GWVs, and/or homogeneous illness subgroups. Issues to be considered in "optimizing" the consensus case definition include:

- Specificity, i.e., the degree to which the case definition describes a symptom profile specifically associated with military service in the 1991 Gulf War, distinguishing the symptom pattern(s) affecting Gulf War veterans from ambient symptoms reported by non-deployed veteran comparison groups

- Sensitivity, i.e., the degree to which the case definition successfully "captures" the excess symptomatology associated with service in the 1991 Gulf War

- Reliability, i.e., the degree to which veterans' symptoms are ascertained in a consistent, interpretable manner (including symptom occurrence, severity, and duration)

- Portability, i.e., the degree to which the case definition is suitable for use with different study designs and in different research settings (e.g., clinical trials, case-control biomarker studies, population-based surveys)
- Strategy for considering diagnosed medical and psychological conditions as exclusionary criteria and/or as comorbid conditions as most appropriate for optimizing specificity and sensitivity for research purposes
- Subgroup identification, i.e., the potential for the case definition to be used in studies that require that subgroups of potential importance are identified or distinguished from one another (e.g., subgroups with prominent symptoms in a given domain, subgroups with/without comorbid conditions, etc.)
- The potential for the case definition, optimized for research purposes, to be used in clinical practice, and any special considerations in that regard
- Other case definition characteristics deemed important by the consensus panel

5.3.5.2 Specific Objectives for Establishing a Consensus Case Definition for Chronic Multisymptom Illness in Gulf War Veterans

The action plan for developing and publishing a consensus case definition for chronic multisymptom illness will address the objectives summarized below. The plan recognizes the need for a consensus case definition to be used by all clinical and epidemiologic studies of Gulf War veterans conducted under the strategic plan. Activities will be initiated upon adoption of the strategic plan and implemented with a targeted completion date within two years:

ORD will solicit and fund the development of a consensus case definition.

- Datasets that are most informative for providing systematic data on chronic symptoms and diagnosed conditions in population-based samples of Gulf War veterans and nondeployed 1990-1991 era veterans will be obtained.
- Methods to evaluate case definitions will be developed.
- Analytic approaches useful for revising existing case definitions or devising new case definitions will be developed.
- Analytic results will be reviewed.
- Case definition criteria will be developed.
- A report will be submitted.

5.3.5.3 Mechanism for Implementing the Case Definition Objectives

The case definition effort will use appropriate solicitation and funding mechanisms most capable of supporting:

- completion of the case definition within the desired two-year timeframe,
- use of analytic methods that are most scientifically credible for defining cases as objectively as possible,
- project execution by investigators whose expertise is most relevant for developing a symptom-based case definition for chronic multisymptom illness in Gulf War Veterans.

5.4 Genetics/Genomics/Systems Biology

5.4.1 Goal

To advance the understanding of the biological networks involved in Gulf War Veterans' Illnesses by applying genetic, genomic, and systems biology approaches. Molecular sources of inter-individual variation in the response to the environmental toxins which may have caused the diseases will be elucidated. Genetic variability has long been suggested as a potential contributing factor in Gulf War illness, and may explain, in part, why some veterans became ill in connection with 1991 Gulf War deployment, while others did not. The overarching aim is to identify genetic and genomic factors which may modify the spectrum of symptoms affecting Gulf War Veterans, with a view that could enable predictive personalized therapy for Veterans. This will require identifying comprehensive models describing the biological networks regulating the disease phenotype. Several studies have provided preliminary evidence that Gulf War illness may be associated with genetic factors [33, 45, 71-73, 79, 106] , including those associated with certain enzymes that act to neutralize adverse effects of neurotoxicant exposures. Questions concerning specific genes that may have played a role in Gulf War illness have focused on genetic variability in enzymes such as paraoxonase (PON1) and butyrylcholinesterase (BChE), which bind and metabolize aceytylcholinesterase (AChE) inhibitors to provide protection from their adverse effects.

5.4.2 IOM Recommendations

The IOM has noted that “given the high prevalence of persistent symptoms and the steady advances in our understanding of genetics, molecular diagnostics, and imaging, it is now possible to plan and carry out adequately powered studies to identify inherited genetic variants, molecular profiles of gene expression, other epigenetic markers (for example, modifications of DNA structure related to environmental exposures), specific viral exposures, signatures of immune activation, and brain changes identified by sensitive imaging measures that distinguish Gulf War Veterans who have persistent medical symptoms from healthy deployed or non-deployed Veterans.” [53].

5.4.3 RACGWVI Recommendations

The RAQCGWVI noted that “a question often asked about Gulf War illness is why some Gulf War military personnel developed chronic symptoms during and after deployment, while others who served alongside them remained well. There is more than one possible reason for this. Genetic and other differences between individuals can dictate different reactions to a given exposure. Additionally, different individuals encountered varying doses and combinations of exposures in theater, over different durations. Identifying specific factors responsible for these differences would provide important insights into the biological nature of Gulf War illness, as well as its causes. It could also help prevent similar problems in future deployments.” [91, p. 250].

5.4.4 ORD Research

There are no completed studies that explored the association of genetic variants with GWVI in Veteran cohorts. The Cooperative Studies Program is currently recruiting cohorts that will enable studies into the genetics of GWVI. Some examples of past research show the potential of these types of studies in Gulf War Research.

An ORD-funded study entitled “Patterns of Microarray Gene Expression in Gulf War Illness” examined 20,000 genes by microarray immediately before, immediately after and 4 hours following an exercise challenge. Ill Gulf War Veterans demonstrated a dysregulation of immune function cassette genes, as demonstrated by decreased NK cytotoxicity and altered gene expression associated with NK cell function. Pro-inflammatory cytokines, T-cell ratios, and dysregulated mediators of the stress response (including salivary cortisol) were also altered in ill Gulf War Veterans compared to control subjects [110].

A small mechanistic study used a systems biology approach to assess the immune network response to an exercise challenge in veterans with and without chronic multisymptom illness. Statistical analysis of the identified biological networks supported an autoimmune component in chronic multisymptom illness etiology [9].

"HIV-1 Genetic Determinants of Drug Resistance Development" was an ORD-funded retrospective cohort study which found that high sensitivity microarray genotyping predicted antiretroviral therapy response better than standard sequencing. This enables VA clinicians to tailor therapy for their patients with the best antiretroviral therapy regimens likely to suppress these resistant variants [67].

ORD researchers conducting genetic research in schizophrenia have found that functional polymorphisms in the core promoter of chromosome 15q14 locus of CHRNA 7 are associated with schizophrenia and with diminished inhibition of P50 auditory evoked responses. This finding is one of few demonstrations of a functional polymorphism in a gene associated with schizophrenia that directly affects a neuronal function. These results support the hypothesis of a familial neurobiological risk factor for the illness, as well as development of a drug to treat the condition [81].

5.4.5 Research Plans and Funding Mechanisms

Genetic, genomic and systems biology approaches can define those genes and networks that govern the clinical responses evoked by xenobiotic compounds such as environmental toxins. Integrating large-scale, high-dimensional molecular and clinical data, as are generated in human genomics studies, holds promise for causally associating such networks with the variable clinical response observed in ill GWVs. While genome sequence is a key driver of variation between individuals, environment sources should also be considered. Age, diet, gender, exposure to xenobiotic compounds, and many other environmental variables have been shown to impact the expression and function of disease genes. These variables, among others, may act through epigenetic, mutational, and/or stimulatory means modifying expression in the cell.

Goal 1. The VA will enable both established and emerging genetics, genomics and systems approaches by:

- recruiting prospectively appropriate cohorts of veterans who volunteer to undergo thorough health assessments and donate biological samples including DNA using the Cooperative Studies Program (CSP) mechanism;
- conducting ORD-initiated studies based on the CSP cohorts;
- funding investigator-initiated studies that access data and biological material collected from the CSP cohorts, or previously recruited cohorts.

Goal 2. Whether studies focus on a small set of genetic variants - for example in biological pathways with relevance in the detoxification of hazardous agents - or genome wide scans for genetic variants to discover those that are associated with the GWVI, the overarching principles that will guide genetic, genomic and systems biology research will be the:

- design of approaches that enable both discovery and replication;
- in-depth characterization of the clinical phenotype by survey mechanism - including longitudinal assessments - to enhance the likelihood of identifying genetic/genomic signals;
- coordination of phenotyping approaches across ill Gulf War Veteran cohorts and research projects to enable comparison of the resulting data and the replication mentioned in (i); this should include external comparison;
- careful selection of control cohorts based on population study principles;
- focus on identifying the genetic variants that contribute to disease through genetic approaches (e.g, sequencing, quantitative PCR, etc.).

Goal 3. Two cohorts will be developed as the central sources for genomics approaches. The Gulf War Era Cohort and Biorepository (CSP #585) will be a primary source for the discovery of candidate genetic variants. The Million Veteran Program (MVP, CSP #G002) is currently not specifically targeting Gulf War Era Veterans for enrollment, but is expected to enroll a number of Gulf War Era Veterans large enough to enable genomic studies on this subgroup. Thus, it is expected that this cohort will have particular utility for replication studies that follow-up on discoveries made in the Gulf War Era Cohort and Biorepository (CSP #585).

- **Gulf War Era Cohort and Biorepository (CSP #585)**

    - This large-scale longitudinal study, which is under development, will recruit a cohort of Veterans from the Gulf War era to develop a research database that integrates epidemiological, survey, clinical, and self-reported environmental exposure data. Blood and DNA specimens will be collected to establish the biorepository to enable a deeper level of research. Both users and non-users of VHA Healthcare will be recruited. Participants will also consent to be contacted about enrolling in other research projects.
    - *Challenges and opportunities:* This study is currently conducted as a pilot project with the aim to establish standard operating procedures for phenotyping, sample collection and storage (targeted enrollment up to 3000 in the pilot phase). The timeline for transitioning the program into full operation is targeted to complete recruitment at the end of year two of the five year period this strategic plan is covering. This will enable the completion of research studies that are based on this cohort within the governance of this plan. Indeed, it is desired to avail existing data and samples for research studies already during the recruitment phase. These might for example include smaller targeted genetics studies, which require fewer cases than full human genome scans. These might also include "deep-phenotyping" studies which conduct more comprehensive assessments such as longitudinal electronic medical record analysis [17], imaging, expression profiling, or metabolomics studies; Veterans will be invited to return to the clinical centers for these studies. As these more focused studies will primarily be investigator-initiated programs, a web-based system should be installed to inform potential grant applicants of the recruitment status of this cohort in close to real-time and facilitate collaborations. During the recruitment phase a CSP-directed program to obtain genetic/genomic data on cases and controls will be devised, with the intention to collect genome sequence information using next generation sequencing (NGS) technology.

- **Million Veteran Program (MVP; CSP #G002)**

    - The VA Office of Research and Development launched the Million Veteran Program (MVP) in early 2011. The MVP is an important partnership between VA and Veterans. The goal of MVP is to better understand how genes affect health and illness in order to improve healthcare for Veterans. MVP will establish one of the largest databases of genetic and health information to be used for future studies that may lead to new ways of preventing and treating illnesses in Veterans and all Americans. The

goal of MVP is to partner with Veterans receiving services in the VA Healthcare System who volunteer to share their health information, as well as genetic material. This project is expected to enroll one million users of the VA Healthcare System, with representative sampling from all deployments including the 1990-1991 Gulf War. Veterans who choose to be actively involved in this program will:

- Complete surveys about health and health-related behaviors;
- Provide a blood sample (containing DNA and other substances) that will be stored for future research;
- Complete an optional health assessment;
- Allow secure access to VA and VA-linked medical and health information, including past and future health records; and
- Allow future contact for invitation to participate in additional research studies

- *Challenges and Opportunities:* As the recruitment of this cohort is not exclusively targeted towards Gulf War Era Veterans, a mechanism to monitor the sample size of the Gulf War Era Subgroup will be set up. This will allow potential investigators who intend to base their studies on this cohort to assess which projects are feasible and facilitate collaborations. A mechanism will be set up to assess which veterans are enrolled in both cohorts, the MVP (CSP #G002) and the Gulf War Era Cohort and Biorepository (CSP #585).

- **Other Cohorts:**

VA researchers will continue adding data and specimens to develop the research capacity of the ORD biorepository studies. These are available for investigator-initiated projects:

- Veterans Administration Biorepository (CSP #501) is a cooperative effort to collect high quality biological specimens linked to clinical information from consenting Veterans for use in biomedical research on ill Veterans. Initial efforts have focused on collection of post-mortem central nervous system tissue (brain and spinal cord) from Veterans diagnosed with Amyotrophic Lateral Sclerosis (ALS), which has been reported to occur at higher rates in Gulf War Veterans.
- Gulf War Veterans' Illnesses Biorepository (CSP #501B): This pilot project will gather critical information and test the feasibility of developing a collection of high quality post mortem biological specimens from Gulf

War Veterans.

- *Challenges and Opportunities*: There will be a need for a query tool to easily and quickly determine for which cohorts various data elements are available.

5.5 Biomarkers

5.5.1 Goal

To identify biomarkers that may be present in ill Gulf War Veterans. Biomarkers are quantitative biological measures that can facilitate the diagnoses of GWVI and allow monitoring disease progress and a patient's response to treatment. Biomarkers of GWVI may represent molecular or cellular events that can be identified as a link to a specific environmental exposure or to a health outcome. Results from imaging technologies can also be considered surrogate biomarkers when they associate with disease or disease progression.

For GWVs with chronic multisymptom illness, no laboratory testing methods are available to accurately diagnose individual patients, but studies from different research groups have identified objective biological measures that significantly distinguish groups of ill GWVs healthy controls. Identified differences relate primarily to brain structure and function [11, 12, 31, 38, 42, 69, 70, 103], function of the autonomic nervous system [16, 31, 39, 66, 82, 95, 102, 104], neuroendocrine alterations [29, 30, 113], immune parameters [96, 107, 110, 115], and coagulation indicators [6, 41]. These biological findings are generally considered preliminary, since most have been evaluated in one study, or a limited number of studies, using different measures and methods. Taken together, however, such studies have been useful in providing insights concerning the diverse biological processes that may underlie the causes of chronic multisymptom illness, and point toward areas of research that can potentially lead to useful biomarkers.

As FDA guidelines suggest, biomarker application can be used to predict disease progression or success of therapeutic strategies. Prognostic biomarkers characterize risk for developing a disease or its progression. Predictive biomarkers characterize individual response to particular therapeutic strategies. A pharmacodynamic biomarker displays whether a biological response has occurred in response to a particular therapeutic strategy. While a surrogate endpoint is a biomarker that substitutes for a particular clinical endpoint, this could include neuroimaging as a marker of brain change in conjunction with a particular treatment trial that would display an objective marker of change after treatment.

The path to development of biomarkers has also been summarized by FDA as including biomarker discovery, qualification, and then application. The FDA defines these three steps by the following "definitions:

- **Biomarker discovery**
    - Discovery of a differentiating signature in a measurement as a candidate biomarker.
    - In-depth investigations of the mechanisms of action and biological pathways the candidate biomarker reflects. This is the best source of information on the likely relevance, specificity and robustness of the candidate biomarker.

- **Biomarker qualification**
    - Development of a robust and practical method for biomarker detection.
    - Proof-of-principle in controlled experimental settings.
    - Establishing that the biomarker adequately selects and characterizes the presence and / or severity of the outcome of interest in specific patient populations.
    - Understanding the candidate biomarkers' clinical performance with regard to the level of sensitivity and specificity achieved under a specific context of use.
    - Identification of clinical factors which might interfere with biomarker interpretation.

- **Biomarker application**
    - Use of the biomarker to predict disease progression / success of therapeutic interventions etc. in the context for which it was qualified."

5.5.2 IOM Recommendations

There have been several studies demonstrating that chronic multisymptom illness is associated with specific and quantifiable changes detected using blood-based analysis and neuroimaging techniques suggesting that the identification of a reliable set of biomarkers is a realistic goal for chronic multisymptom illness.

According to the IOM, "many of these symptoms (Gulf War) are difficult to categorize as they have no known cause, no objective findings on clinical examination, no diagnostic biomarkers, no known tissue pathology, and no curative therapy. The inadequate basic

understanding of the root cause of these symptoms highlights the limitations of current medical science and clinical practice. The [IOM] committee recognizes that symptoms that cannot be easily quantified are sometimes dismissed—incorrectly—as insignificant, and that they receive inadequate attention—and funding—by the medical and scientific establishment." [56]. "The committee recommends rigorous, adequately powered studies to identify biomarkers that distinguish Gulf War veterans who have persistent multisymptom illness (MSI) from healthy deployed or non-deployed veterans. Such biomarkers might include signatures of immune activation, brain changes detected through imaging, inherited genetic variants, molecular profiles of gene expression, other epigenetic markers (e.g., modified DNA structures), or specific viral exposures."

5.5.3 RACGWVI Recommendations

"Findings from studies of this type can therefore be affected by many of the problems described in relation to Gulf War illness research, that is, potential inaccuracies in identifying "exposed" vs. "unexposed" groups, the lack of useful biomarkers of exposure, and individual variability in specific exposures and vulnerability to those exposures. Given such limitations, it is important that this literature be considered broadly, taking into account patterns of associations across multiple studies and populations. Such studies can potentially provide insights into the pathophysiology of CFS and lay the groundwork for developing biomarkers and treatments." [91, p. 285].

Specific RAC recommendations stated that biomarker research should include:

5.5.3.1 "Identification of objective measures that distinguish veterans with Gulf War illness from healthy veterans.

The Committee places a high priority on identification of biological markers for Gulf War illness and measurable differences between groups of symptomatic and healthy Gulf War veterans. In light of findings from current and ongoing studies describing associations between Gulf War illness and neurological, immune, endocrine, genetic, and biochemical alterations, the Committee recommends the following research:

- Studies that utilize state-of-the-art neuroimaging technologies to characterize aspects of brain structure and function that may distinguish veterans with Gulf War illness, including illness or exposure subgroups, from healthy Gulf War veterans.
- Comprehensive evaluation of autonomic nervous system function associated with Gulf War illness, as well as illness and exposure subgroups.

- Research that investigates biological and genetic variability potentially linked to differences in vulnerability to Gulf War exposures, including studies that evaluate associations between Gulf War illness and genetic polymorphisms and activity levels of enzymes associated with uptake and metabolism of neurotoxic exposures.
- Studies that evaluate alterations in central proinflammatory and inflammatory processes in Gulf War veterans affected by Gulf War illness.
- Comprehensive evaluation of immune parameters associated with Gulf War illness, including parameters that may differ among illness and/or exposure subgroups.
- Comprehensive evaluation of hypothalamic-pituitary-adrenal axis and other neuroendocrine parameters in association with Gulf War illness, including parameters that may differ among illness and/or exposure subgroups.
- Studies that determine the extent to which other physiological characteristics that distinguish CFS, FM, and MCS patients from healthy controls are also associated with Gulf War illness.
- Studies that utilize new technologies (proteomic, lipidomic, genomic, and metabolomic methods) capable of identifying unique molecular characteristics of Gulf War illness, and of illness and exposure subgroups." [91]

5.5.3.2 "Studies that characterize effects of neurotoxic exposures associated with Gulf War illness.

Due to the consistency of findings relating Gulf War illness to neurotoxic exposures during the war, the Committee gives high priority to studies that further characterize specific effects of Gulf War related neurotoxic exposures, and recommends the following research:

- Studies that utilize animal models to characterize persistent molecular, cellular, systemic, and behavioral effects of individual and combined exposure to pyridostigmine bromide, pesticides and insect repellants used in the Gulf War, and low-level sarin.
- Studies that utilize animal models to characterize persistent effects of Gulf War-related exposures, alone and in combination, on central proinflammatory processes and their biological mediators in the central nervous system and target organs." [91].

5.5.4 ORD Research

Some examples of ORD-funded research in this area are given below.

The study "Structural Magnetic Resonance Imaging in Gulf War-Era Veterans" found a significant association between higher levels of estimated sarin/cyclosarin exposure and both reduced white matter and increased right lateral ventricle and left lateral ventricle volumes. These findings suggested subtle but persistent central nervous system pathology in Gulf War veterans potentially exposed to low levels of sarin/cyclosarin and argue for further investigation of the long-term effects of low-dose sarin/cyclosarin exposures in humans [42].

The study "Effects of Gulf War Illness on Brain Structure, Function and Metabolism: MRI/MRS at 4 Tesla" examined imaging biomarkers to determine whether US troops who may have been exposed to the organophosphate chemical warfare agents sarin and cyclosarin when a munitions dump at Khamisiyah, Iraq, was destroyed after the Gulf War in 1991 have metabolic, structural, or functional changes in the basal ganglia and other regions of the brain, which are not accounted for by confounders such as post traumatic stress disorder (PTSD), depression, and/or alcoholism. The findings suggested that low-level exposure to sarin and cyclosarin can have deleterious effects on brain structure and brain function more than a decade later [12].

In the ORD-funded study "Glucocorticoid Responsivity in Gulf War Veterans" hydrocortisone was administered to GW veterans with (PTSD+, n=12) and without (PTSD-, n=8) chronic PTSD in a randomized, placebo-controlled, double-blind challenge. The PTSD+ group showed greater cortisol and ACTH suppression, reflecting greater peripheral glucocorticoid receptor responsiveness, and did not show an hydrocortisone-induced decrement in delayed recall or retention. Positron-emission tomography demonstrated that while the two groups had comparable relative regional hippocampal [^{18}F]FDG uptake at baseline, only the PTSD- group had an hydrocortisone-associated decrease in hippocampal [^{18}F]FDG uptake. The investigators concluded that the differences in brain metabolic responses between GWveterans with and without PTSD may reflect differences in peripheral and central glucocoid receptor responsiveness [113].

Tissue factor and Gulf War-associated chronic coagulopathies were studied in a group of 64 Gulf War Veterans and controls. Significant differences between the two groups were observed for three of eight coagulation parameters. The results of this study supported the hypothesis of coagulation system activation in chronic multisymptom illness. This is a new potential biomarker for Gulf War research [6].

5.5.5 Research Plans

VA Researchers will search for new biomarkers and validate them. Biomarkers of illness, neurotoxicant exposure and risk factors for chronic disease will be specifically targeted. The focus will be to identify biomarkers that are elevated at baseline assessment and will help define disease pathophysiology for ill GWVs. ORD will adopt the FDA strategy of biomarker development by first encouraging investigator-initiated, Program Project and CSP studies of biomarker discovery, then qualification of each identified biomarker, and finally applying the biomarkers to assess clinical efficacy of treatment trials in the area of which it was qualified as relevant. Therefore, biomarker development will focus on these areas where initial studies have identified preliminary marker differences in GW veterans with chronic multisymptom illness or relevant neurotoxicant exposures. For studies assessing chronic sequelae of GW-relevant neurotoxicant exposures, comparison groups of other occupationally exposed groups will also be compared. Further biomarker qualification in these areas including identifying clinical factors that could cause interference with biomarker interpretation including better defining genetic polymorphisms predicted to have a functional significance and epigenetic modifications of down regulating markers and of risk factors for chronic disease vs. self-limiting symptoms will be assessed. Finally, identified and qualified biomarkers will be used to predict disease progression or success of therapeutic interventions. Implicit in these studies and strategy will be that carefully-defined phenotypes will be used and that specific case definitions and standard collection of biodata (blood, tissue, and imaging) will be implemented whenever possible in order to adequately compare results of biomarker studies and assess biomarker development effectiveness. Also whenever possible, human studies will include blood collection, processing and banking in anticipation of downstream analysis. This could prove instrumental in treatment studies to have pre- and-post-samples to assess for potential surrogate biomarkers.

Biomarker qualification studies for areas where initial biomarkers of discovery have shown promise but require further study and validation will include but not be limited to the following (see below). Whenever practical, studies should consider combining qualification of multiple biomarkers in the same study populations (i.e., brain and blood markers of inflammation).

- Advanced neuroimaging techniques (MRI, PET, DTI, MEG) to further delineate surrogate biomarkers of GWVI from promising preliminary studies.

- Immune response mediator biomarkers that are associated with chronic inflammation including proinflammatory cytokines, chemokines and other immune functions.
- Hypothalamic-Pituitary-Adrenal axis biomarkers in ill GWVs including cortisol and other measures of neuroendocrine function (including epigenetic studies).
- Blood coagulation studies of platelet tissue factor and other relevant markers of inflammation
- Broad biomarkers of neurologic and/or neurodegenerative effects in ill GWVs and/or neurotoxicant exposures (degeneration stains, glial activation stains, myelin stains in post-mortem tissue)
- Blood and CSF studies of proteomics, metabolomics and lipidomic markers in ill GWVs.
- Biomarkers of autonomic system dysfunction in ill GWVs.
- Biomarkers of irritable bowel syndrome (IBS) from altered gastrointestinal flora or microbiome that may relate not only to gastrointestinal symptoms but other symptoms of chronic multisymptom illness as well.
- CSP #501B and #585 now pilot studies for brain and tissue biorepository (CSP #501B) and blood biorepository and cohort development (CSP #585) will be developed into full research programs as appropriate. This extremely valuable CNS tissue and blood biodata will allow for biomarker development and qualification studies as tissue and blood samples will be shared with independent researchers and studies evaluating potential biomarkers in ill GWVs. These biorepositories will allow independent researchers with important biomarker hypotheses the ability to analyze tissue and blood samples without the costly and time-consuming recruitment of these samples.
- In order for the GW biorepositories to provide the most valuable and useful data to GW biomarker researchers, standard procedures for sample collection of blood and tissue samples and standard case definitions for GWVI will be employed.

Promising recent VA pilot studies in biomarkers will be evaluated for expansion to larger studies in the future. VA has the existing research infrastructure to conduct small pilot studies and move the studies with the most promising results on to larger studies.

The VA funding mechanisms for Biomarkers will be via RFAs, Program Projects and CSP. VA researchers are likely also to leverage funding from other sources.

5.6 Animal Models

5.6.1 Goal

To use animal models to characterize the persistent molecular, cellular and functional effects associated with individual and combined exposures/conditions encountered in the Gulf War. Animal models have advanced science and improved public health. While it may not be possible to develop a "perfect" animal model that reflects all features of the illnesses facing GWVs, animal models can readily be used to characterize the wide variety of effects associated with exposures that may underlie the pathogenesis of conditions observed in ill veterans. Animal models have the advantage of providing post-exposure evidence obtained directly from any organ or target tissue. Modeling the persistence of effects due to exposures presumably occurring years earlier in ill veterans can be achieved in a short time frame using rodent (rats/mice) models. Finally, a very wide variety of effect "domains," from molecular to cellular changes, genomic to proteomic, to functional alterations in physiology and behavior, can readily be assessed in experimental animals. The need to identify therapies to treat ill Veterans could also be addressed by screening potential treatments in animal models, and this emphasis on treatments should guide animal studies as Gulf War research moves forward.

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Animal studies have been used to evaluate the effects of a variety of GW-related exposures and conditions [91]. Recent animal-based studies of exposures implicated in chronic multisymptom illness reveal the involvement of subtle cell-signaling processes that may underlie persistent symptoms exhibited by ill veterans [1, 99, 105]. Further characterization of these effects in animal models may lead to the identification of targets for therapeutic intervention.

5.6.2 IOM Recommendations

The IOM Gulf War Report (Vol. 8) noted that: "Because the committee was not attempting to link health outcomes to exposures other than deployment to the Persian Gulf Theater, for which there is no known animal model, it did not review toxicologic, animal, or experimental studies comprehensively." [56] The IOM report called for "a renewed research effort…to better identify and treat multisymptom illness in Gulf War veterans" [56], and studies that couple animal models and biomarkers may be useful in achieving that goal.

5.6.3 RACGWVI Recommendations

Most studies that evaluate biological effects of hazardous exposures are done in animals, for ethical reasons. As noted in the RACGWVI Report [91], a number of animal studies recently have identified biological effects of Gulf War exposures and combinations of exposures that were previously unknown [1, 99, 105]. Due to the consistency of findings relating chronic multisymptom illness to neurotoxic exposures during the war, the Committee gave high priority to studies that further characterize specific effects of Gulf War-related neurotoxic exposures, and recommended the following research:

- Studies that utilize animal models to characterize persistent molecular, cellular, systemic, and behavioral effects of individual and combined exposure to pyridostigmine bromide, pesticides and insect repellants used in the Gulf War, and low-level sarin.
- Studies that utilize animal models to characterize persistent effects of Gulf War-related exposures, alone and in combination, on proinflammatory processes in the central nervous system and peripheral target organs.
- Studies that identify markers indicative of past exposure to Gulf War-related neurotoxic compounds that can be applied to Gulf War veterans. This includes studies that identify persistent or "downstream" changes in biochemical processes in relation to past neurotoxicant exposure(s), and studies that identify persistent changes in the central nervous system and in autonomic function associated with exposure to Gulf War-related neurotoxicants.

5.6.4 ORD Research

Examples of past ORD-funded research in animal models are given below.

The prevalence of irritable bowel syndrome (IBS) in Gulf War Veterans is so high that the condition is presumptively connected to service during the 1990-1991 Gulf War. In order to study IBS, VA researchers have developed a rat model of chronic visceral and somatic hypersensitivity in the colon. It was found that the application of intracolonic lidocaine reversed the effects of hypersensitivity in the rats [116]. This same treatment was successfully applied to patients suffering from IBS [89].

In another project, the femoral nerve in the mouse was used to study motor neuron regeneration for treating peripheral nerve injuries. By using surgical procedures on the

muscle and removing Schwann cells from the nerve, it was possible to influence the tendency of the neurons to project into the quadriceps muscle or the skin [74]. These results are encouraging for patients suffering from peripheral neuropathy and other sensory deficits.

5.6.5 Research Plans

The VA funding mechanism for animal models will be RFAs. VA researchers also are likely to leverage other funding mechanisms as well. The Biomedical Laboratory Research and Development Service (BLRD) at ORD solicits proposals that further the goal of improving the health and lives of veterans of the 1990-1991 Gulf War who have a complex of chronic symptoms at an excess rate. Areas of interest include studies in animals that can contribute to improved understanding of the pathobiology of GWVI, including research on objective indicators of biological processes or abnormalities in GWVI. The new information on potential origins of chronic multisymptom illness identified in the IOM and RACGWVI reports, combined with the development of novel assessment approaches, provide guidance for topic areas focused on animal models. These could include, but are not limited to, characterization of persistent effects of GW-related exposures, alone and in combination, on:

- sensitive indices of neuropathology used in contemporary neuroscience.
- neuroinflammatory processes associated with glial activation in the central nervous system.
- autonomic nervous system pathology and function.
- systemic immune parameters, with an emphasis on those parameters that sensitize ill veterans to chronic multisymptom illness.
- sensitive indicators of altered hypothalamic-pituitary-adrenal axis function.

These research studies should be integrated with those from case definition, genomics, and biomarker sections of this document to determine endpoints/markers/systems to be evaluated in animal studies.

Implicit in all of the above topics is the need to utilize the data obtained to identify, test (in animal models) and implement (in ill veterans) off-the-shelf therapies for GWVI.

5.7 Improve Coordination and Communication with Stakeholders

5.7.1. Goal

To improve coordination and communication among Federal partners, researchers, and the private sector.

5.7.2. Introduction

Institute of Medicine, Report on Gulf War and Health, Vol. 8 (2010): The committee believes that a continued and targeted research program is the most likely path to assist VAs and other health-care providers in diagnosing and treating the health problems of Gulf War Veterans and preventing illness in future Veterans [56].

Research Advisory Committee on Gulf War Illnesses, Gulf War Illness and the Health of Gulf War Veterans, Scientific Findings and Recommendations (2008): That the Department of Defense and the Department of Veterans Affairs collaborate in establishing a comprehensive federal Gulf War Research plan and a strategy to coordinate and manage federal programs to ensure that priority research objectives are satisfactorily achieved [91].

5.7.3. Inter-Governmental Coordination Efforts

This section describes the VA and DoD agencies that are involved in Gulf War Illness Research.

Within VA, two organizations, the Office of Research and Development (ORD) and the Office of Public Health (OPH), are involved in Gulf War Veterans' Illnesses Research. ORD and OPH internally coordinate and share information on this topic. In early 2011, ORD and OPH initiated formalized quarterly meetings of senior staff and, as appropriate, scientific program managers and VA investigators.

5.7.3.1 Office of Research and Development (ORD)

The Office of Research and Development (ORD) supports the discovery of new knowledge by developing VA researchers and health care leaders and creating innovations that advance health care for our Veterans and the nation. ORD funds

research and sets research priorities in four areas: biomedical, clinical, rehabilitation, and health services research.

ORD staff members participate in regularly scheduled meetings of the Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI), the Gulf War Steering Committee (GWSC), and the Gulf War Veterans' Illnesses Task Force.

5.7.3.2 Office of Public Health (OPH)

The work of the Office of Public Health (OPH) includes epidemiological research and large-scale surveillance studies. OPH coordinates and supports Institute of Medicine (IOM) studies that consolidate current knowledge of the Gulf War and other deployment health conditions.

ORD and OPH complement one another in that OPH performs high level surveillance studies (e.g., prevalence, mortality), while ORD funds VA investigators to perform basic scientific and applied medical research. Results of OPH studies support ORD's research agenda (e.g., increased prevalence of a particular condition in a certain Veteran population could be an indicator that a certain research project may be needed for further study to seek a mechanism and a treatment).

5.7.3.3 Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI)

The Research Advisory Committee on Gulf War Veterans' Illnesses was established by Congress in 1998. It makes recommendations to the Secretary of Veterans Affairs on government research relating to the health consequences of military service in the Southwest Asia theater of operations during the Gulf War.

5.7.3.4 Gulf War Steering Committee (GWSC)

VA organized a committee of experts from its own internal advisory board and on recommendation from RACGWI to facilitate the development of this strategic plan in 2011. The group holds conference calls and meets in person on request of VA's Chief Research and Development Officer to advise on scientific and strategic aspects of developing its Gulf War Research portfolio.

5.7.3.5 DoD's Congressionally Directed Medical Research Programs (CDMRP)

Outside of VA, ORD coordinates with DoD's Congressionally Directed Medical Research Programs (CDMRP), specifically its Gulf War Illness Research Program (GWIRP). In a number of cases, VA investigators have successfully competed for research funding from CDMRP.

CDMRP views Gulf War multisymptom illness as characterized by persistent symptoms such as chronic headache, widespread pain, cognitive difficulties, unexplained fatigue, gastrointestinal problems, respiratory symptoms, and other abnormalities that are not explained by traditional medical or psychiatric diagnoses. CDMRP estimates that this complex set of chronic symptoms may affect as many as 200,000 Veterans of the 1990-1991 Gulf War, of the over 697,000 deployed to that region. The CDMRP GWIRP focuses its funding on projects that relate to GWI.

The vision for the CDMRP GWIRP is to "improve the health and lives of veterans who have Gulf War Illness," and the mission is to "fund innovative Gulf War Illness research to identify effective treatments, improve definition and diagnosis, and better understand pathobiology and symptoms." [14] ORD and the CDMRP (GWIRP) currently maintain several levels of coordination:

- The VA Gulf War Research Program Manager is invited to present the VA Gulf War research portfolio as part of the GWIRP vision-setting meeting each year. The VA GW research portfolio and upcoming requests for applications (RFAs) are discussed at this time. This allows both agencies to coordinate their research priorities.
- The VA GW research portfolio and the GWIRP research portfolio are presented and discussed at one or more of the three annual meetings of the VA Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI). This allows the RACGWVI to be aware of the activities within each agency's GW research program so that appropriate recommendations may be formulated.
- Representatives from the GWIRP are invited to present at VA Gulf War Steering Committee (GWSC) meetings so that the committee is aware of the scope and potential overlap between the VA and DoD programs.

5.7.3.6 Deployment Health Working Group (DHWG)

The DHWG is an interagency working group co-chaired by VA (OPH) and DoD that meets monthly (successor to the original Persian Gulf Veterans Coordinating Board). The DHWG reports to VA/DoD joint committees. The DHWG is composed of staff from OPH (environmental health, epidemiology, communications), ORD (including the leads for deployment health research and GW research), and Veterans Benefits Administration (VBA). The working group shares information on deployment health in all areas, environmental exposures, DoD/VA data sharing, surveillance, surveys, research, and other topics as needed. CDMRP and researchers should present programs and findings to the DHWG on a regularly scheduled basis.

5.7.3.7 Veterans Service Organizations

ORD and OPH provide briefings to a number of Veterans Service Organizations on at least an annual basis (sometimes more frequently when requested). In addition, VSOs are on the distribution lists for VA press releases and announcements of new publications on Gulf War topics; they receive copies in bulk.

5.7.4 ORD Coordination Efforts Among Researchers

Besides monitoring research that is already funded, ORD also has a responsibility to bring researchers together when appropriate and encourage coordination and collaboration.

5.7.5 Research, Goals and Action Plans

This section outlines the goals for research coordination and communication in this plan, the objectives associated with each goal, and timelines for meeting the objectives. The rationale for these goals and objectives can be linked to the IOM and RACGWI recommendations quoted in the Introduction (Section 5.7.2).

Goal 1: Scientific coordination of research efforts on Gulf War Veterans' Illnesses using a targeted approach in order to facilitate focused, well-planned research in the areas included in this document (cohorts and survey data; case definitions; genetics/genomics, biomarkers; animal models; treatments; translation) and perhaps others; allow addition of promising new avenues of research that arise in the course of the planned effort; and support on-going discussion of the diagnostic and treatment implications of research findings as they develop.

- Involvement of the ORD's Gulf War Steering Committee (GWSC) in providing regular advice for the VA Gulf War Research Program. Members will be added as appropriate.
- To supplement face-to-face meetings, virtual meetings of the GWSC should be conducted as needed to discuss research findings and provide advice regarding possible new initiatives, treatments, and translational applications.

Goal 2: Inter-agency coordination of funding and scientific initiatives to support a targeted, planned effort that promotes optimal utilization of resources for research on Gulf War-related Veterans' Illnesses.

- ORD and OPH will coordinate research on Gulf War Veterans' Illnesses that is funded and/or conducted by VA so that research goals and strategies are efficient and congruent.
- Representatives from CDMRP and VA will meet regularly to discuss topics for RFAs and research initiatives to be funded through the agencies in support of the scientific goals of the research strategic plan.
- Representatives from CDMRP's GWIRP will be invited regularly to the GWSC meetings to discuss DoD's research program.

Goal 3: Communication of results and hypotheses to the scientific community devoted to the topic of Gulf War Veterans' Illnesses, Veterans, health professionals who treat Veterans, the scientific community at large and the public.

- ORD will work to improve communication among Gulf War researchers using new online methodologies.
- VA will convene a meeting of Gulf War researchers in 2012 to improve sharing of research results. Regular meetings thereafter will be conducted, consistent with VA travel policies.
- VA will continue to participate in monthly meetings of the DHWG to share information about research programs with DoD.
- RACGWI will continue to conduct meetings to review research results and advise VA.
- ORD will continue to communicate with Veterans' groups on research results, treatment options, and policy changes through a variety of mechanisms.

- ORD will communicate with clinical centers in order to gain insights on issues and treatment alternatives that might influence the Gulf War Research program.

Goal 4: On-going dialogue and communication with Gulf War Veterans and their families regarding the results of the research initiatives and possible health, functional and treatment implications of this research.

- Work with OPH to develop targeted material (e.g., brochures, fact sheets, Q&As) regarding the results of research initiatives for Gulf War Veterans and their families and caregivers.
- Work with OPH to disseminate material to VHA healthcare facilities for redistribution to Veterans and their family members and caregivers.
- Work with OPH to distribute information to Veteran Service Organizations and other stakeholders working on behalf of Veterans for redistribution.
- Make resources available on the ORD website and link the website to other VA sites such as OPH's VA Gulf War website and to VA's A to Z website.

Goal 5: Enhance, manage, and coordinate lines of communication among clinicians who treat Gulf War Veterans in VHA, uniformed services (including the Public Health Service) and the private sector to provide current research findings, updates to standards of practice, and new modalities of care for ill Gulf War Veterans.

- Provide information on research studies to OPH so that they may incorporate research results into their educational/informational interactive forum with clinicians (webinars, in-person sessions with internet access, etc).
- Work with OPH to determine the most effective and efficient means of presenting new information and capturing the intended audience.
- Construct several Outlook groups to widely promote forums and webinars.
- Provide the latest clinical and research information to OPH for inclusion on their website.
- Ensure that the latest research findings are communicated to clinicians through meetings, seminars, webinars, and other means.

5.8 Translate Research Findings To Practice

5.8.1 Goal

To translate research findings into practice as rapidly as possible. Without exception, this is a problem in every field of medical, scientific, and engineering research. It is important to accomplish this translation, so that the benefits of research will be experienced by individuals the research was intended to help.

5.8.2 Research and Activities

VHA's Vision of Excellence includes providing exemplary services that are both patient-centered and evidence-based. For that reason, it is critical that research results that are relevant to Veterans be translated into our clinical treatments and processes of care. It is necessary to identify the barriers to implementing new treatments, whether they are technical or administrative, and to put strategies in place to determine how research can itself accelerate the application of new knowledge in clinical settings.

The translation of research findings can be placed into two categories:

- Type 1 translation, in which basic laboratory findings are turned into treatment concepts that are tested through clinical research studies such as randomized controlled studies. NIH Clinical & Translational Science Awards (CTSA) focus on Type 1 translation.
- Type 2 translation, in which accepted findings from clinical research results are implemented as part of routine clinical care practices. VA's Health Services Research and Development (HSRD) and Quality Enhancement Research Initiative (QUERI) focus on Type 2 translation.

There are also situations in which clinical research findings are equivocal, in which case, a hybrid approach ("pre-implementation") can be used, in which a medical procedure or treatment is provided to patients while additional data are collected in a systematic manner to allow future determinations of comparative effectiveness.

Successful translation requires collaboration between researchers and clinicians to determine the type of research that is appropriate for a given treatment. Clinical findings suggest the types of questions that are most relevant to clinicians and therefore can guide research planning to topics that are more likely to be used in actual practice. In the early phases of implementation, clinicians can also identify what they perceive as barriers to the evidence-based approach suggested by the research findings. Likewise, collaboration might indicate that "de-implementation" be done with a procedure if follow-

up research suggests that the procedures/practices are not effective, wasteful of resources, or potentially harmful.

It is not possible to predict in advance whether any specific basic research finding can lead to a treatment concept that stands the test of clinical research. Additionally, initial positive findings in early phase clinical research studies frequently are overturned by subsequent clinical trials. It is important, therefore, to communicate this uncertainty with honesty and sensitivity, and, in particular, researchers interested in translation have a particular obligation to support a trusting patient-clinician exchange. This includes not overplaying preliminary results, however positive they may be initially. Researchers also need to expect the enduring nature of the patient-clinician relationship. A dashed hope based on a flawed research insight could lead to loss of trust in healthcare in general, with potential serious consequences.

VHA has successful models of researcher-clinician collaboration that embrace these principles. For example, Gulf War Veterans are generally pleased with treatment programs at the War Related Illness and Injury Study Centers (WRIISCs) where the physicians use a team approach to treat patients holistically; communication between patients and providers is essential and usually determines whether a patient stays in the VA healthcare system. The WRIISCs, under the direction of OPH, offer a number of special clinical programs for Veterans who have post-deployment health concerns. These programs focus on difficult-to-diagnose or medically unexplained symptoms and military environmental exposure concerns. These Centers are at the forefront of translating research into practice in the VA. The Centers offer a National Referral Program which provides comprehensive multidisciplinary health evaluations. The WRIISCs also perform primary clinical research, provide exposure assessment clinics, and tele-health services.

In addition to assuring the implementation of results of clinical studies, WRIISCs have also used the hybrid approach for situations such as Complementary and Alternative Medicine (CAM) treatments, providing a requested treatment while doing the types of assessment needed to establish overall effectiveness. Preliminary results have been positive, but more analyses of CAM programs need to be conducted.

The WRIISCs are also an educational resource for combat Veterans, their family members and loved ones, and Veteran healthcare providers. Their educational programs provide information on topics ranging from environmental exposures and deployment health conditions, to self management techniques for chronic health concerns.

Once a promising technology or treatment has been selected to go forward, it continues to be subject to an adoption process that varies widely. One method is to set up

specialty centers, where a particular treatment or treatment program is available. Another method is by developing educational programs for both Veterans and healthcare providers in the VA.

VA is also committed to Clinician Education and Training. VA OPH is developing accessible, flexible and user-friendly training regarding health aspects of the Gulf War including Gulf War Veterans' Illnesses to educate primary care physicians, compensation and pension examiners, environmental health clinicians, mental health professionals and social workers about the health effects, including gender specific health effects of service in the 1990–1991 Gulf War.

OPH programs, the Environmental Agents Service, and WRIISCs are coordinating with Patient Care Services, the Office of Academic Affairs, Veterans Integrated Service Networks, and VA Medical Centers to improve training on the unique exposure concerns of 1990–1991 Gulf War Veterans as well as returning OEF/OIF Veterans, and provide educational and clinical tools for evaluation of exposure risk and the health outcomes relevant to these risks.

5.8.3 Research and Action Plans - Funding Mechanisms

When Gulf War research results show a successful treatment, each successful treatment will be translated into clinical practice.

Moving treatments that have been shown to be successful in the research laboratory to clinical practice require different combinations of the following:

- Establish an evidence base through large well-designed research studies that can be published in leading journals.
- Use the VA Quality Enhancement Research Initiative (QUERI) program to facilitate the translation of appropriate treatments and technologies from research to clinical practice. QUERI is aimed at improving the quality of healthcare for Veterans. QUERI contributes to this effort by implementing research findings and innovations into routine clinical practice.
- Continuing education of VA healthcare providers is important because of the constant advances that are being made in research and the need to incorporate recent advances.
- Coordination by ORD with the War Related Illness and Injury Centers to disseminate research findings to these three centers.
- Encourage Gulf War Researchers to apply for the Career Development Awards available through VA to build research capacity.

- Encourage and support research and clinical studies that involve Type 1 and Type 2 translation. Hybrid implementation and the principles of "pre-implementation" and "de-implementation" are important components of translating research into practice.
- Encourage close collaboration between clinicians and researchers in designing research projects irrespective of whether Type1 or Type 2 translation is anticipated.
- Support research in many different areas that can produce new treatments. These include research programs involving biomarkers, genetics and genomics, pharmacogenomics, proteomics, lipidomics, and other basic medical research topics as outlined in earlier sections of this document.
- Evaluate complementary and alternative medicine (CAM) research results from non-Veteran studies for potential implementation in VHA in instances where high quality evidence exists.
- Encourage pilot research projects evaluating possible new treatments. It is likely that ORD support of these studies would be a reasonable pathway for translating research into practice.
- Require that the outcomes of any new treatment procedures are subjected to rigorous statistical evaluation. Tracking patient outcomes would be essential to evaluating the utility of such projects. This might include reviewing records, tracking patient satisfaction, determining cost effectiveness, monitoring follow-up visits, and tracking medication usage and other indicators of wellness.

The VA funding mechanisms for translation of research results into practice will be initial studies through RFAs, followed by CSP development of multisite efficacy trials. WRIISC and QUERI mechanisms will be ultimately used for implementation studies.

6.0 CONCLUSIONS

The first "Working Plan" for Research on Persian Gulf War Veterans' Illnesses was published in 1995-1996 [83, 84]. Progress in medical and scientific research since this first Gulf War "Working Plan" was put forward include mapping the human genome, advances in medical imaging, and advances in medical informatics and electronic health information, to name but three technologies that were not available in 1995-96.

Examples of advances made by VA researchers have included: a survey of 30,000 Gulf War and Gulf War era veterans showing that 35% of Gulf War veterans suffer from multisymptom illness compared to 10% of veterans who did not deploy [40, 63]; imaging studies that have shown alterations in brain structure in Gulf War Veterans exposed to sarin/cyclosarin [12, 42]; and a pilot study demonstrating the efficacy of Continuous Positive Airway Pressure (CPAP) to partially relieve some symptoms of multisymptom Illness [2].

The leadership of VA Office of Research and Development and others who prepared this Strategic Plan for Gulf War Research, have recognized that these and other substantial advances have been made. Collectively, they suggest new and innovative approaches to future Gulf War research.

The overall goal of the *Gulf War Research Strategic Plan 2012-2016* is to improve the health and well-being of Gulf War Veterans and to utilize emerging knowledge to prevent similar war-related illnesses in the future.

Progress has been made in Gulf War Research, yet much work remains to be done to fully achieve effective treatment and prevention of multisymptom illness and similar conditions. This Plan has been formulated to accelerate this progress and to identify diagnostic biomarkers and effective treatments within the timeframe of the Plan. The *Gulf War Research Strategic Plan 2012-2016* will be reviewed annually by the Gulf War Steering Committee, the National Research Advisory Council, and the Research Advisory Committee on Gulf War Veterans' Illnesses, and updated as needed.

APPENDIX I. Major Activities Involved in Linking Multiple Datasets into a Usable Interactive Database

Based on the experience gained by developing the Pre-9/11 Report, the Post-9/11 Report and their supporting data system, SWAVETS, members of the VA Gulf War Integrated Project Team offer the following high-level overview of the major activities involved in linking multiple datasets and integrating data into a usable database. Not all of the activities listed below will be required for all linkage projects. Similarly, some linkage projects may require additional tasks not documented here. In considering the outlined activities, several points deserve emphasis:

- While much of the work in any data linkage project will focus on determining how data may be matched across multiple datasets, such projects must also incorporate all applicable requirements relative to information protection and information security.
- Successful linkage projects require up-front consideration of both information technology-related and administrative parameters.
- Efficient linkage projects typically require that multiple activities be conducted in parallel.

Information Protection

1. Develop a comprehension of Federal and organizational (agency-specific) requirements that results in the implementation of measures that meet or exceed privacy, information security and protection of human subject requirements.
2. Ensure compliance with all aspects of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), if applicable.
3. Verify compliance with Confidential Information Protection and Statistical Efficiency Act (CIPSEA) requirements, if applicable.

Information Security

1. Verify that an applicable Authorization to Operate (ATO) is in place for the information system(s) to be used in the data linkage project.
2. Ensure compliance with the certification and accreditation (C&A) requirements.
3. Check to make sure that the linkage project team has completed all agency-required training pertaining to information security and healthcare data utilization.
4. Ensure that project team members have undergone appropriate background checks, if applicable.
5. Double-check that all appropriate contracting requirements have been met, if applicable.
6. Ensure that inter-agency relationships are formalized through current memorandums of understanding (MOUs).
7. Ensure that protocols for data sharing and data transfer are current and in place through appropriate data agreements.
8. Work with the Information Security Officers to ensure that appropriate clearances have been obtained for data access and data sharing.

Information Technology

1. Define the operating environment for the data linkage project, including identification of both the development and the production servers and the platform (e.g., SQL, Oracle, etc.) that will be used.
2. Determine how the users will access or interface with the linked datasets (e.g., dashboards).
3. Verify that server capacities are adequate to support the linkage project.
4. Develop disaster recovery procedures in the event of a catastrophic event.

Administration

1. Establish the scope and objectives for the effort.
2. Identify the data to be used in the data linkage project.
3. Determine authoritative sources for all data to be used in the linkage project.
4. Develop standardized definitions for the study cohort and for all characteristics (variables) of interest for the study population.
5. Develop business rules and associated data requirements for selecting and retrieving data from the defined authoritative data sources.
6. Identify the data integrator for the linkage project. (Note that the data integrator may be an individual, a group of individuals, an organization or an agency.)
7. Develop a data dictionary, a user's manual and other documentation for the linkage project.
8. Determine requirements and procedures for user acceptance testing and user training.

Data Selection

1. Identify the datasets to be integrated.
2. For each data table, identify the variables of interest and develop a structure for that data table.
3. Create a master person-table (one record per individual; no duplicates). This master table defines the study cohort and serves as the centerpiece of the database.
4. Perform data checks to identify and remove duplicates, invalid records, etc., from the master person-table.

Data Linkage

1. Develop a structure for the linked datasets. Again, note that the master person-table serves as the center of this structure, and that supporting information is connected to this master person-table through selected characteristics. (See next bullet.)
2. Select appropriate identifier(s) to link the master person-table to other data tables. The selected identifier (e.g., social security number, scrambled social security number, etc.) or set of identifiers should be chosen in a way that results in the greatest number of accurate, usable records.
3. Define the desired sets of linked data tables that will be needed to support the project.
4. Develop multidimensional models, using the available data, to create data "cubes," in accordance with the project objectives.
5. Note that different identifiers may be used to support different linkages.

6. Note also that datasets are matched on a linking variable or set of variables. Data linkage does not involve appending datasets except, on occasion, during updates (see below).

Data Validation

1. Develop appropriate procedures for verifying and validating linked data.
2. Perform validation checks throughout the entire course of the linkage project.

Data Reporting and Analysis

1. Define the specific reports and analyses required to support the linkage project objectives.
2. Determine the format for the required reports and analyses.
3. Determine how the reports and analyses will be transmitted and shared with the project team.
4. Implement the reporting and analysis in accordance with the defined requirements.
5. If the linkage project includes an exploratory analysis component, determine who will conduct the analyses, how the data will be transferred to the analyst, and the platform on which the exploratory analyses will be conducted.

Training

1. Determine whether end users will require training to fully understand and utilize the linked data.
2. Determine how the training should be delivered.
3. Implement the training program in accordance with the defined requirements.

Updates and Maintenance

1. Determine how frequently the data will be updated.
2. Determine the mechanism for updating the linked datasets.
3. Determine whether the updated information will be delivered as a “write-over” of the original dataset(s), or whether new data will be appended to the existing data files.
4. Implement the updates in accordance with the defined requirements and schedule.

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APPENDIX III. List of Abbreviations

ACTH	Adrenocorticotropic Hormone
ALS	Amyotrophic Lateral Sclerosis
ATO	Authorization to Operate
BBB	Blood-Brain Barrier
BLRD	Biological Laboratory Research and Development
C&A	Certification and Accreditation
CAM	Complementary and Alternative Medicine
CBT	Cognitive Behavioral Therapy
CCEP	Comprehensive Clinical Evaluation Program
CDMRP	Congressionally Directed Medical Research Programs
CFS	Chronic Fatigue Syndrome
CIPSEA	Confidential Information Protection and Statistical Efficiency Act
CNS	Central Nervous System
CPAP	Continuous Positive Airway Pressure
CSF	Cerebrospinal Fluid
CSP	Cooperative Studies Program
CSRD	Clinical Sciences Research and Development
CTSA	Clinical and Translational Science Awards
DHWG	Deployment Health Working Group
DMDC	Defense Manpower Data Center
DoD	Department of Defense
DSI	Diffusion Spectral Imaging
DTI	Diffusion Tensor Imaging
DZ	Dizygotic
FDG	Fluorodeoxyglucose (F-18)
fMRI	functional Magnetic Resonance Imaging
GLUL	Glutamate-Ammonia Ligase
GW	Gulf War
GWAS	Genome-Wide Association Studies
GWIRP	Gulf War Illness Research Program
GWRSP	Gulf War Research Strategic Plan
GWSC	Gulf War Steering Committee
GWV	Gulf War Veteran
GWVI	Gulf War Veterans' Illnesses
GWVITF	Gulf War Veterans Illnesses Task Force
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HSRD	Health Services Research and Development
IBS	Irritable Bowel Syndrome
IOM	Institute of Medicine
KTO	Kuwait Theater of Operations
MEG	Magneto-Encephalography
MMUS	Multiple Medically Unexplained Symptoms

MOU	Memorandum of Understanding
MRI	Magnetic Resonance Imaging
MSI	Multisymptom Illness
MVP	Million Veteran Program
MZ	Monozygotic
NCVAS	National Center for Veterans Analysis and Statistics
NGS	Next Generation Sequencing
NIH	National Institutes of Health
OHI	Office of Health Information
OPH	Office of Public Health
ORD	Office of Research and Development
PCR	Polymerase Chain Reaction
PCS	Patient Care Services
PET	Positron Emission Tomography
PGIRCC	Persian Gulf Interagency Research Coordinating Council
PGVCB	Persian Gulf Veterans Coordinating Board
PHS	Public Health Service
PON1	Paraoxonase/arylesterase 1
PTSD	Post-Traumatic Stress Disorder
QUERI	Quality Enhancement Research Initiative
RACGWVI	Research Advisory Committee on Gulf War Veterans' Illnesses
RFA	Request For Application
RRD	Rehabilitative Research and Development
RWG	Research Working Group
SDB	Sleep Disordered Breathing
SWAVETS	Southwest Asia Veterans System
TSPO	Translocator Protein
UDX	Undiagnosed
USPIO	Ultra-Small Paramagnetic Iron Oxide
VA	Department of Veterans Affairs
VBA	Veterans Benefits Administration
VERA	Veterans Equitable Resource Allocation
VHA	Veterans Health Administration
VISN	Veterans Integrated Service Network
VSO	Veterans Service Organization
WRIISC	War Related Illness and Injury Study Center

DRAFT RECOMMENDATION, Research Advisory Committee on Gulf War Veterans Illnesses, June 19, 2012

The Institute of Medicine, the Secretary of Veterans Affairs, and the United States Congress want to find treatments for Gulf War illness, the chronic multisymptom disease that destroys the quality of life of 250,000 Gulf War veterans and threatens current and future troops subject to similar risks.

- The 2010 Institute of Medicine Gulf War and Health Report called for "a renewed research effort with substantial commitment to well-organized efforts to better identify and treat multisymptom illness in Gulf War veterans." (pp. 260-261)

  "Veterans who continue to suffer from these discouraging symptoms deserve the very best that modern science and medicine can offer . . . to speed the development of effective treatments, cures, and, it is hoped, preventions. . . [W]e believe that, through a concerted national effort and rigorous scientific input, answers can likely be found." (p. x)

- Secretary of Veterans Affairs Eric Shinseki declared on Feb. 27, 2010, "At VA, we advocate for Veterans – it is our overarching philosophy and, in time, it will become our culture."

  "This new approach is the first step in a still unfolding comprehensive plan of how VA will treat and compensate Veterans of the Gulf War era."

- In the Veterans Benefits Act of 2010, Congress directed VA to enter into an agreement with the Institute of Medicine "to carry out a comprehensive review of the best treatments for chronic multisymptom illness in Persian Gulf War veterans."

  "[U]nder [this] agreement, the Institute of Medicine shall convene a group of medical professionals who are experienced in treating individuals who served as members of the Armed Forces in the Southwest Asia Theater of Operations of the Persian Gulf War during 1990 or 1991 and who have been diagnosed with chronic multisymptom illness or another health condition related to chemical and environmental exposure that may have occurred during such service." (Public Law 111-275)

Some VA and Department of Defense staff members disagree. They say, "Not on my watch."

- They have cut the budget for VA Gulf War illnesses research by two-thirds for FY2013, from $15.0 to $4.86 million. This cut was never discussed with the Research Advisory Committee, which was established by the Congress to provide independent advice to the Secretary on proposed Gulf War health research plans. Of the $15.0 million budgeted and approved by the Secretary and Congress for FY2012, staff have spent $4.98 million. Appendix A.

- They have changed the Gulf War Illness Research Strategic Plan so that they are not obliged to spend even this $4.86 million on Gulf War illness research. They can spend it on any illness found in Gulf War veterans, however few. In addition to gutting the strategic plan financially, they have eliminated the urgency, commitment, focus, and follow-up called for by the IOM and the working groups of VA staff and outside advisors who wrote the original plan. The new draft of the plan is not effective and is not recommended as it currently stands. Appendix B.

- They have misrepresented to the Secretary of Veterans Affairs and to Congress the amount of research dollars being spent on Gulf War health, by including studies that have little or nothing to do with Gulf War veterans and by loading the Gulf War totals with the entire amount of studies that address problems common to veterans of all eras, although Gulf War veterans constitute a tiny fraction of these veterans. Appendix C.

- They have transformed the new Institute of Medicine treatment study into a literature review by an inexpert committee that has been indoctrinated to believe that Gulf War illness is, or may be, psychiatric, when science has conclusively shown it is not, including the IOM's own 2010 report. The obvious purpose is to manipulate the new IOM committee into reaching a conclusion that reverses the 2010 report and misdirects future treatment and research. This result is the exact opposite from the intent of Congress in ordering the report. Appendix D.

- They have refused to initiate the IOM survey ordered by Congress to determine the rate of multiple sclerosis in Gulf War veterans. Appendix E.

- They have commissioned a mammoth survey of Gulf War era veterans that omits the questions necessary to identify multisymptom illness and includes excessive questions on stress and anxiety. Such an approach is designed to produce psychiatric findings, while minimizing multisymptom illness, the signature health problem of the 1990-91 war. In research, the answers you get depend on the questions you ask. Appendix F.

These actions repeat the pattern of the last twenty years, as has been has been well documented in Congressional reports. E.g., "Gulf War Veterans Illnesses: VA, DOD Continue To Resist Strong Evidence Linking Toxic Causes To Chronic Health Effects," Nov. 1997. Appendix G.

Today, these actions must be recognized for what they are. Reversing the recommendation of the Institute of Medicine is bad science. Undermining the policy of the Secretary of Veterans Affairs is insubordination. Twisting the intent of Congress is law breaking. Misrepresenting information to the Secretary and to Congress is lying.

They have said, "Not on my watch." So be it.

The Research Advisory Committee has no confidence in the ability or desire of VA staff to formulate and execute an effective VA Gulf War illness research program. Staff particularly includes the Office of Research and Development, the Office of Public Health, and Department of Defense personnel from the Office of Force Health Protection and Readiness who interface with them. Some staff members are well-intentioned, but they are not the ones calling the shots.

The Committee recommends that the obstructive actions outlined above be thoroughly investigated to identify the individuals responsible and that appropriate actions be taken to remove them from positions of authority and influence over Gulf War illness research. Until this occurs, the prospect of meaningful progress is illusory.

Appendix A

Research and Development Program Funding
(dollars in thousands)

Description	2011 Actual	2012 Budget Estimate	2012 Current Estimate	2013 Request	2012-2013 Inc/Dec
OEF/OIF/OND					
Pain	$11,961	$10,531	$11,961	$13,961	$2,000
Post deployment Mental Health	$41,143	$39,203	$41,143	$46,043	$4,900
Sensory Loss	$23,731	$23,076	$23,731	$23,166	($565)
Spinal Cord Injury	$30,204	$32,870	$30,204	$29,486	($718)
Traumatic Brain Injury and Other Neurotrauma	$21,464	$18,528	$24,464	$28,564	$4,100
Prosthetics	$17,393	$11,674	$17,393	$17,393	$0
Women's Health	$10,654	$11,935	$11,935	$11,935	$0
Gulf War Veterans Illness	$4,980	$15,013	$4,980	$4,862	($118)

http://www.va.gov/budget/docs/summary/Fy2013_Volume_II-Medical_Programs_Information_Technology.pdf (p. 3A-5)

The official VA budget for FY2013 cuts Gulf War illness research two-thirds from $15 million in the FY12 budget to $4.9 million for FY13. VA's budget presentation (above) attempts to minimize this cut by comparing the FY13 budget to the amount actually spent in FY12, $4,980,000. Far from excusing the cut, this means that staff also cut Gulf War illness research spending in FY12 by two-thirds compared to what Congress and the Secretary approved.

The massive FY13 cut was never revealed to the Research Advisory Committee on Gulf War Veterans Illnesses prior to being implemented, contrary to the statute that created the Committee, which states that the purpose of the Committee is "to provide advice to the [Secretary of Veterans Affairs] on proposed research studies, research plans, or research strategies relating to the health consequences of military service in the Southwest Asia theater of operations during the Persian Gulf War." Public Law 105-368.

VA staff attempts to explain the cut on the grounds that VA researchers are not interested in Gulf War illness research. However, VA researchers account for approximately one-half of the projects funded by the DoD CDMRP Gulf War illness research program, often the same projects rejected by VA. And VA's Office of Research and Development frequently designs top-down research projects on

subjects of interest to them, but have consistently underfunded those projects relating to Gulf War illness or diverted them to other purposes.

Appendix B

The Gulf War Research Strategic Plan was prepared over a five month period in late 2011 and early 2012 by eight working groups made up of VA staff members and outside advisors from the Research Advisory Committee on Gulf War Veterans Illnesses, the Gulf War Steering Committee, and the National Research Advisory Committee. It was structured as a response to the challenge posed by the 2010 Institute of Medicine Gulf War and Health report. The following language from that report was included in the Executive Summary and the Background sections of the Strategic Plan.

The IOM report concluded with a call for "a renewed research effort with substantial commitment to well-organized efforts to better identify and treat multisymptom illness in Gulf War veterans . . . to alleviate their suffering as rapidly and completely as possible." [41]

In the preface to the report, the chairman of the IOM committee, Dr. Stephen Hauser, a former president of the American Neurological Association, emphasized the need "to speed the development of effective treatments, cures, and, it is hoped, preventions." He stressed that the committee regarded this goal as achievable: "We believe that, through a concerted national effort and rigorous scientific input, answers can likely be found." [41]

These quotations from the IOM report were deleted by VA staff unilaterally during the past four months. It is inexplicable why anyone want to delete the Institute of Medicine's call to action and belief that with rigorous research treatments can be found – especially if the goal is to encourage researchers to become involved in this work.

In place of the IOM language, the following text has been inserted.

VA is committed to studying and treating chronic multisymptom illness and any other conditions affecting Gulf War Veterans. No Veteran should feel that his/her particular ailment is less important to VA than any other.

The hard message underlying this pious statement is that even the $4.9 million remaining in the Gulf War illness research budget will not be spent on Gulf War illness. It can be spent wherever VA chooses. As Appendix C demonstrates, this means continuing to do what VA has been doing.

Other major unilateral changes to the Strategic Plan are summarized on the following pages.

Appendix C

VA staff prepared the following reports on VA Gulf War research spending for FY09, FY10, and FY11. These reports form the basis for Gulf War research totals reported to the Secretary and to Congress in the Annual Report to Congress on Federally Sponsored Research on Gulf War Veterans Illnesses, which is mandated by statute (Section 707 of Public Law 102-585, as amended by section 104 of Public Law 105-368 and section 502 of Public Law 111-163).

As described in the attached analyses by Research Advisory Committee staff, the reports consistently misrepresent as Gulf War research expenditures that have little or nothing to do with Gulf War veterans. For example, the FY09 report includes $5.6 million for a project identified as the "VA Gulf War Biorepository Trust." In fact, this project is an ALS brain bank, which at last report included only "four or five" Gulf War brain samples out of eighty-eight total. Another example is the $5.5 million expenditure listed on the FY10 report, representing part of the purchase of a 7-Tesla MRI scanner, although the recipient of the scanner submitted no study protocol or grant submission identifying any Gulf War-related use of this equipment.

The reports have further inflated the totals by including 100% of research involving illnesses such as ALS. While ALS is disproportionately found in Gulf War veterans, it affects less than one hundred veterans, who constitute only a tiny fraction of US veterans with ALS. Attributing all ALS research as Gulf War research vastly overstates the amount of federal Gulf War research.

Only a small part of the studies reported relate to Gulf War illness, the chronic multisymptom disease that is the signature health problem of this war – affecting an estimated 250,000 Gulf War veterans. A review of the statutes mandating the Annual Report to Congress makes clear that this illness was the focus of Congress in enacting this legislation. The numbers reported by VA dramatically overstate VA research devoted to this problem.

Appendix D

In the Veterans Benefits Act of 2010, Congress directed VA to enter into an agreement with the Institute of Medicine "to carry out a comprehensive review of the best treatments for chronic multisymptom illness in Persian Gulf War veterans and an evaluation of how such treatment approaches could best be disseminated throughout the Department of Veterans Affairs to improve the care and benefits provided to veterans."[i]

This law is being deliberately executed contrary to the intent of Congress to revive the discredited theory advanced by government officials in the past that this illness is psychiatric. If allowed to proceed, this action will produce exactly the opposite result from what Congress desired. The progress that has been made since the 2010 IOM Gulf War and Health report will be reversed, and VA doctors will be directed to prescribe the wrong medications and to conduct the wrong research.

The law provided that "under [the] agreement, the Institute of Medicine shall convene a group of medical professionals who are experienced in treating individuals who served as members of the Armed Forces in the Southwest Asia Theater of Operations of the Persian Gulf War during 1990 or 1991 and who have been diagnosed with chronic multisymptom illness or another health condition related to chemical and environmental exposure that may have occurred during such service."

In December 2011, the IOM convened a committee to carry out this law.[ii] However, this committee is not made up of medical professionals experienced in treating Gulf War veterans with this condition. Rather, it is made up of individuals with no expertise in treating ill Gulf War veterans.

As Congress is aware, the IOM, when asked to review a subject, will typically appoint a committee of doctors and scientists who are trained in the general area but who have no direct expertise in the specific subject to be reviewed. The purpose is to ensure a fresh, impartial review of the scientific literature.

In this case, however, Congress required a different process. Congress knew that there are no effective treatments for these veterans to be found in the scientific literature. As the 2008 Research Advisory Committee report concluded, "No effective treatments have been identified for Gulf War illness."[iii] Thus, in addition to funding new research, Congress sought to do its part by directing the IOM to convene a group of doctors who actually treat patients "diagnosed with chronic multisymptom illness or another health condition related to chemical and environmental exposure," to see what their experience might show that the medical literature did not. By agreeing to appoint a committee

with no expertise in this topic instead, VA staff and the IOM have ignored the direction of Congress and ensured that the review will be a waste of time and money.

Far worse, committee members have been indoctrinated with the false idea that Gulf War multisymptom illness is psychiatric. At the February 29, 2012 meeting of the committee, five of the eight speakers chosen for the agenda delivered that message,[iv] despite the fact that all comprehensive reviews of the scientific literature plainly state that exactly the opposite is true, including the IOM's own recent review.

- "The excess of unexplained symptoms reported by deployed Gulf War veterans cannot be reliably ascribed to any known psychiatric disorder." 2010 Institute of Medicine report.[v]
- "Studies indicate that the large majority of Gulf War veterans with chronic multisymptom illness do not have psychiatric disorders." 2008 RAC report[vi]
- "A substantial proportion of Gulf War veterans are ill with multisymptom conditions not explained by wartime stress or psychiatric illness." 2004 RAC report[vii]

Something is seriously wrong here. Most of the speakers are representing a view that has been refuted by the scientific literature. It is not hard to see what is happening, because it has happened before. Many government officials have historically sought to characterize the health problems of Gulf War veterans as psychiatric. If the new IOM committee can be fooled into reporting on psychiatric treatments, it will revive that discredited theory.

The government's historical position that the illness was psychiatric has never been constrained by contrary facts. This phenomenon has been well documented in Congressional reports. E.g., "Gulf War Veterans Illnesses: VA, DOD Continue To Resist Strong Evidence Linking Toxic Causes To Chronic Health Effects," Nov., 1997. http://www.gpo.gov/fdsys/pkg/CRPT-105hrpt388/pdf/CRPT-105hrpt388.pdf

As a result, ill Gulf War veterans were routinely dismissed as malingerers or medicated with psychiatric drugs that did not improve and often exacerbated their condition. In addition, tens of millions of dollars were spent on research based on the premise that the illness was psychiatric. For example, fifty-seven percent of VA's 2003 Gulf War research expenditures were directed at studies of psychological factors and stress. 2008 RAC report, pp. 293-294.

As science has progressed, new VA leadership has sought to change these practices. The Secretary of Veterans Affairs determined in 2004 that VA would no longer fund Gulf War illness research based on the stress hypothesis. http://www.veteransadvantage.com/cms/content/va-will-no-longer-fund-gulf-war-illness-studies The current Secretary of Veterans Affairs has made Gulf War health issues a priority and initiated numerous reforms to align VA activities with current science.

However, bureaucrats remain in place as administrations come and go, and important segments of the government have continued to suggest that the illness is psychiatric long after science resolved that it is not. Regrettably, past government efforts to minimize and mischaracterize the health problems of Gulf War veterans have extended to influencing and misusing IOM reports. These activities have been the subject of two Congressional hearings in 2004 and 2009, and are discussed in the 2008 RAC report, pp. 53-55, and in the following memorandum.
http://www.gulfwarvets.com/cgi-bin/ultimatebb.cgi?ubb=get_topic;f=1;t=000670;p=0

For example, one innocuous conclusion of a 2006 IOM committee was that there was "no unique syndrome" in Gulf War veterans. In fact, whether these health problems were unique, or whether they technically constituted a syndrome, were questions of minor consequence. The veterans were unquestionably ill. But for four years government officials spun the phrase into media stories, Congressional testimony, and advice to veterans and their doctors that there was no evidence of any special health problem in Gulf War veterans. See, eg, "Study: Gulf War syndrome doesn't exist," Associated Press, Sep. 13, 2006.
http://www.msnbc.msn.com/id/14801666/ns/health-health_care/t/study-gulf-war-syndrome-doesnt-exist/#.T5lZcXMW9os

No topic in Gulf War health research has been more thoroughly studied than psychiatric illness. That is how we know with certainty that psychiatric illness is actually much lower in Gulf War veterans than in veterans of other wars (not surprising in view of the short duration of the war) and that it does not explain the widespread chronic multisymptom illness in this population. 2008 RAC report, pp. 61-74.

In a letter to three veterans who protested the February 29 agenda, IOM President Dr. Harvey Fineberg stated that "the committee members themselves decide on the presentation topics and speakers." However, it is not plausible that a committee made up of people new to a topic would request the names of individual speakers, particularly five speakers on psychiatric messages when the literature says the problem isn't psychiatric. The names of the specific speakers must have originated with IOM staff and government bureaucrats.[viii]

The letter further stated that the IOM committee is tasked with "summarizing the available scientific and medical literature regarding the best treatments for chronic multisymptom illness among Gulf War veterans." As noted above, this is not what Congress, with good reason, ordered.

The consequences of these changes from what Congress ordered are fundamental. If the new IOM committee proceeds to review treatments for psychiatric disorders, notwithstanding the fact that Gulf War multisymptom illness is not psychiatric, the review will most certainly not improve veterans' care. To the contrary, the eventual report will counsel physicians to treat Gulf War veterans with multisymptom illness as

psychiatric patients, re-establishing the erroneous and often harmful practices that prevailed in the past. Research will also be misdirected toward psychiatric mechanisms, as in the past.

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[i] Veterans' Benefits Act of 2010, Sec. 805, Public Law 111-275, http://www7.nationalacademies.org/ocga/laws/PL111_275.asp

[ii] http://www.iom.edu/Activities/Veterans/GulfWarMultisymptom/2012-FEB-29.aspx

[iii] 2008 Report of the Research Advisory Committee on Gulf War Veterans Illnesses, November 2008, p. 1. http://www.national-toxic-encephalopathy-foundation.org/gwsreport.pdf

[iv] http://iom.edu/Activities/Veterans/GulfWarMultisymptom/2012-FEB-29.aspx ("presentations")
Clauw, slide 7: "Overlap Between Multisymptom Illness and Psychiatric Disorders");
Dusik, title: "Chronic Stress and Its Role in Emotional, Somatic, and Cognitive Symptoms";
Engel, slide 8 titled in red "Gulf War Veterans Illnesses: Proposed Etiologies", concluding in red with "stress, PTSD, or somatization";
Kendler, title" "Vulnerability, Stress Exposure and Depression: Mediation and Moderation");
Kroenke, slide 10, continuum from "Medical" symptoms to "Psychiatric"; and slide 11 "SAD Triad, somatization/anxiety/depression".

[v] 2010 Institute of Medicine Gulf War and Health report, p. 109

[vi] 2008 Research Advisory Committee on Gulf War Veterans Illnesses report, p. 73

[vii] 2004 Research Advisory Committee on Gulf War Veterans Illnesses report, p. 21 http://www.va.gov/RAC-GWVI/docs/Committee_Documents/ReportandRecommendations_ScientificProgressinUnderstandingGWVI_2004.pdf

[viii] In response to the veterans' letter, IOM staff invited Dr. Golomb to speak at a subsequent meeting on March 11, but followed her with another speaker, Dr. Hunt, who presented the position that science doesn't know whether the illness is psychiatric or physical. IOM staff has now invited a total of six speakers to present a view that the 2010 IOM report determined to be invalid. http://www.iom.edu/Activities/Veterans/GulfWarMultisymptom/2012-APR-12.aspx ("presentations")
Hunt, slides 6, 7 showing doctors' opinions evenly divided as to whether the illness is "mostly a physical disorder" or "mostly a mental disorder" (from an eleven-year-old paper by Dr. Hunt and Dr. Engel, one of the Feb. 29 speakers).

Appendix E

The following exchange of emails demonstrates that VA has never executed Congress's 2008 order to contract with the Institute of Medicine to conduct a comprehensive epidemiological study to determine the risk of multiple sclerosis in Gulf War veterans.

The 2010 IOM study referred to below was not a study to determine Gulf War veterans' risk of having multiple sclerosis. Rather, it was a literature review, which found nothing in the literature because there has been no epidemiological study as required by Congress.

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On Tue, Mar 27, 2012 at 7:05 AM, MFUA <MFUA@nas.edu> wrote:
Anthony-
In response to your question: VA has not to date entered into a specific contract with NAS/IOM to perform the epidemiologic study described in Section 804 of PL 110-389.
David.

From: ANTHONY HARDIE [mailto:anthony.d.hardie@gmail.com] Sent: Saturday, March 24, 2012 2:50 AM To: MFUA Cc: Jim Binns; Lea Steele; Roberta White; Kimberly A. Sullivan Subject: Re: Status of MS IOM Study

Dr. Butler,
Thank you very much for the information.

Could you further advise whether VA ever entered into a specific contract with NAS/IOM on this issue, as specified in the first lines of Section 804 of PL 110-389?

Thank you again.

Anthony

Anthony Hardie
Madison, Wis.
Email: anthony.d.hardie@gmail.com

On Thu, Mar 22, 2012 at 6:24 AM, MFUA <MFUA@nas.edu> wrote:
Mr. Hardie-

The Institute of Medicine conducted a review of the scientific literature regarding multiple sclerosis and Gulf War-era veterans as part of the effort that resulted in the report Gulf War and Health Volume 8 – Update of Health Effects of Serving in the Gulf War. This report was published in 2010 and may be read and downloaded without cost from links available at the following website:
http://www.nap.edu/catalog.php?record_id=12835
MS was addressed on pages 124-126.

No additional funding has been provided to the National Academies to perform the epidemiologic study described in Section 804 of PL 110-389.

David A. Butler, PhD
Scholar | Director, Medical Follow-up Agency
National Academy of Sciences, Institute of Medicine

From: ANTHONY HARDIE [mailto:anthony.d.hardie@gmail.com] Sent: Sunday, March 18, 2012 3:58 AM To: Butler, David Cc: Jim Binns; Lea Steele; Roberta White; Kimberly A. Sullivan Subject: Status of MS IOM Study

Dear Mr. Butler,

I understand that you are the IOM staff contact for the following:

Multiple Sclerosis (MS) in Vietnam and Gulf War-era Veterans,
Study Director: David Butler, 334-2524 (Keck 872); Chair:
N/

Could you please tell me whether this review, above, is one and the same as the review mandated by law in PL 110-389 on Oct. 10, 2008 (full text below my signature block), "to conduct a comprehensive epidemiological study for purposes of identifying any increased risk of developing multiple sclerosis as a result of service in the Armed Forces during the Persian Gulf War in the Southwest Asia theater of operations or in the Post 9/11 Global Operations theaters"?

If so, can you please tell me how can I obtain any interim reports, as described in the text of the law, below? And, I note that the final report is due Dec. 31, 2012; when do you expect the final report to be released to the public?

Thank you in advance for any information you may be able to provide.

Anthony

Anthony Hardie
Madison, Wis.
Email: anthony.d.hardie@gmail.com
Cell: (608) 239-4658

****
PL 110-389, October 10, 2008.

SEC. 804. NATIONAL ACADEMIES STUDY ON RISK OF DEVELOPING MULTIPLE SCLEROSIS AS A RESULT OF CERTAIN SERVICE IN THE PERSIAN GULF WAR AND POST 9/11 GLOBAL OPERATIONS THEATERS.

(a) IN GENERAL.—The Secretary of Veterans Affairs shall enter into a contract with the Institute of Medicine of the National Academies to conduct a comprehensive epidemiological study for purposes of identifying any increased risk of developing multiple sclerosis as a result of service in the Armed Forces during the Persian Gulf War in the Southwest Asia theater of operations or in the Post 9/11 Global Operations theaters.

(b) ELEMENTS.—In conducting the study required under subsection (a), the Institute of Medicine shall do the following:
(1) Determine whether service in the Armed Forces during the Persian Gulf War in the Southwest Asia theater of operations, or in the Post 9/11 Global Operations theaters, increased the risk of developing multiple sclerosis.
(2) Identify the incidence and prevalence of diagnosed neurological diseases, including multiple sclerosis, Parkinson's disease, and brain cancers, as well as central nervous system abnormalities that are difficult to precisely diagnose, in each group as follows:
(A) Members of the Armed Forces who served during the Persian Gulf War in the Southwest Asia theater of operations.
(B) Members of the Armed Forces who served in the Post 9/11 Global Operations theaters.
(C) A non-deployed comparison group for those who served in the Persian Gulf War in the Southwest Asia theater of operations and the Post 9/11 Global Operations theaters.
(3) Compare the incidence and prevalence of the named diagnosed neurological diseases and undiagnosed central

nervous system abnormalities among veterans who served during the Persian Gulf War in the Southwest Asia theater of operations, or in the Post 9/11 Global Operations theaters, in various locations during such periods, as determined by the Institute of Medicine.
(4) Collect information on risk factors, such as pesticide and other toxic exposures, to which veterans were exposed while serving during the Persian Gulf War in the Southwest Asia theater of operations or the Post 9/11 Global Operations theaters, or thereafter.

(c) REPORTS.—
(1) INTERIM REPORT.—The contract required by subsection (a) shall require the Institute of Medicine to submit to the Secretary, and to appropriate committees of Congress, interim progress reports on the study required under subsection (a). Such reports shall not be required to include a description of interim results on the work under the study.
(2) FINAL REPORT.—The contract shall require the Institute of Medicine to submit to the Secretary, and to appropriate committees of Congress, a final report on the study by not later than December 31, 2012. The final report shall include such recommendations for legislative or administrative action as the Institute considers appropriate in light of the results of the study.

(d) FUNDING.—The Secretary shall provide the Institute of Medicine with such funds as are necessary to ensure the timely completion of the study required under subsection (a).
(e) DEFINITIONS.—In this section:
(1) The term ''appropriate committees of Congress'' means—
(A) the Committee on Veterans' Affairs of the Senate; and
(B) the Committee on Veterans' Affairs of the House of Representatives.
(2) The term ''Persian Gulf War'' has the meaning given that term in section 101(33) of title 38, United States Code.
(3) The term ''Post 9/11 Global Operations theaters'' means Afghanistan, Iraq, or any other theater in which the Global War on Terrorism Expeditionary Medal is awarded for service.

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Appendix F

Appendix G

Gulf War Veterans Illnesses: VA, DOD Continue To Resist Strong Evidence Linking Toxic Causes To Chronic Health Effects," U.S. House of Representatives, Committee on Government Reform and Oversight, Nov., 1997.
http://www.gpo.gov/fdsys/pkg/CRPT-105hrpt388/pdf/CRPT-105hrpt388.pdf

Projected FY2011 ORD Support for Ongoing Gulf War Research Projects

FullName	VAMC	Title	Focus	Total FY 2011*	Start Date	End Date
Clinical Trials				$ 472,817		
Lin, Henry C. (M.D.)	Albuquerque, NM	Bacterial Overgrowth Associated with Chronic Mult-Symptom Illness Complex	Treatment of GW veterans with gastrointestinal symptoms	$ 168,600	10/01/08	09/30/11
Sanders, Kathryn (Ph.D.)	West Haven, CT	Testing the Feasibility of MC CBT for Veterans with IBS	Treatment of Irritable Bowel Syndrome (IBS)	$ 93,153	07/01/10	09/30/11
Cook, Dane B. (Ph.D.)	East Orange, NJ	Impact of Exercise Training on pain and Brain Function in Gulf War veterans	Treatment of pain in GW veterans with resistance exercise training	$ 104,167	10/01/10	09/30/15
Kearney, David J (M.D.)	Seattle, WA	A randomized controlled trial of a mindfulness based intervention for Gulf War Syndrome	Treatment of attention, concentration, and working memory with mindfulness training	$ 106,898	10/01/10	09/30/12
Biomarkers				$ 1,683,571		
Fiore, Louis D. (MD)	Boston, MA	CSP #501 - VA Gulf War Biorepository Trust	Gulf War Brain and DNA Bank for ALS	$ 938,151	08/01/02	09/30/12
Kowall, Neil (M.D) McKee, Ann (M.D.) Renner, Stephen (M.D.)	Boston, MA	CSP #501B - VA Gulf War Biorepository Trust	Gulf War Tissue Repository and DNA Bank - full autopsy collection of tissues	$ 237,878	10/01/10	09/30/12
Oddone, Eugene Z. (M.D.)	Durham, NC	Genetic Epidemiology of ALS Veterans	Identify genes that may confer susceptibility to the development of ALS and examine the interplay between environmental exposures and genetic susceptibility to ALS	$ 242,775	07/01/08	09/30/12
Provenzale, Dawn	Durham, NC	CSP #585 – Gulf War Era Cohort and Blood Biorepository	Recruit new National Cohort of GW Veterans (VHA and non-VHA users) and collect blodd and survey data.	$ 5,110	04/01/10	09/30/13
Cook, Dane B. (Ph.D.)	East Orange, NJ	Imaging of Pain Modulation in Veterans with Unexplained Muscle Pain	Functional imaging of Gulf War veterans with unexplained musculoskeletal pain	$ 259,657	10/01/08	09/30/12
Gulf War Veterans Illnesses				$ 372,422		
Li, Mian (M.D., Ph.D.)	Washington, DC	Autonomic Functions of Gulf War Veterans with Unexplained Illnesses	Autonomic dysfunction as an underlying cause of unexplained symptoms in GW veterans	$ 72,667	09/30/06	06/30/11
Li, Mian (M.D., Ph.D.)	Washington, DC	Motor Neuron Function of Gulf War Veterans with Excessive Fatigue	Loss or damage of motor nerve cells in GW veterans with muscle and joint pain, muscle spasm, or fatigue	$ 25,712	09/30/06	12/31/10
Bach, Ronald R. (Ph.D.)	Minneapolis, MN	Tissue Factor and Gulf War-Associated Chronic Coagulopathies Gulf War-Associated Chronic Coagulopathies: Tissue Factor, Coagulation, and Immune System Activation	Impaired blood flow and circulation as a cause of cognitive difficulties, somatic pain, fatigue	$ 161,644	04/01/06	09/30/11
Verne, G. Nicholas	Cincinnati, OH	Somatic hypersensitivity in Veterans with IBS	Evaluation of altered central pain processing in IBS	$ 112,400	04/01/09	03/21/12

* Includes 12.4% administrative overhead *

Projected FY2011 ORD Support for Ongoing Gulf War Research Projects

FullName	VAMC	Title	Focus	Total FY 2011*	Start Date	End Date
Model Systems of GW Exposures/Illnesses				$ 3,198,141		
Greenwood, Beverley (Ph.D., FACG.)	Oklahoma City, OK	Central Mechanisms Modulatying Visceral Sensitivity	Central nervous system control of gastrointestinal pain (IBS)	$ 269,714	10/01/08	09/30/12
Turner, Eric E.	San Diego, CA	Transcription factors regulating sensory gene expression and pain pathways	Regulation of central pain	$ 168,600	04/01/09	03/31/13
Vandenbark, Arthur A.	Portland, OR	Immunoregulation of Myelin Specific T Lymphocytes	New treatment for MS	$ 365,944	01/01/09	12/31/12
Bedlack, Richard	Durham, NC	CSP #567 A Clinical Demonstration of an EEG Brain-Computer Interface for ALS Patients	New treatment for ALS	$ 741,771	10/01/08	01/01/12
Hinrichs, David	Portland, OR	Multiple Antigenic Peptides to Alter the Course of Autoimmune Disease	New treatment for MS	$ 388,973	04/01/10	03/31/14
Bourdette, Dennis N.	Portland, OR	Lipoic Acid Therapy for Experimental Autoimmune Encephalomyelitis	New treatment for MS	$ 168,600	10/01/09	09/30/13
Singh, Inderjit	Charleston, SC	Neuroprotection and Myelin Repair Mechanisms in Multiple Sclerosis	New treatment for MS	$ 159,945	10/01/10	09/30/14
Shiromani, Priyattam J.	Charleston, SC	Sleep Neurobiology and Circuitry	Control of sleep	$ 378,896	10/01/10	09/30/14
Kowall, Neil W.	Boston, MA	Epigenetic mechanisms relevant to the pathogenesis of ALS	Genetic mechanisms underlying ALS	$ 182,650	01/01/11	12/31/14
Schlosser, Rodney J.	Charleston, SC	Nanoparticle Coupled Antioxidants for Respiratory Illness in Veterans	Nanoparticle (sand) derived respiratory illness	$ 140,500	04/01/11	03/31/15
Greenwood, Beverley (Ph.D., FACG.)	Oklahoma City, OK	Understanding Pain of Gastrointestinal Origin in Women that Serve in OEF/OIF	Central nervous system control of gastrointestinal pain (IBS)	$ 84,300	04/01/11	03/31/15
Shetty, Ashok (Ph.D.)	Durham, NC	Memory and Mood Enhancing Therapies for Gulf War Illness	Development of new therapy for ill Gulf War Veterans	$ 148,248	07/01/11	06/30/15

$ 5,726,951

Total Anticipated for ORD in FY 2011

* Includes 12.4% administrative overhead *

Projected FY2010 ORD Support for Ongoing Gulf War Research Projects

FullName	VAMC	Title	Focus	Total FY 2010*	Start Date	End Date
Clinical Trials				$ 291,175		
Tuteja, Ashok K. (M.D., M.P.H.)	Salt Lake City, UT	Diarrhea-Predominant Irritable Bowel Syndrome in Persian Gulf Veterans	Treatment of GW veterans with gastrointestinal symptoms	$ 104,982	01/01/06	12/31/09
Lin, Henry C. (M.D.)	Albuquerque, NM	Bacterial Overgrowth Associated with Chronic Mult-Symptom Illness Complex	Treatment of GW veterans with gastrointestinal symptoms	$ 168,600	10/01/08	09/30/11
Sanders, Kathryn (Ph.D.)	West Haven, CT	Testing the Feasibility of MC CBT for Veterans with IBS	Treatment of Irritable Bowel Syndrome (IBS)	$ 17,593	07/01/10	09/30/11
Biomarkers				$ 6,389,115		
Fiore, Louis D. (MD)	Boston, MA	CSP #501 - VA Gulf War Biorepository Trust	Gulf War Brain and DNA Bank	$ 586,413	08/01/02	09/30/08
Klimas, Nancy G. (M.D.)	Miami, FL	Immunologic Mechanisms and Biomarkers in Gulf War Illness	Immune dysfunction as a mediator of persistent illness in both CFS and ill GW veterans	$ 56,200	04/01/06	03/31/10
Oddone, Eugene Z. (M.D.)	Durham, NC	Genetic Epidemiology of ALS Veterans	Identify genes that may confer susceptibility to the development of ALS and examine the interplay between environmental exposures and genetic susceptibility to ALS	$ 353,309	07/01/08	09/30/12
Cook, Dane B. (Ph.D.)	East Orange, NJ	Imaging of Pain in Veterans with Unexplained Muscle Pain	Functional imaging of Gulf War veterans with unexplained musculoskeletal pain	$ 258,076	10/01/08	09/30/12
Weiner, Michael W. (M.D.)	San Francisco, CA	Effects of Gulf War Illness on Brain Structure, Function and Metabolism: MRI/MRS at 4 Tesla	Magnetic Resonance Imaging (MRI) and Spectroscopy (MRS) of Gulf War veterans	$ 5,135,117	01/01/05	12/31/09
Gulf War Veterans Illnesses				$ 625,148		
Li, Mian (M.D., Ph.D.)	Washington, DC	Autonomic Functions of Gulf War Veterans with Unexplained Illnesses	Autonomic dysfunction as an underlying cause of unexplained symptoms in GW veterans	$ 101,863	09/30/06	12/31/08
Li, Mian (M.D., Ph.D.)	Washington, DC	Motor Neuron Function of Gulf War Veterans with Excessive Fatigue	Loss or damage of motor nerve cells in GW veterans with muscle and joint pain, muscle spasm, or fatigue	$ 103,549	09/30/06	12/31/08
Bach, Ronald R. (Ph.D.)	Minneapolis, MN	Tissue Factor and Gulf War-Associated Chronic Coagulopathies Gulf War-Associated Chronic Coagulopathies: Tissue Factor, Coagulation, and Immune System Activation	Impaired blood flow and circulation as a cause of cognitive difficulties, somatic pain, fatigue	$ 158,089	04/01/06	09/30/11
Mitchell T. Wallin (M.D., M.P.H.)	Washington, DC	Multiple Sclerosis in Gulf War Veterans	Evaluation of the risk of developing MS in GW veterans	$ 120,886	10/01/07	09/30/10
Verne, G. Nicholas	Cincinnati, OH	Somatic hypersensitivity in Veterans with IBS	Evaluation of altered central pain processing in IBS	$ 112,400	04/01/09	03/21/12
Provenzale, Dawn	Durham, NC	CSP #585 – Gulf War Era Cohort and Blood Biorepository	Recruit new National Cohort of GW Veterans (VHA and non-VHA users) and collect blodd and survey data.	$ 28,361	04/01/10	09/30/13

* Includes 12.4% administrative overhead *

Projected FY2010 ORD Support for Ongoing Gulf War Research Projects

FullName	VAMC	Title	Focus	Total FY 2010*	Start Date	End Date
Model Systems of GW Exposures/Illnesses				$4,094,030		
Greenwood, Beverley (Ph.D., FACG.)	Oklahoma City, OK	Central Mechanisms Modulatying Visceral Sensitivity	Central nervous system control of gastrointestinal pain	$267,687	10/01/08	09/30/12
Turner, Eric E.	San Diego, CA	Transcription factors regulating sensory gene expression and pain pathways	Regulation of central pain	$168,600	04/01/09	03/31/13
Shetty, Ashok (Ph.D.)	Durham, NC	Behavior of Neural Stem Cells in a Rat Model of GWS	Effects of pyridostigmine bromide, DEET, and permethrin	$ 136,900	04/01/07	03/31/10
Panter, Scott (Ph.D.)	San Francisco, CA	Direct Delivery of Neurotoxins to the Brain by an Intranasal Route	Effects of pyridostigmine bromide, DEET, and permethrin	$ 67,752	01/01/06	12/31/09
Vandenbark, Arthur A.	Portland, OR	Immunoregulation of Myelin Specific T Lymphocytes	New treatment for MS	$ 361,972	01/01/09	12/31/12
Bedlack, Richard	Durham, NC	CSP #567 A Clinical Demonstration of an EEG Brain-Computer Interface for ALS Patients	New treatment for ALS	$ 2,368,460	10/01/08	01/01/12
Hinrichs, David	Portland, OR	Multiple Antigenic Peptides to Alter the Course of Autoimmune Disease	New treatment for MS	$ 332,743	04/01/10	03/31/14
Bourdette, Dennis N.	Portland, OR	Lipoic Acid Therapy for Experimental Autoimmune Encephalomyelitis	New treatment for MS	$224,126	10/01/09	09/30/13
Elmets, Craig A.	Birmingham, AL	Bacterial Host Defense Mechnaisms in Polyaromatic Hydrocarbon Carcinogenesis	Effects of oil well fire smoke on carcinogenesis	$ 165,790	01/01/06	09/30/10
				$ 11,399,468		
				Total Anticipated for ORD in FY 2010		
UTSW Medical Center	Dallas, TX	Gulf War Veterans Illnesses' Research IDIQ Contract	Close-out costs for previously approved task orders and data transfer (no new task orders)	$ 2,288,755		
				$ 13,688,223		
				Total ORD and Obligated Contract in FY 2010		

* Includes 12.4% administrative overhead *

Projected FY2012 ORD Support for Ongoing Gulf War Research Projects (June, 2012)

FullName	VAMC	Title	Focus	Total FY 2012	Start Date	End Date
Clinical Trials				**$ 1,330,796**		
Lin, Henry C. (M.D.)	Albuquerque, NM	Bacterial Overgrowth Associated with Chronic Mult-Symptom Illness Complex	Treatment of GW veterans with gastrointestinal symptoms	$ 158,219	04/01/09	03/31/13
Kearney, David J. (M.D.)	Seattle, WA	A randomized controlled trial of a mindfulness based intervention for Gulf War Syndrome	Treatment of GW veterans with gastrointestinal symptoms	$ 112,394	10/01/10	09/30/12
Cook, Dane B. (Ph.D.)	East Orange, NJ	Impact of Exercise Training on Pain and Brain Function in Gulf War Veterans	Treatment of pain in GW veterans with resistance exercise training	$ 202,910	07/01/11	06/30/16
Georgopoulos, Apostolos (M.D.)	Minneapolis, MN	MEG Synchronous Neural Interactions (SNI) in Gulf War Veterans	Treatment of pain in GW Veterans using magnetoencephalography	$ 406,888	10/01/11	09/30/12
Ashford, J. Wesson (M.D., Ph.D.)	Palo Atlo, CA	rTMS for the Treatment of Chronic Pain in GW1 Veterans	Treatment of chronic pain in GW Veterans using repetitive transcranial magnetic stimulation	$ 231,825	01/01/12	12/31/15
Bourdette, Dennis N. (M.D.)	Portland, OR	A Randomized Trial of a Formal Group Program for Fatigue in Multiple Sclerosis	Treatment of fatigue in multiple sclerosis patients	$ 218,560	01/01/12	12/31/14
Biomarkers				**$ 2,992,735**		
Fiore, Louis D. (MD)	Boston, MA	VA Gulf War Biorepository Trust (CSP 501)	Gulf War Brain and DNA Bank	$ 561,079	08/01/02	09/30/13
Madison, Roger D. (Ph.D.)	Durham, NC	Differential Gene Expression in Pathologies Associated with Neuronal Hyperexcitability: Links to Gulf War Illness	Identify genes that may be related to neuronal regeneration in Gulf War Veterans	$ 70,250	04/01/03	12/31/11
Cook, Dane B. (Ph.D.)	East Orange, NJ	Imaging Pain Modulation in Gulf War Veterans with Chronic Muscle Pain	Functional imaging of Gulf War veterans with unexplained musculoskeletal pain	$ 262,184	10/01/08	09/30/12
Provenzale, Dawn (M.D.)	Durham, NC	Gulf War Era Cohort and Biorepository (CSP 585)	Gulf War era repository of blood specimens	$ 1,861,344	04/01/10	09/30/13
Kowall, Neil (M.D.) Christopher Brady (Ph.D.)	Boston, MA	VA Gulf War Veterans' Illnesses Biorepository (CSP 501B)	Gulf War Tissure Bank	$ 237,878	10/01/10	09/30/12
Gulf War Veterans Illnesses				**$ 125,170**		
Verne, G. Nicholas (Ph.D.)	Cincinnati, OH	Somatic Hypersensitivity in Veterns with IBS	Evaluation of altered central pain processing in IBS	$ 125,170	04/01/09	03/31/12

* Includes 12.4% administrative overhead*

Projected FY2012 ORD Support for Ongoing Gulf War Research Projects (June, 2012)

FullName	VAMC	Title	Focus	Total FY 2012	Start Date	End Date
Model Systems of GW Exposures/Illnesses				**$ 2,372,845**		
Greenwood, Beverley (Ph.D., FACG.)	Oklahoma City, OK	Central Mechanisms Modulating Visceral Sensitivity	Central nervous system control of gastrointestinal pain (IBS)	$ 90,574	10/01/08	03/31/13
Bedlack, Richard (M.D., Ph.D.)	Durham, NC	A Clinical Demonstration of an EEG Brain-Computer Interface for ALS Patients (CSP 567)	New treatment for ALS	$ 1,686	10/01/08	01/01/13
Vandenbark, Arthur A. (Ph.D.)	Portland, OR	Immunoregulation of Myelin Specific T Lymphocytes	New treatment for MS	$ 168,600	01/01/09	12/31/12
Bourdette, Dennis N. (M.D.)	Portland, OR	Lipoic Acid Therapy for Experimental Autoimmune Encephalomyelitis	New treatment for MS	$ 168,600	10/01/09	09/30/13
Hinrichs, David (Ph.D.)	Portland, OR	Multiple Antigenic Peptides to Alter the Course of Autoimmune Disease	New treatment for MS	$ 168,600	04/01/10	03/31/14
Elmets, Craig (M.D.)	Birmingham, AL	Host Defense Mechanisms in Polyaromatic Hydrocarbon Compounds	Mechanisms of toxicity of polyaromatic hydrocarbon pollutants	$ 168,600	10/01/10	09/30/14
Singh, Inderjit (Ph.D.)	Charleston, SC	Neuroprotection and Myelin Repair Mechanisms in Multiple Sclerosis	New treatment for MS	$ 259,707	10/01/10	09/30/14
Shiromani, Priyattam (Ph.D.)	Charleston, SC	Sleep Neurobiology and Circuitry	Control of sleep	$ 303,406	10/01/10	09/30/14
Chase, Michael H,	'est Los Angeles, C	Prevention of Hippocampal Neurodegeneration due to Age and Apnea	New treatment for neurodegenerative effects of sleep apnea	$ 270,322	01/01/11	12/31/14
Kowall, Neil (M.D.)	Boston, MA	Epigenetic Mechanisms Relevant to the Pathogenesis of ALS	Genetic mechanisms underlying ALS	$ 168,600	01/01/11	12/31/14
Schlosser, Rodney J. (M.D.)	Charleston, SC	Nanoparticle Coupled Antioxidants for Respiratory Illness in Veterans	Nanoparticle (sand) derived respiratory illness	$ 168,600	04/01/11	03/31/15
Greenwood, Beverley (Ph.D., FACG.)	Oklahoma City, OK	Understanding Pain of Gastrointestinal Origin in Women that Serve in OEF/OIF	Central nervous system control of gastrointestinal pain (IBS)	$ 168,600	04/01/11	03/31/15
Shetty, Ashok (Ph.D.)	Durham, NC	Memory and Mood Enhancing Therapies for Gulf War Illness	Development of new therapy for ill Gulf Wat Veterans	$ 266,950	04/01/11	12/31/15
				$ 6,821,546		
				Total Distributed by ORD in FY 2012		

* Includes 12.4% administrative overhead*