

Research Advisory Committee on Gulf War Veterans' Illnesses

July 18-19, 2007, Committee Meeting Minutes

Dallas, Texas



DEPARTMENT of VETERANS AFFAIRS

**Research Advisory Committee on Gulf War Veterans' Illnesses
VA Eastern Kansas Healthcare System (T-GW)
2200 S.W. Gage Blvd. Topeka, KS 66622**

I hereby certify the following minutes as being an accurate record of what transpired at the July 18-19, 2007, meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

/signed/

James H. Binns

Chairman

Research Advisory Committee on Gulf War Veterans' Illnesses

Table of Contents

Attendance Record..... 5

Abbreviations 6

Welcome, introductions, and opening remarks..... 11

Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME): a disease characterised by neuro-immune features and virus infection..... 11

Gulf War Illness and Chemical Exposure Research Program at University of Texas Southwestern Medical Center, Dallas: Implementation of the Research Recommendations of the VA RAC-GWI 17

Neuroimaging Introduction and Overview..... 18

Gulf War Illness Neuroscience Projects Overview 18

Testing Hypotheses of Changes in Prefrontal Function Related to Gulf War Syndrome..... 19

Fronto-Striatal Systems in Depression and Gulf War Illness 20

Conjunction Memory Paradigm: Preliminary Data..... 20

EEG Program for Gulf War Research 20

MR Spectroscopy at 3T 21

DTI Sub-Core: Imaging Protocol and Prelim Data 21

Perfusion and Regional Cerebral Blood Flow (rCBF) Using MRI Arterial Spin Labeling (ASL).... 21

Committee discussion – Day 1 21

Public Comment – Day 1 28

Day 2..... 31

MRI Reveals Evidence of Structural Brain Differences Among Veterans Deployed to the first Gulf War..... 31

Environmental Medicine and Gulf War Illnesses: Does the map fit the territory?..... 35

Update on Research in Persian Gulf War Veterans Illnesses 37

2007 RAC Report: Discussion of Recommendations 38

Update on VA Gulf War research programs 45

Public Comment – Day 2..... 47

Appendix..... 51

Presentation 1 – Jonathan Kerr..... 51

Presentation 2 – Robert Haley..... 76

Presentation 3 – Richard Briggs..... 101

Presentation 4 – John Hart, Jr..... 103

Presentation 5 – Michael Motes 119

Presentation 6 – Wendy Ringe..... 136

Presentation 7 – Jim Bartlett 151

Presentation 8 – Thomas Ferree..... 170

Presentation 9 – Sergey Cheshkov..... 177

Presentation 10 - Roddy McColl..... 184

Presentation 11 – Richard Briggs..... 193

Presentation 12 – Roberta White..... 201

Presentation 13 – Bill Meggs..... 212

Presentation 14 – Beatrice Golomb..... 264

Presentation 15 – Lea Steele..... 293

Attendance Record

Members of the Committee

James H. Binns, Chairman
Carrolee Barlow
Floyd Bloom
Beatrice A. Golomb
Anthony Hardie
Marguerite Knox
William J. Meggs
Mary D. Nettleman
James P. O'Callaghan
Steve Smithson
Lea Steele
Roberta White

Committee Consultant

Jack Melling

Committee Staff

Laura Palmer

Designated Federal Officer

William Goldberg

Guest Speakers

James Bartlett
Richard Briggs
Sergey Cheshkov
Thomas Ferree
Robert Haley
John Hart
Jonathan R. Kerr
Roddy McColl
Michael Motes
Wendy Ringe

Abbreviations

AChE	Acetylcholinesterase
ACTH	Adrenocorticotrophic hormone
AFIP	Armed Forces Institute of Pathology
ALS	Amyotrophic lateral sclerosis
ASL	Arterial spin labeling
ATSDR	Agency for Toxic Substances and Disease Registry
CCEP	Comprehensive Clinical Evaluation Program
CDC	U.S. Centers for Disease Control and Prevention
CDMRP	Congressionally Directed Medical Research Programs
CEO	Chief executive officer
CFS	Chronic fatigue syndrome
CoQ10	Coenzyme Q10
CRADO	Chief Research and Development Officer (VA)
DFO	Designated federal officer
DOD	U.S. Department of Defense
DTI	Diffusion tensor imaging
EEG	Electroencephalogram
EPA	U.S. Environmental Protection Agency
ERP	Event-related potential
FDA	U.S. Food and Drug Administration
fMRI	Functional magnetic resonance imaging
FY	Fiscal year
GAO	U.S. Government Accountability Office
GWVIRP	Gulf War Veterans' Illnesses Research Program (DOD - CDMRP)
GWVIS	Gulf War Veterans' Information System
HPA	Hypothalamic-pituitary-adrenal axis
IDIQ	Indefinite delivery, indefinite quantity
IOM	Institute of Medicine
LHON	Leber's hereditary optic neuropathy
MCS	Multiple chemical sensitivity
MEG	Magnetoencephalography
Mn-SOD	Manganese superoxide dismutase
MRI	Magnetic resonance imaging
MPSS	Massive parallel signature sequencing
MRS	Magnetic resonance spectroscopy
MS	Multiple sclerosis
mtDNA	Mitochondrial DNA

NIH	National Institutes of Health (US)
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OPHEH	Office of Public Health and Environmental Hazards (VA)
ORD	Office of Research and Development (VA)
PB	Pyridostigmine bromide
PCR	Polymerase chain reaction
PTSD	Posttraumatic stress disorder
RAC-GWVI	Research Advisory Committee on Gulf War Veterans' Illnesses
RFA	Request for applications
ROS	Reactive oxygen species
SNP	Single nucleotide polymorphism
SPECT	Single photon emission computed tomography
UBO	Unidentified bright objects
UC Irvine	University of California at Irvine
UK	United Kingdom
UTSW	University of Texas Southwestern School of Medicine
VA	U.S. Department of Veterans Affairs

**Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
July 18-19, 2007**

**Wednesday, July 18: Meeting Held in Simmons Biomedical Research Bldg (NIB), Room 11.120
University of Texas Southwestern School of Medicine
6000 Harry Hines Blvd. (North Campus)
Dallas, Texas**

[Please Note: The meeting will be held in a different location Thursday, July 19]

***Wednesday, July 18
Agenda***

8:00 – 8:30	Informal gathering, coffee	
8:30 – 8:35	Welcome, introductory remarks	Jim Binns, Chairman Res Adv Cmte Gulf War Illnesses
8:35 – 10:05	Research on Chronic Fatigue Syndrome (CFS): a disease characterized by neuroimmune features and virus infection	Dr. Jonathan Kerr St. George's University of London
10:05 – 10:20	Break	
10:20 – 12:00	University of Texas Southwestern (UTSW) School of Medicine Gulf War Illness Research Program	Dr. Robert Haley Univ. of Texas Southwestern School of Medicine
12:00 – 1:00	Lunch	
1:00 – 1:30	UTSW Gulf War Research: Neuropsych testing, neuro projects, and research on word retrieval and emotional memory circuits	Dr. John Hart Univ. of Texas at Dallas
1:30 – 2:00	UTSW Gulf War Research: Studies of attention and executive function	Dr. Bart Rypma Univ. of Texas Southwestern School of Medicine / Univ. of Dallas
2:00 – 2:30	UTSW Gulf War Research: Frontostriatal systems in depression and Gulf War illness: Material-specific memory in the medial temporal lobes	Dr. Wendy Ringe Univ. of Texas Southwestern School of Medicine
2:30 – 3:00	UTSW Gulf War Research: Visual-auditory memory conjunction	Dr. James Bartlett Univ. of Texas at Dallas
3:00 – 3:15	Break	

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***Wednesday, July 18
Agenda (cont.)***

3:15 – 3:20	UTSW Gulf War Research: Introduction and overview of neuroimaging studies	Dr. Richard Briggs Univ. of Texas Southwestern School of Medicine
3:20 – 3:35	UTSW Gulf War Research: Electroencephalography and electrical impedance tomography	Dr. Tom Ferree Univ. of Texas Southwestern School of Medicine
3:35 – 3:45	UTSW Gulf War Research: Magnetic resonance spectroscopy	Dr. Sergey Cheshkov Univ. of Texas Southwestern School of Medicine
3:45 – 3:55	UTSW Gulf War Research: Diffusion tensor imaging	Dr. Roderick McColl Dr. K.S. Gopinath Univ. of Texas Southwestern School of Medicine
3:55 – 4:05	UTSW Gulf War Research: Perfusion and regional cerebral blood flow (rCBF) using MRI arterial spin labeling (ASL)	Dr. Richard Briggs Univ. of Texas Southwestern School of Medicine
4:05 – 4:10	UTSW Gulf War Research: Image registration	Dr. Nasser Kehtarnavaz Ali Gholipour Univ. of Texas at Dallas
4:10 – 5:00	Discussion regarding University of Texas Southwestern School of Medicine Gulf War Illnesses Research Program	Committee
5:00 – 5:30	Public Comments	

**Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
July 18-19, 2007**

**Thursday, July 19: Meeting Held at the Hilton Anatole
2201 Stemmons Freeway
Dallas, Texas**

***Thursday, July 19
Agenda***

8:00 – 8:30	Informal gathering, coffee	
8:30 – 9:10	Magnetic Resonance Imaging (MRI) reveals evidence of structural brain changes in Gulf War veterans	Dr. Roberta White Boston University School of Public Health
9:10 – 10:30	Environmental Medicine and Gulf War Illnesses: Does the Map Fit the Territory?	Dr. William Meggs East Carolina University School of Medicine
10:30 – 10:45	Break	
10:45 – 11:30	Update on recently published research relevant to the health of Gulf War veterans	Dr. Beatrice Golomb University of California at San Diego School of Medicine
11:30 – 12:00	Committee business: Report discussion and update	Dr. Lea Steele Res Adv Cmte Gulf War Illnesses
12:00 – 1:00	Lunch	
1:00 – 1:15	University of Michigan conference on multisymptom illnesses	Dr. Daniel Clauw University of Michigan School of Medicine
1:15 – 1:45	Update on VA Gulf War research programs	Dr. Bill Goldberg VA Office of Research and Development
1:45 – 2:15	Public comments	
2:15	Adjourn	

The July 18-19, 2007, meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses was held on July 18 in Room 11.120 of the Simmons Biomedical Research Building (NIB) at the University of Texas Southwestern School of Medicine, 6000 Harry Hines Blvd., Dallas, Texas. On July 19 the meeting was held at the Hilton Anatole, 2201 Stemmons Freeway, Dallas, Texas.

Welcome, introductions, and opening remarks

James H. Binns, Jr. Chairman

Chairman James Binns called the meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (hereinafter referred to as the "Committee") to order at 8:30 a.m. He welcomed Committee members, visiting scientists, Department of Veterans Affairs (VA) staff, and members of the public. He noted that the most recent VA study had found 175,000 Gulf War veterans, or 1 in 4 who served, are ill with chronic multisymptom illness. He extended special thanks to the ill veterans who were attending as Committee members and members of the audience. They remind us that this is not an abstract, scientific topic bringing us together. The transcending reality is that these 175,000 veterans were injured while serving their country in wartime. He also extended particular thanks to Dr. Robert Haley and his colleagues from the University of Texas Southwestern School of Medicine (UTSW) for inviting the Committee and members of the public to visit their campus that day. He also thanked them for undertaking the important task of understanding, and ultimately solving this problem.

Chairman Binns noted that Dr. Daniel Clauw was not able to attend the meeting because the University of Michigan had just been awarded a large National Institute of Health (NIH) clinical and translational sciences research grant. Dr. Clauw is the principal investigator on this project, and was required to attend meetings related to this project. He would therefore not be able to present an overview of the University of Michigan's conference on chronic multisymptom illness, as he was scheduled to do so the following day. Chairman Binns stated that, in light of this, his intention was to continue Thursday's meeting without a lunch break. This should allow the Committee to adjourn the meeting at 1:00 p.m.

Chairman Binns introduced the meeting's first speaker, Dr. Jonathan Kerr. Dr. Kerr is the director of a chronic fatigue syndrome (CFS) research program at St. George's in London. The program includes the development of a diagnostic test using mass spectroscopy and elucidation of CFS pathogenesis through analyses of gene expression. Chairman Binns noted that Dr. Kerr and his five colleagues were engaged and committed to the task with respect to CFS that UTSW had undertaken with respect to Gulf War illnesses. Chairman Binns was certain that attendees would find Dr. Kerr's research program impressive, including the fact that it had been accomplished on a total budget to date of 1 million pounds, or 2 million U.S. dollars.

Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME): a disease characterised by neuro-immune features and virus infection

Jonathan R Kerr MD, PhD

Sir Joseph Hotung Clinical Senior Lecturer and Honorary Consultant in Microbiology

Dept. of Cellular & Molecular Medicine, St George's University of London, U.K.

Dr. Kerr presented an overview of his group's CFS research, which was focused on elucidating a gene expression signature, the role of virus infection in the ongoing disease, as well as identifying protein biomarkers. ([See Appendix – Presentation 1.](#)) Their research indicates that there are genetic subtypes among CFS patients, reflected by different genetic expression profiles.

Following Dr. Kerr's presentation, Dr. Carolee Barlow, a Committee member, asked if the data from the massive parallel signature sequencing (MPSS) indicated higher or low levels of a particular viral genome. Dr. Kerr stated it provided a signature sequence for the entire genome. Dr. Barlow wondered if this data could help determine what was causative versus predisposing. She raised the question because gelsolin mutations are known to predispose to amyloidosis. One may be able to go in and determine if the identified differences were due to gelsolin gene expression differences. This might "pull out" the patients who are predisposed to CFS because they have an underlying gelsolin abnormality. She asked whether the resolution of the MPSS could reveal this. Dr. Kerr stated that there were not enough data to make this determination. He was getting ready to submit a grant proposal to look at differential expression of several of the target genes identified, and single nucleotide polymorphisms (SNPs) in general. Dr. Barlow asked if Dr. Kerr was planning to look at the whole genome or simply at variants in the genes already identified by MPSS. Dr. Kerr stated that they would be looking at variations in each of the identified genes.

Dr. Mary Nettleman, a Committee member, asked if Dr. Kerr could expound more on the "novel" virus that they had identified as possibly playing a role in CFS, as well as how they had characterized it. Dr. Kerr replied that they were currently conducting real-time polymerase chain reaction (PCR) tests, as well as regular PCR, to detect the presence of these markers. Dr. Nettleman asked if "novel" meant the virus was previously unknown or known, but not known to cause this disease. Dr. Kerr stated that it was a known mammalian virus, but preferred not to reveal more detail about its specifics.

Dr. Floyd Bloom, a Committee member, noted that Dr. Kerr's geographical distribution findings were very striking. This led back to Dr. Barlow's point: Are vulnerabilities or specific causative agents being revealed? Dr. Bloom asked if Dr. Kerr had plans to go back and look at family members from the same regions to see if the general population showed some of these characteristics. Dr. Kerr stated that they had identified family members and did have plans to investigate this aspect more. Dr. Barlow stated this was a key question to address. If there is a genetic predisposition to developing CFS, the controls must be a very different cohort. Models are available to evaluate affected family members and unaffected family members. Dr. Kerr agreed with this assessment.

Dr. Nettleman asked how Dr. Kerr's CFS research might relate to Gulf War illnesses. Dr. Kerr stated that there were significant overlaps between CFS and Gulf War illnesses. He noted that there were a lot of autonomic problems documented in CFS. His group hopes to look at gene expression in ill Gulf War veterans to determine the similarities and differences with their CFS patients. Dr. Nettleman stated that it has always struck her, with respect to Gulf War illnesses, that it affected such a large male cohort. This is unusual and generally a marker that "something is going on." There are also genetic correlations with gender and different proteins. She suggested this might be a focus for Dr. Kerr's future research. Dr. Kerr noted that one of their CFS subtypes was predominantly male.

Dr. Golomb commented that it would be interesting to see if ill Gulf War veterans were more likely to have variation in genes that might be involved in mitochondrial function. She stated that some studies have suggested that some immunological characteristics of non-Gulf War CFS patients differ from ill Gulf War patients. This may relate to the subgroup profiles, perhaps relating to groups that are more common in non-Gulf War veterans, or related to environmental exposures. Discussion followed about transcription factors that appeared to be down- and up-regulated in these patients.

Dr. Barlow asked if Dr. Kerr had ever performed the analyses in the opposite direction, i.e., identifying which clinical subtypes cluster together. Dr. Kerr stated that they had done this analysis. Dr. Barlow asked if they had been able to identify subgroups, not based on the genes differentially expressed, but across all CFS characteristics. It might be worthwhile to see if groups really stand out as being different.

It might also answer Dr. Golomb's question, i.e., if two groups stand out and one has a higher incidence in males, this might help understand the difference between Gulf War syndrome clusters and the CFS clusters. Dr. Golomb noted that there are occupational differences in men and women. Some of the occupations that involve more toxic exposures commonly involve men. Dr. Nettleman commented that symptom expression profiles are quite varied in the Gulf War population as well.

Dr. Steele, a Committee member and scientific director, thought it was remarkable that Dr. Kerr was able to identify gene subtypes that were highly correlative with symptom and severity types in different realms. She thought it was important to determine how the subtypes correlated with triggering events or exposures. Dr. Kerr's studies showed gene expression that varied on a geographical basis. It would be interesting to see if the agricultural community subtype was more common in the ill Gulf War veterans, for example, and then see if this correlated further with severity or symptom profiles. It would be of interest to tease out etiologic factors for the illness with these subtypes.

Dr. Steele asked if Dr. Kerr's group had been able to characterize the subtypes in a descriptive way, e.g., that a group had upregulation of X, down regulation of Y, etc. Dr. Kerr replied that they had just gotten some screening data on this and were planning to analyze the data. Dr. Golomb noted that the issue remained as to how much was related to vulnerability and how much was related to the effects of chemicals on DNA expression. Dr. Barlow cautioned Dr. Kerr that, while it was great to do the clustering, he should also do a more unbiased approach to find unique signatures. Dr. Kerr stated that he was aware of this concern. He stated that he believed this was a heterogeneous disease.

Dr. Bloom asked Dr. Kerr to speak a little about the natural history of CFS, in particular the age of onset and prognosis for natural recovery. Dr. Kerr stated that the CFS population included children, adolescents, and adults up until 60-or-70-years-of-age. Six months of disease is required for diagnosis, and people can spontaneously remit but generally don't get back total function. They may become sick again with other stressors. Dr. Golomb commented that some do stabilize and recover, but others remain ill. Dr. Steele added that, like Gulf War illness, the percentage of those who recover was relatively low, while a smaller percentage fully recovers.

Mr. Anthony Hardie, a Committee member, asked if the "novel" virus infections were triggers or unrelated to symptoms and perhaps opportunistic. Dr. Kerr stated this wasn't understood yet. Dr. Golomb stated that it was a good point that the viral infection may be opportunistic. It may potentiate the illness, but may not be a primary etiological factor. Dr. Kerr stated that it could also be the other way. We just don't know. Dr. Steele asked if Dr. Kerr would be testing for the "novel" virus in his Gulf War patients. Dr. Kerr stated that he would.

Dr. Haley, director of the UTSW Gulf War research program, commented that the heterogeneity of these patients was the most interesting part in this challenge. When this is solved, they will probably find homogeneity factors within the subgroups. So how the subgroups are derived is critical. Dr. Kerr stated that he hadn't shown the original clustering data. Basically they clustered the relative quantities of each of the 89 genes in all of the CFS patients. Dr. Haley stated that this was a problem that he had been interested in for 15 years. He noted that there are numerous ways to look for subgroups, e.g. cluster and factor analysis, etc. Many, like Dr. Haley, use factor analysis. However, the first time one does the analysis; it probably doesn't make much difference. The advantage of factor analysis is that once the factors are identified, there is a mathematical description of these factors that can be applied *a priori* in another group. But cluster analysis requires that the clusters be derived *de novo* every time. Dr. Haley thought Dr. Kerr may have something here, and suggested that he go back and redevelop these groups as factors. Dr. Kerr could then apply the factor weights in his next study and create the same groups with

the same mathematical definitions. This would allow him to test hypotheses instead of redefining the sample variation.

Dr. Golomb stated that the opposite viewpoint was that one should not use factor groupings that might have been specific to one's sample and analysis. Dr. Haley agreed that one's initial study might generate spurious findings but that doing this research multiple times in multiple groups, one would hope to arrive at some factors that do replicate. This does not happen with cluster analysis. One can not perpetuate a cluster. Dr. Haley stated that Dr. Kerr's data were objective measures and could provide great building blocks for establishing factors. Cluster analysis is an exploratory approach in his opinion. Now that the evidence indicates that something is going on, one should go back and derive a factor model, particularly gene factors in this case.

Chairman Binns asked the scientific Committee members if they might comment on the significance of Dr. Kerr's research. Dr. Barlow stated it was impressive that Dr. Kerr started off using gene expression profiling using chips from one set of patients, found several genes of interest, and confirmed 83 of these genes in an independent population. It isn't just the methodological differences, but it was an entirely different patient populations. This was really strong evidence that there was a gene expression profile for CFS patients. Now that this information has been collected, one can go back and refine the data to better understand this link. As Dr. Haley stated, one could go back, in a more unbiased fashion, and see what the clinical profiles can tell us about genetic signatures. Dr. Golomb commented that it was important to note that all of the groups had all the symptoms. Dr. Kerr stated that they had been diagnosed based on the CDC case definition. Dr. Golomb stated that she had always been enthusiastic about finding underlying physiological mechanisms to ultimately define subgroups, rather than subgrouping by symptoms.

Dr. Golomb asked the Committee and scientific audience members whether other researchers had considered looking at other tissue types, e.g., muscle, for gene expression, or was the focus generally on blood samples. Dr. Steele commented that research had been done on spinal fluid. Dr. Barlow stated that it was difficult to obtain these other samples, and if blood gave the signature needed, it was best to start there. The next phase was to elaborate more on what can be determined from the genetic distinctions, for example, which differences may relate to predisposing factors and which things may be causative. She noted that there were several new algorithms that could be run on Dr. Kerr's arrays. It would be important to sequence the genes in the CFS and CFS family cohorts. This would help determine if there really was a genetic predisposition. It would be incredibly helpful to the military because it could identify soldiers with this predisposition and help make determinations about deployment.

Chairman Binns asked if Dr. Barlow was suggesting that Dr. Kerr focus on a particular gene, e.g. NTE. Dr. Barlow stated that in her own work with NTE, they found that subtle deficiencies lead to very different phenotypes in animal models. NTE is also known to be affected by pesticides, and important for glial/neuronal interactions. There may be other just as important genes. However, Dr. Barlow stated that the full sequence of NTE should be covered. Dr. Golomb suggested taking subgroups of individuals with an apparent trigger event and see if there are differences in their manifestations and gene expressions. Dr. Kerr noted that many of their CFS patients were not able to identify a trigger event. Dr. Golomb wondered if he could pick the patients for whom there was a strong case for a single apparent trigger event.

Dr. O'Callaghan noted that the Committee had heard a lot about proinflammatory, neuroimmune processes associated with Gulf War illness. This was an exciting new area, but it was too early to comment too much about the glial/neuronal contributions to Gulf War illness. He noted that Dr. Kerr's nf-kappaB findings fit in nicely here.

Dr. Steele stated that she knew that the objectives of Dr. Kerr's work were to characterize the disease and identify markers, but also to identify treatments. She asked Dr. Kerr to share his thoughts about possible treatment studies for his CFS patients. Dr. Kerr stated that six of the gene signatures might suggest known or experimental therapies. There have been treatments with antibodies and anti-cancer drugs. There was a very small trial of Etanercept showing benefit in six patients. They hope to repeat this trial, and are also interested in testing interferon beta. Unfortunately, they have not acquired the funding to do this yet. Dr. Kerr stated that there had been concern that interferon beta could mimic the symptoms of CFS. The reviewers, however, had seemed more receptive to testing Etanercept again. Dr. Golomb asked whether there had been evidence of unfavorable side effects associated with Etanercept. Dr. Kerr stated that individuals may have a higher risk of tuberculosis, but one could switch to another anti-TNF alpha drug.

Chairman Binns asked Dr. Kerr if he would discuss how he manages his research program. Dr. Kerr discussed the specific arrangements and coordination of the six researchers involved in his program. The group was about to start a CFS clinic, but did not have plans to see Gulf War veterans at this time.

Ms. Denise Nichols, an audience member, asked Dr. Kerr if there were any military veterans in his sample. Dr. Kerr stated that this question was not specifically asked, but he was sure that there were none in the cohort. Ms. Nichols noted that many Gulf War veterans "wander" into CFS clinics and don't identify themselves as veterans. She suggested that he double-check whether there were veterans in his cohort or not. Ms. Nichols also asked whether Dr. Kerr's Gulf War veterans study had been funded. Dr. Kerr said they had been awarded 30,000 pounds to repeat their gene expression studies in Gulf War veterans. Chairman Binns asked Dr. Haley if the UTSW program would include gene expression studies. Dr. Haley indicated that it does.

Mr. Hardie asked Dr. Kerr if they were tracking their CFS patients over time, and if so, were they seeing a progression of their disease and/or additional diseases arising. Dr. Kerr stated that the original plan was to follow ten patients for one year, but they will need to look at more than ten in light of the heterogeneity of the gene expression. Mr. Hardie asked if there were any plans to follow these patients for more than one year. Dr. Kerr stated that there were no such plans at this time.

Dr. Roberta White, a Committee member, commented that in all of the work in CFS and disorders with a psychoimmunologic component, she was most concerned about how stress and stressors were discussed. She stated that stress was not well-defined and this issue is very important in Gulf War-related illnesses. As part of the Committee, she plans to keep track of these types of definitions. Dr. Kerr agreed. Dr. Golomb noted that outcomes can be extremely different depending on what the actual "stressor" is.

Chairman Binns stated that he should take this opportunity to officially welcome Dr. White to the Committee. He noted that Dr. White had spoken to the Committee previously, and that the Committee was very familiar with her recent neuroimaging work in Gulf War veterans.

Dr. Steele noted that Dr. William Reeves had spoken to the Committee about CFS genomic studies at the Centers for Disease Control (CDC). Dr. Nancy Klimas had also spoken to the Committee about her planned gene expression studies in CFS and ill Gulf War veterans. Dr. Steele asked Dr. Kerr if he had a sense of how his gene expression profiles would (or would not) correlate with the CDC findings. Dr. Kerr stated that the CDC studies only used microarray data. These studies did not include a real-time PCR component as his study did. The real-time PCR allowed for more specific differentiating of the gene expression. Dr. Steele said that she understood Dr. Kerr to be saying that CDC had "cast a wide net" and it isn't clear what they had "pulled in." Dr. Kerr agreed with this analogy. CDC had used several

different mathematical and statistical approaches with their microarray data, but at the end of the day, their data doesn't tell one which genes were important nor which therapies should be developed.

Dr. Golomb wondered whether it was expected that there would be specific genes that are important, or could there be a wide range of genes that relate to a certain function, e.g., energetic function. She also wondered if there were known instances in which clusters were defined by a microarray, but later became irrelevant when PCR data were analyzed. Dr. Kerr stated that he was not aware of data or studies that looked at this question. Dr. Barlow commented that the issue with PCR and arrays was that both have an intrinsic false-positive, so one can not say one is more "right" than the other. However, if one does both in independent cohorts, one could corroborate findings. Dr. Golomb understood that this made the data much "better." She was just curious about whether there were any examples where such findings were reported, understanding that false-positives are possible. Dr. Barlow stated that they had, when clusters were driven by a handful of genes with very large differences.

Chairman Binns stated that Dr. Kerr's presentation would stimulate Committee discussions for the remainder of the day and long into the future. He noted that it was remarkable what this small group of U.K. researchers had been able to accomplish and that their work had touched on many themes that the Committee has been examining. He noted that ill Gulf War veterans in the audience had identified with the symptom patterns presented by Dr. Kerr. Chairman Binns stated that he was very glad that Dr. Kerr was able to come and share these findings with the Committee.

The meeting recessed for a break at 10:09 a.m.

The meeting resumed at 10:28 a.m.

When the meeting reconvened, Chairman Binns began by noting that this was a time of great significance in the effort to address Gulf War illnesses. Over the past fifteen years, the U.S. government had spent over 300 million dollars researching the health of Gulf War veterans, and the Committee is charged to advise on this research. But he has had to tell the VA Secretary at the end of each year that federal research has not yet contributed to the one goal for Gulf War research that is in the Committee's charter, that is, that the research make a difference to the health of ill Gulf War veterans.

The program that UTSW was undertaking represented a very different approach to this problem. Chairman Binns said that this approach would not have been taken had it not been for the fact that the \$300 million spent to date had not produced the desired results. He stated that since the Committee met in Dallas in November 2006, UTSW and VA had entered into a contract. This contract, in effect, made the UTSW program VA's Gulf War illnesses research program. All involved in Gulf War illnesses—ill veterans, Committee members, VA officials—were grateful for UTSW's willingness to take on this assignment. However, this task came with a great deal of responsibility and expectations. UTSW was no longer one of many research groups pursuing individual pieces of this tragic puzzle. It had been given all the pieces and been asked to put them together. UTSW's work was not going to be measured by how many papers are published, but measured against the standard mentioned earlier, i.e., whether this research makes a difference to the health of ill Gulf War veterans. Chairman Binns added that, even if it were not in the Committee's charter, it is the only standard that matters in the eyes of a much more important group, the 175,000 ill Gulf War veterans who have been sick for sixteen years. These veterans' hopes now rest with UTSW researchers.

Assuming the funding is provided as planned, UTSW will receive 75 million dollars over the next five years to study this problem. And at the end of the day, UTSW researchers will go down as the people who solved this problem or those who did not. Chairman Binns stated that Committee members were

there to help UTSW in this mission. The Committee believed in this mission, as well as the UTSW researchers. There was no other group in this country that was more qualified. The justification for giving all of this money and responsibility to one institution was not that UTSW was “good,” but rather the benefit that comes from having a comprehensive, coordinated research program versus than the usual random collection of studies produced by research solicitations. Chairman Binns noted that the Committee had just heard about the advantages of what a smaller team could do when assembled in one location. To succeed, UTSW would have to take advantage of this by coordinating operations closely. The Committee has an obligation to offer its ideas to the UTSW researchers and to ask questions. The Committee must subject the UTSW program to the same scrutiny that it has used in reviewing other VA Gulf War research. The Committee wants to do this to help the UTSW program succeed. Chairman Binns hoped that the researchers present would accept the Committee’s comments in this spirit.

Gulf War Illness and Chemical Exposure Research Program at University of Texas Southwestern Medical Center, Dallas: Implementation of the Research Recommendations of the VA RAC-GWI

Robert Haley, MD

Professor, University of Texas Southwestern School of Medicine, Dallas, TX

Dr. Haley gave an overview of the development and activities of the UTSW Gulf War illness research program. ([See Appendix – Presentation 2.](#))

During the presentation of the stratification to be used in the national survey sample, Dr. Steele asked how two groups were designated as being in “high risk” or “low risk” zones for sarin exposure. She noted that multiple incidents potentially associated with sarin exposure had been identified and there could be a danger of misclassification that would “water down” the results. Dr. Haley noted that they had assessed different location strata and indicated he could provide an entire session on the details of how the survey had been developed.

During the discussion of exploring mechanistic questions about how various exposures affect cellular processes in mice, Dr. Barlow noted that if something is negative in a particular system it could be negative for reasons specific to mice. Dr. Haley acknowledged this, and added that it could take more than one year to see effects. These are problems that the merit review committee will have to address. Dr. Golomb noted that results could also be negative for a variety of other reasons. Dr. Haley agreed and noted that the merit review committee was composed of National Academy scientists, some of the best “minds” in this area. The first batch of preclinical proposals would be reviewed by the merit review committee in September 2007. So these proposals were still in their formative stage and input was welcomed.

Dr. Barlow observed that these studies provide models, which were great for hypothesis generation. However, Dr. Haley had the opportunity to work with human patients and negative results in the animal studies shouldn’t dictate that the research wouldn’t be pursued in clinical applications. Dr. Haley stated that the survey and clinical and preclinical projects were separate efforts aimed at figuring out what was happening in humans. At some point, these efforts should be examined to inform each other, but not determine each other.

During the discussion of the case definition(s) used in the National Survey, Dr. Steele commented that she didn’t think it would be a surprise or controversial if a new case definition were identified. It is entirely possible that none of the existing case definitions is the “best” one. However, a problem with Objective #1 is that the Seabees are not representative of the Gulf War veteran population as a whole. Dr. Haley agreed with this point. Dr. Steele stated that it was important to optimize the best case definition in a

representative sample. Dr. Haley said that the first step is to see how radically, if at all, the Seabees have changed since the original study. Dr. Golomb stated that she didn't think case definitions would ultimately be based on symptoms alone. They are going to be based on patterns identified with objective markers. Dr. Haley agreed, noting that other diseases, like Legionnaire's disease, Toxic Shock syndrome, AIDS, etc., were initially symptom-based case definitions. However, over time they were based on objective measures and that was what he would like to see happen here.

Chairman Binns thanked Dr. Haley. He noted that there was a full hour reserved for discussion of the plan outlined by Dr. Haley.

The meeting recessed at 12:03 p.m. for lunch

The meeting reconvened at 1:04 p.m.

Neuroimaging Introduction and Overview

Richard W. Briggs, PhD
Department of Radiology, Division of Neuroradiology, Neuroimaging Laboratory
Gulf War Illness and Chemical Agent Exposure Program
University of Texas Southwestern Medical Center, Dallas, TX

Dr. Richard Briggs provided an overview of the proposed neuroimaging components of UTSW's Gulf War illness research program. ([See Appendix – Presentation 3.](#))

Following his presentation, Dr. Briggs introduced Dr. John Hart.

Gulf War Illness Neuroscience Projects Overview

John Hart, Jr., MD
Professor, Brain and Behavioral Sciences and Neurology
University of Texas at Dallas and University of Texas Southwestern School of Medicine

Dr. Hart provided an overview of the neuroscience projects that would be undertaken by the UTSW Gulf War research program. ([See Appendix – Presentation 4.](#)) In response to a point made about the need for longitudinal neurocognitive data, Dr. Steele asked Dr. White if she had this type of data for the Fort Devens cohort. Dr. White said she had collected it for some subsets but not the entire cohort. She also had longitudinal data for a DOD cohort that she had assembled to compare treatment-seeking Gulf War era veterans, both deployed and nondeployed. But it didn't consist of the same battery of tests listed by Dr. Hart. Dr. Hart indicated that he would like to speak with Dr. White about this and that they were willing to adapt their approach if necessary.

Dr. Thomas Ferree, PhD, asked Dr. Hart to clarify the relationship between function and deficits in subcortical areas versus cortical areas. Dr. Hart stated that they were able to examine deep areas of the brain. However, the cortical areas of the brain, which are more practical to reach, are a reflection of the deep structures. He had included the thalamus research to show where something might "go out." Part of Dr. Clausson's work is to find individuals with basal ganglia strokes. Dr. Hart has had patients with thalamic strokes. He can do a lesion model, and Dr. Ferree was right that they could use the cortical memory area changes to double-check if there was a memory problem.

Dr. Golomb noted that Gulf War veterans reported increased problems with all of the neurocognitive functions about which they have been surveyed. She wondered if it was appropriate to just look at the brain areas related to the specific problems listed. Dr. Hart stated that some of the neuropsych studies would address these concerns. The neuropsychological core paradigms are being developed as they go along. While these are the ones planned right now, they will be trimmed back. Also, there are multiple different individuals working in other areas. He couldn't address every issue, but had selected these to target first. Dr. Hart stated it was fair to question whether a veteran responded in a particular way because this is what he had been asked, and that there could be a need to examine other brain regions.

Dr. William Meggs, a Committee member, noted that fatigue was a prominent part of this illness. He asked Dr. Hart what was the effect of fatigue on memory and how would this affect his testing. Dr. Hart stated that there were two experiments included in the portfolio to address this issue. Continuous performance test, piloted in fMRI and EEG trials, produces fatigue on a short-term memory test. Electrically, they will see a drop in alpha and gamma changes and they are working to measure this right now. Fatigue also comes in with relation to the attention and executive function testing. Dr. Hart indicated that they were randomizing the testing and scheduling of the tests to address this concern.

Mr. Mike Hood, an audience member and Gulf War veteran, noted that many of the veterans returning now had a certain "look." Dr. Hart stated that those involved in the program had kept in mind how their findings might be applied to veterans of the current conflicts. Dr. Golomb noted that the signature injury among current Iraqi conflict veterans was traumatic brain injury, which had potentially different characteristics. Dr. Hart agreed that there were different characteristics in imaging and also performance-wise. This "look" can be the result of several different things, and he has seen several different "looks." This was how this research had been targeted, i.e., to provide an investigative model.

Dr. O'Callaghan asked if they were looking at chemical interactions of glutamate inhibitors in these studies. Dr. Hart said that he would like to do this research, targeting "sick" glutamate neurons that are partially functional. From a neurotoxic point of view in subcortical areas, can one stabilize these "sick" neurons? This is one of the hypotheses that they have been debating. Dr. O'Callaghan stated that another option was glutamate overload. Dr. Hart agreed, but noted that the data were hard to get.

Discussion followed about maintaining the afternoon schedule of presentations. Dr. Briggs asked the remaining speakers to limit their comments to the highlights. Chairman Binns indicated that audience questions may need to be limited until the discussion period scheduled for later in the afternoon. He asked that if questions were asked that they be brief, be made into a microphone, and that the individual identify themselves.

Dr. Briggs introduced Dr. Michael Motes, a University of Texas at Dallas researcher.

Testing Hypotheses of Changes in Prefrontal Function Related to Gulf War Syndrome

Michael A. Motes, PhD

Postdoctoral Research Fellow, Center for Brain Health, University of Texas at Dallas, TX, and University of Texas Southwestern Medical Center.

Dr. Motes discussed his group's neuroimaging research on age-related cognitive deficits and how it would be applied in their Gulf War research. ([See Appendix – Presentation 5.](#))

Dr. Briggs introduced Dr. Wendy Ringe.

Fronto-Striatal Systems in Depression and Gulf War Illness

Wendy Ringe, PhD

Assistant Professor, Department of Psychiatry

University of Texas Southwestern Medical Center, Dallas, TX

Dr. Ringe discussed research on the involvement of fronto-striatal systems in depression and how this could be used to examine characteristics of depressed mood in Gulf War illness patients in relation to major depressive disorder. (See Appendix – Presentation 6.) She then provided a brief presentation on high resolution fMRI findings related to material-specific memory in the medial temporal lobes. ([See Appendix – Presentation 6.](#)) She indicated that these methods could be informative in studying memory deficits in Gulf War veterans.

Dr. Briggs then introduced Dr. James Bartlett.

Conjunction Memory Paradigm: Preliminary Data

James Bartlett, PhD

Professor, Department of Brain and Behavioral Sciences

University of Texas at Dallas, TX

Dr. Bartlett gave an overview of his group's proposed behavioral and fMRI research to capture aspects of brain function that underlie memory problems in Gulf War veterans. The proposed research will compare the three subcategories of Gulf War illness identified by Dr. Haley with healthy controls. ([See Appendix – Presentation 7.](#))

Chairman Binns thanked Dr. Briggs and all of the speakers for their presentations.

The meeting recessed at 3:05 p.m. for a break.

The meeting reconvened at 3:18 p.m.

Dr. Briggs introduced the next presentations, indicating that they would describe subcores of the neuroimaging core technical projects proposed for the UTSW Gulf War program. ([See Appendix – Presentation 3.](#)) He noted that the technical work is subservient to the clinical and neuroscience goals of the program. The individual projects were motivated by specific questions brought to this team of researchers. However, because identifiable differences are expected to be complex, it was important to develop the most advanced array of neuroimaging techniques possible. These projects would need to include technical development, testing, and implementation of the techniques.

Dr. Briggs introduced Dr. Thomas Ferree.

EEG Program for Gulf War Research

Thomas Ferree, PhD

Assistant Professor, Department of Radiology

University of Texas Southwestern School of Medicine, Dallas, TX

Dr. Ferree gave an overview of the types of information provided by electroencephalograms (EEGs) and UTSW's proposed use of EEG in combination with functional magnetic resonance imaging (fMRI) for Gulf War illness research. ([See Appendix – Presentation 8.](#))

Dr. Briggs introduced Dr. Sergey Cheshkov.

MR Spectroscopy at 3T

Sergey Cheshkov, PhD
Assistant Professor, Department of Radiology
University of Texas Southwestern School of Medicine, Dallas, TX

Dr. Cheshkov gave an overview of 1.5T magnetic resonance spectroscopy (MRS) findings in ill Gulf War veterans and how UTSW planned to expand this research using 3T capabilities. ([See Appendix – Presentation 9.](#))

Dr. Briggs introduced Dr. Roddy McColl.

DTI Sub-Core: Imaging Protocol and Prelim Data

Roddy McColl, Ph.D
Dept. of Radiology, University of Texas Southwestern School of Medicine, Dallas, TX

Dr. McColl gave an overview of diffusion tensor imaging (DTI), including DTI findings in multiple sclerosis patients, and UTSW plans for using DTI in evaluating Gulf War veterans. ([See Appendix – Presentation 10.](#))

Perfusion and Regional Cerebral Blood Flow (rCBF) Using MRI Arterial Spin Labeling (ASL)

Richard W. Briggs, PhD
Department of Radiology, Division of Neuroradiology, Neuroimaging Laboratory
Gulf War Illness and Chemical Agent Exposure Program
University of Texas Southwestern Medical Center, Dallas, TX

Dr. Briggs provided an overview of magnetic resonance imaging (MRI) arterial spin labeling (ASL) research done at UTSW and plans to combine this technique with single photon emission computed tomography (SPECT) in their Gulf War research. ([See Appendix – Presentation 11.](#))

Chairman Binns thanked Dr. Briggs and the speakers who presented that afternoon.

Committee discussion – Day 1

To begin the discussion of the UTSW program, Chairman Binns asked the Committee to provide general comments or ask general questions they had about the proposed UTSW Gulf War research that had been presented.

Dr. Jack Melling, consultant to the Committee, commented that the aim of this work seemed to be to make a difference. He interpreted “to make a difference” to mean the development of diagnostic tests and treatment regimens. The research program, in his opinion, should be integrated at the earliest possible stage with what is needed to deliver these end products, for example, treatments for ill veterans. He had seen many cases where high quality research failed to achieve timely delivery of what was required to

those who required it. This is something that needs to be avoided in this case. Dr. Melling stated he was giving this message to the Committee, colleagues at VA, and as a reminder, to Dr. Haley and his colleagues at UTSW. Dr. Melling indicated that everyone needs to remember that “it is never too soon to be prepared for success.” All of the indications are that the UTSW research will be successful. Collectively, “we” must be prepared to move this forward to get it to where it is needed, that is, to make it available to 175,000 ill Gulf War veterans.

Dr. White stated that she had pages of comments to share with Dr. Haley. Generally, she was impressed with the level of cognitive neuroscience and the imaging program that had been presented. She indicated that she had three major overarching responses to the presentations. Two words that came to mind were “integration” and “translation.” While she hadn’t seen the overall core, she hoped that there was a translational core in place, that is, that key clinical individuals were already planning for the diagnostic and treatment paradigms that could be applied at the present time. There are some hypotheses concerning treatment applications and some drugs already being used in other kinds of neurological patients. In the types of environmental health centers that she has run, they have a translational core from day one. In one of her centers, they met weekly on these issues.

Dr. White pointed out that another central issue is that the success of all of these elegant studies rests on who comes in for testing. She was worried about focusing on individuals with the previously identified Syndrome 1, 2, and 3. First, the proposed sample of 80 individuals was not large. One strategy may be to decrease the number of tests conducted and increase the number of subjects. However it is done, the selection of subjects and the basis for selection are going to guide what the researchers would be able to find. There are lots of ways to “slice and dice” the data in terms of exposure, clinical syndromes, genetic profiles, etc. However, with only eighty people, they will not be able to “slice it and dice it” very many ways. This issue, in her opinion, was key for a huge part of the program. Finally, she indicated that she hadn’t heard anything about the exposure assessment aspect of the program, and would like to hear more about this component. For example, how would exposures be assessed or modeled? How would exposure information be integrated with the other data? This related to causation. However, it may also relate to parceling out some of the comorbid factors and other issues. She thought it was a very exciting program, and looked forward to seeing it unfold.

Dr. Nettleman stated that she would echo Dr. White’s comments. She was struck that it would be hard to put a big sample through the comprehensive imaging program at UTSW. If one would put 10,000 veterans through the neuroimaging program, we would know a lot about Gulf War illness. If we put smaller numbers through, we might know something about a small number of people. Dr. Nettleman asked Dr. Haley if the national survey data would be available in a public database, and if he would provide her with a copy of the survey. Dr. Haley indicated that was possible.

Ms. Marguerite Knox, a Committee member, stated that the program was exciting. She asked Dr. Haley how they would select Phase Two (blood sampling) subjects using the national survey data. Dr. Haley said that blood would be collected from all of the special strata—twins, Seabees, Haley and Steele syndrome individuals, etc., as well as random samples of subsyndromic and well individuals. This would provide an estimated 2064 individuals in the total sample. Ms. Knox asked if these samples would be compared with earlier samples. Dr. Haley stated that this was possible because some of the individuals had been in previous studies.

Chairman Binns stated that, from his perspective, it was obvious UTSW had a tremendous neuroimaging capability. He noted that an alumni organization with which he had been involved at one point had selected UTSW for its upcoming meeting on advances in brain research. Chairman Binns asked Dr. Haley about the cost of the neuroimaging component of this program in relation to the entire research

program. Dr. Haley stated that the neuroimaging component would run about \$20 million over two years. Chairman Binns noted that was about two-thirds of the monies that were allotted for the program in those years. He stated that his “gut feel” was that more money was going into this component than there should be. It was obvious that UTSW was going to “nail this nail.” There would be no doubt that there was brain damage in Gulf War veterans, along with findings about memory, etc. However, coming back to Dr. Melling’s point, how many times do we have to show these veterans have memory problems? It is very interesting to appreciate what is going on in so many ways in the brains of these ill veterans. They would find “17 ways from Sunday” how these veterans were ill and what was abnormal about their brains. However, he found himself comparing it to what might they find if they were to study Dr. Kerr’s patient population in the same way.

Chairman Binns related a situation where Dr. Jose Montoya at Stanford had noticed that some of his infectious disease patients had chronic fatigue and noted that they had high viral antibody levels. Just to treat those high viral levels, Dr. Montoya began giving them an antiviral drug. Serendipitously, he began getting reports that the patients’ chronic fatigue was markedly better. Chairman Binns guessed that all of these parameters that could have been studied might have found something, but patients would not have improved. He wished that Dr. Haley had somebody out there “dreaming up” these types of trials and therapies that will get to the core of the problem, rather than defining all of the ways to describe the problem.

Dr. Golomb commented that she shared similar reservations. She stated that the original neuroimaging studies were critically important because evidence was needed of objective changes correlated to illness in Gulf War veterans. The original studies were pivotal in producing these findings. Her only hope is that these findings will correlate with UTSW’s new findings and be helpful. However, in and of themselves, she didn’t see this as taking a step forward for discovering underlying mechanisms or potential treatments. She found the magnitude of this particular effort to be troubling. This was not because she didn’t have favorable feelings towards the research. But she was not sure that this was the right approach or major direction for use of the funding.

Dr. Steele stated that she had a sense of unease about the program as well. She echoed that the neuroimaging projects presented were dazzling. However, the underlying goal was to improve the health of ill Gulf War veterans. She had a feeling that a lot of money was being spent to “paint a picture” of the pathology when we really need to explain the nature of the pathology and determine how to address it. She stated that some money should be spent to characterize it, but questioned whether so much of the budget should be devoted to this aspect. Perhaps there was a bridge between the two, but it was not clear to what extent there were clinical applications of much of the research. An effort to identify clinical applications and treatments was of primary importance. Some people might say you can never identify “too much”, but this is not a luxury that can be justified, given the sixteen years that have passed for these veterans.

Dr. White agreed. She thought that treatment research should begin now. It is valuable to have some focused studies of the type described because they provide markers for treatment. Some of the neurocognitive changes and specific imaging findings, especially those that relate to function, might provide evidence to support successful treatment. However, her major concern was that treatment applications be considered today. She noted that she was surprised to hear herself saying this because she understood the position of “How do we treat if we don’t understand the problem?” However, a lot of effort today needs to be put towards thinking creatively about treatment. Dr. Steele stated that perhaps the focus of the neuroimaging projects could be to identify those most capable of identifying and testing treatment hypotheses.

Dr. Golomb stated that other research programs have administered treatments, exposed animals and looked at mechanisms, and then correlated these findings with neuroimaging findings. These questions examined both animal and human models. The reality is that sometimes the mechanisms associated with symptoms may be treated even when the brain pathology is not. Understanding biological mechanisms can be important beyond what one can find in brain imaging studies. Dr. Golomb indicated that an imaging component to the program was not disputed, but rather the magnitude of its role in the total program.

Dr. Meggs commented that there were several cases where knowing the mechanism elucidated a treatment that someone would never have identified on a treatment “fishing trip.” However, if one did find a treatment on a “fishing trip,” it may help elucidate the mechanism. It is hard to say which way to go. Should one use a shotgun approach for treatment or look at mechanisms? Dr. Meggs stated that all of the different imaging modalities would find abnormal results, but there probably would be overlap in the findings. This is true in stroke and Alzheimer’s patients. Once the pilot studies are completed, it may become obvious that some or all of the modalities can be “thrown away.”

From his experience putting together coordinated research plans in alcoholism, substance abuse, and neuroAIDS, Dr. Bloom stated that until the diagnostic reproducibility of the syndrome was established, we don’t have “ground to put our foot on.” Until we establish the variety of syndromes within this diagnostic category, we don’t have a chance intellectually and logically to define a therapy. Most therapies for brain-related disease have come from wrong hypotheses. We still don’t know why antipsychotics or antidepressants work on some people whom they help. Many of the neurocognitive and structural imaging methods discussed that afternoon were helping to define how many types of schizophrenias there were. Knowing the brain structure and genotype of an ill individual helps in finding new ways to approach these illnesses. However, these are illnesses that no one doubts are illnesses. Dr. Haley’s program is an immensely positive effort. While it doesn’t lead to the treatment of anybody, Dr. Bloom stated he didn’t know if there was reason to believe that there were good treatments for this illness. He questioned whether it was worthwhile to look for treatments before establishing the reality of this diagnosis for the people who decide whether a war-related illness is compensable to those who have the problem. We have to establish the reality of the cause and effect, and that this is a real illness. Dr. Bloom stated that he would like to see treatments, but Dr. Haley’s program was devised to find leads to move forward. Dr. Bloom didn’t think we should digress from this until we get answers to these questions. There aren’t a whole lot of drugs in the pipeline to treat this illness. We don’t even know what we are treating. And we don’t know which ones to treat with what.

Dr. Golomb questioned whether neuroimaging was the right and primary approach. Dr. Bloom commented that it was the only way to look at these veterans’ brains while they are alive. Dr. Golomb stated that there were other techniques, e.g., serum markers, muscle biopsies, etc. Dr. Bloom stated that these approaches “didn’t hold a candle” unless they provided information within the diagnostic logic that has been set up for this illness.

Chairman Binns asked Dr. Bloom whether an alternative would be to include gene expression, as Dr. Kerr has done in his CFS research. Could this be a source of useful information as opposed to simply relying on neuroimaging? Dr. Bloom stated that a lot of genetic research was being done to determine the phenotypic expression of brain structure, e.g., small hippocampii, small corpus callosum. This body of research is being well-funded by a lot of other sources. In eighteen months, Dr. Haley’s group will be able to take advantage of some of these genotypic markers and see which ones may be used for identifying vulnerabilities or consequences of having this illness. Brain imaging and genotyping are the two hottest technologies right now. If one could define who may have been more vulnerable in the theater of operations because they had small hippocampii, the twin studies will show this. The two

structural profiles that were not on the list but could be beneficial were: (1) Oxygen 15 SPECT because it has more precision in time and space; and (2) magnetoencephalography (MEG) because it has both the spatial and temporal resolution and doesn't require electrical impedance matching. There are VA facilities equipped with MEG that could help validate some of the observations of event-related potential (ERPs) techniques and EEGs. Dr. Bloom stated that Dr. Haley had developed a very good program with a two-year timeline to decide which of these many possible leads was "the lead." Not to devote every effort to getting quantitative analyses of defined brain regions would be to possibly miss a neurological factor of importance.

Dr. Meggs commented that there were preliminary MRI data showing abnormalities that have been reproduced by another research center. This indicates that brain imaging is an important way to go. However, there may be other ways too.

Dr. O'Callaghan shared his perspective as a member of the UTSW merit review committee. He stated that there was an integration of the preclinical study designs that support and integrate with the neuroimaging research. There also was integration among the investigators on the preclinical side, providing a core animal dosing regimen. His concern was with the funding mechanisms that had been established. He stated that it was difficult to define the tasks for each subcomponent of an individual preclinical project. But the different projects had to move forward together to tie into the core that supported the preclinical program, and related to the neuroimaging projects. This needed to move forward to take advantage of the setup in place.

Dr. Barlow stated that she thought both Dr. Bloom and Dr. White were correct in their positions. It is a difficult challenge to do integration and translation when you haven't worked out the disease syndrome. However, she wondered if some component of the neuroimaging program could be more integrated with the clinical objectives. For example, if there were an experimental therapy used in conjunction with neuroimaging, one could see if there was a change in the imaging marker. Problems will arise if a biomarker is identified that doesn't change as the disease is treated. This will take you back to square one. She did not see any project in the proposed program that considered whether identified markers would be changeable and if so, if they changed as systems get better or worse.

Dr. Barlow also raised the issue of integration overall with this huge imaging component. She wondered if the logic for the program's neuroimaging component was "we want to look at prefrontal cortex and the best modality to do this is modality X. So this is why we use modality X." Or was the logic "we have some researchers that are interested in prefrontal cortex who use modality X by chance, so we are going to go ahead and use it." This neuroimaging program might be given more focus. It might decrease costs that the program can take a broad approach using researchers to which UTSW has access. But if the modality available is not the best for the region of interest, such as the hippocampus, should they divert their resources to look at the prefrontal cortex or should they be looking at the hippocampus?

Mr. Steve Smithson, a Committee member, indicated that the discussion had moved away from general comments, so he would forward his comments to Dr. Haley separately.

Chairman Binns commented that he didn't understand a contract where one gets paid after one has already spent the money. Dr. Goldberg, the Committee's designated federal officer, indicated that he couldn't speak to this point. This was purely a VA contracting issue, which is a process outside of VA's Office of Research and Development (ORD). ORD is not consulted or allowed input into the process. Chairman Binns asked Dr. Haley if he could explain the process. Dr. Haley stated that VA Central Office and UTSW were all "on the same page" and that this was not an adversarial process. When this Congressional allocation was first announced, the Inspector General took a strong position that this be

treated as a grant. The problem was VA does not have granting authority, so the only mechanism available was a contract. The Indefinite Delivery / Indefinite Quantity (IDIQ) contract mechanism was actually the best type for this purpose, and other agencies were also using it for the same purpose. The payment in arrears was something of a problem, and they would be discussing this aspect with VA soon. There have been a series of meetings to work through these hurdles, and the hurdles have been overcome. Dr. Haley was confident that future hurdles would be overcome as well. He also thought there would be a finite number of hurdles and that they would get to point where all of them would be solved.

In response to the question "What is a task order?" Dr. Haley commented that it was an evolving art. The National Survey was one task order. The blood bank was another task order. The paraoxonase lab was another task order. The neuroimaging program consisted of 25 task orders. Every box on the program diagram that he presented was a task order. The clinical science task order addressed bringing patients in for clinical tests. Every modality that probed patients was another task order. Every one of these task orders had deliverables and would follow a standard format. Once the neuroimaging core had been written as task order, the following task orders would use it as a "cookie cutter." It may seem wild and crazy, but it was actually logical and, as in a complex grant, provided a different account number for each project. At the end of the process, they will know exactly how much was spent on each project. While it has been "painful" just conceiving and preparing the task orders, it now seemed logical and would allow the program management core to monitor each project "deliverable." From a management point of view, it was doable.

Chairman Binns asked if Dr. Haley thought changes to task orders would be manageable. Dr. Haley thought that they would be. They would have to sit down and design the change carefully, describe it in the contracting format, and then go to the contracting officer with the details. It will then go through the contracting officer's technical representative, or "coder", who will determine whether the change is reasonable or not. If it is, it will be integrated into the wording of the task order. Chairman Binns hoped that the "coder" would develop enough expertise of his or her own to be able to understand why the proposals are being made and will be able to make decisions based upon the logic of the research. Dr. Haley stated that the "coder" on the contract was doing a terrific job. He noted that the memorandum of understanding and IDIQ contract provides that the merit review committee has the final say on science. So the "coder" doesn't review the science. He is reviewing it from a contracting perspective. Are the proposed task orders and/or change in line with what the merit review committee approved? He doesn't review the science per se. However, he is always present and very knowledgeable and objective. He is catching things that the Inspector General may identify objections to later. He has a lot of contracting experience, which is saving them from future headaches.

Chairman Binns suggested and encouraged Committee members to send their comments to the Committee office, who would organize them and send them together to Dr. Haley. This would provide a record for the Committee. Also, Dr. Haley would receive them as a package, but recognize that these were not Committee recommendations but individual comments. He asked if any Committee members objected or had a better idea about coordinating this.

Mr. Hardie thanked the scientists on behalf of ill Gulf War veterans. This was obviously a vast project that involved individuals from a wide spectrum of specialties. From the concerns that he had heard expressed by the scientists on the Committee, it seemed that the resounding one was how to pare back how much was being spent or how to spend money this way versus that way. Mr. Hardie found it to be of political concern and deep disappointment that this program was the "only show going." If there was more money and it was possible to do more of what was happening at UTSW at other centers, he wondered if the same concerns would be raised. He was pleased that the U.S. Senate was considering an amendment to the Military Construction Act that would appropriate funding for the U.S. Department of

Defense's Congressional-Directed Medical Research Program (CDMRP) for Gulf War research into treatments. If this was successful, there would be at least one annual appropriation again that might be able to provide some of the needed treatment research. For the record, Mr. Hardie stated that it was a big disappointment that about \$20 was being spent per Gulf War veteran today. It was extremely disappointing that sixteen years after the war this is the small pittance appropriated to Gulf War veterans. It was also a disappointment that so much of the funding in previous years was squandered and wasted on stress research or on things that were irrelevant in order to demonstrate that there was nothing wrong with these veterans. It is difficult sixteen years later to be receiving phone calls from ill Gulf War veterans. Mr. Hardie shared that he had just received a phone call that week from a widow of a Gulf War veteran who committed suicide because he was so ill. He didn't know what to tell these veterans or their families. So he sits on this Committee as an ill Gulf War veteran himself. He indicated that he was pleased with the efforts of those in the room but shared his disappointment that this was all that he and other Gulf veterans have.

Dr. Haley indicated that all of the comments and concerns raised around the Committee table about the direction of the program had been raised and discussed by the UTSW group, that is how to spend this money in a way to get us to a diagnostic test, understanding of the physiology, and a treatment. These are the goals. The question is how to use the money, which is an embarrassing amount of money for which he didn't ask, to achieve them. The governing point of all of this research and the approach they have taken is his belief that we don't know what "this" is. Dr. Haley stated that he did not value very strongly any of the previous studies with positive findings, including his own. He didn't think it was a very convincing amount of literature. We don't really have a good idea of what this thing is, and to overestimate or overinterpret that literature would be to squander a huge opportunity. He added that UTSW's MRI spectroscopy study was performed on 26 ill veterans who had Haley Syndromes 1, 2, and 3, from a group of 250 Seabees. He noted that only 40% of the battalion had participated, too, and that the study has been criticized. He said he was not reacting to critics, but the critics are right that this was not "truth." These are tantalizing clues and nothing more.

Dr. Haley said that the real decision point is whether to forget pathophysiology and understanding what is going on in the brain and go right to treatments, or to try to understand the pathophysiology and not go for treatments. Use of the serendipitous approach to find a treatment? If you are lucky, you will win and win quickly and cheaply. But if you aren't lucky, you will never win at all. Dr. Haley stated that DOD and VA tried this approach ten years ago with a doxycycline treatment study and a cognitive therapy and exercise combination study. These studies were negative and cost \$25 million. This was the serendipitous approach. The alternative was the rational approach, which meant they would go in and understand the disease first. Forget treatment for the moment. Once the disease is understood, work could be done designing treatments. Dr. Haley stated that this was a "surer" approach, but it is more expensive and will take longer to do. He indicated that the best thing to do would be to take both approaches with lots of money available to do so. Dr. Haley was confident that UTSW had designed the studies that would get the answers. However every time we cut back, we potentially exclude the "right" answer. He acknowledged that there may be additional things that they could do to broaden the likelihood of finding the right answer.

Dr. Haley added that they were doing a few things that might help them with the serendipitous approach. They have included questions in the national survey to find out if Gulf War veterans were getting better and if so, what treatments were working. If something is revealed, they will then program some money to do a clinical trial. However, he thought it would be a waste of money to go to treatments right now. We don't know anything about this disease. We need to define what the disease is, as well as what its variants and subtypes are. At that point, they can define homogeneous groups on which clinical trials can be conducted. Dr. Haley stated that if he did have a treatment right now, he would have to have a clinical

trial of 10,000 people because of the variety of illnesses. There is so much heterogeneity that a successful drug will have a tiny treatment effect. He noted that it had been sixteen years since the war and thirteen years since research was seriously begun. Ten years ago, people were impatient. We spent \$300 million dollars and we didn't get anywhere. We are impatient now too. But if we come up with a really great answer three or five years from now, people will find the value in this approach. Dr. Haley stated that the rational approach will get us somewhere for sure. If signals arise from the survey results, they may be able to start designing a clinical trial. To maximize the probability at this point, we need to concentrate our money on the things that might get us there and then, as quickly as possible, narrow it down to the things that will get us there. Dr. Haley stated that UTSW needed to put the first year's research money into the broadest projects and preclinical studies. He noted that Dr. Gilman and the merit review committee were wise to make these one-year studies, providing direction for the next year's research. Concentrate the monies up front, create the opportunities, and then focus down in a year or two to clinical trials. This was a judgment call, and this was where UTSW had come down.

Dr. Golomb stated that she didn't disagree about the treatment issue. However, this wasn't just an issue of whether to go for treatments or neuroimaging. The brain is obviously an end organ that is affected. However, there may be mechanisms that might be identifiable through other processes for which the brain is an end organ besides neuroimaging. Dr. Haley stated that he understood Dr. Golomb to be suggesting there may be additional options to include in the clinical core, which he was open to doing. These are things that could be done for a minimal cost. The cost is selecting and bringing the patients in for clinical testing. He indicated that he was in the process of trying to find someone who would test for mycoplasma fermentans in this sample. They want this to be the best biomarker study possible, testing as many hypotheses as possible. If there were suggestions to include in the clinical tests, these would be very helpful.

Chairman Binns thanked Dr. Haley. Dr. Haley stated that he really appreciated the input provided by the Committee. Every time these issues are discussed, they get a different perspective and it will influence what they are doing. He indicated his desire to keep talking about these issues.

Chairman Binns noted that there were several members of the public, many who were ill Gulf War veterans themselves, who wished to speak on the record. He asked these individuals to keep their comments to five minutes or less.

Public Comment – Day 1

Mr. Mike Hood, a Gulf War veteran from Wichita Falls, Texas, spoke to the Committee. He wished to discuss the health problems of veterans who served in the Gulf either prior to or after the 1991 Gulf War, but not during the Gulf War itself. He served two tours in the Gulf, one prior to the Gulf War (1988) and one following the Gulf War (1993). He stated that these veterans are not discussed or considered when it comes to health problems associated with exposures in the Gulf. He discussed his own health problems. While some Gulf War veterans look healthy, he asked whether those present would want a blood transfusion from a Gulf War veteran. He indicated that most would not. He stated that everyone who has served in the Gulf since 1982 should be barred from donating blood.

Mr. Ed Butler, national secretary of Veterans of Modern Warfare, spoke to the Committee. He stated that most of the presentations given that day were very relevant to the multiple sclerosis (MS) and MS-like problems facing many Gulf War veterans. Further, he noted that Veterans for Modern Warfare and the National MS Society were working together to see Congress appropriate \$15 million to the CDMRP for MS research. He asked the Committee if it would support this effort. He commented that, from his

personal observation, it appeared that the MS and MS-like clusters among veterans throughout the country had occurred in veterans who had been exposed to petroleum products while in the Gulf. This included, for example, oil refineries and manufacturing facilities that use petroleum in their products. He noted that Dr. Luanne Metz, a professor at the University of Calgary, was evaluating the number of MS cases found around the coal mining generators in that region. He indicated that she might be a resource for the Committee. He indicated that there were about 5,000 Gulf veterans who had been diagnosed with MS or MS-like symptoms, but noted that it is unknown how many were misdiagnosed. He understood that the Committee was not focused on MS, but wondered if it would support this type of research.

Mr. Kirt Love, a Gulf War veteran, spoke to the Committee. He stated that while some individuals feel it is a "dead end" and didn't need to be discussed, he believed that the Committee needed to consider whether ammonium perchlorate exposure during the Gulf War might contribute to the ill health of Gulf War veterans. He stated that Gulf War veterans were exposed during the ground war to a variety of aerosolized agents and propellants. This exposure was specific to combat deployment versus other deployments to the same region. He stated that soldiers were not warned during the Gulf War that they should not be near the vapor trails of the rocket launchers being used or to protect themselves from this particular exposure. The military is aware that this exposure may be harmful and is studying the effects of this exposure now. Mr. Love noted that ammonium perchlorate was now present in the U.S. water supply. Everyone in the room was probably positive for this type of exposure. He stated that this chemical had properties similar to sarin and other types of agents in theater. It was also testable via urine analysis or other methods. Mr. Love said that no studies of aerosolized ammonium perchlorate had been conducted, even though the government was aware that there were lethal concentrations on weapons ranges around the country. Most of the studies conducted have examined the water supply. This exposure is being trivialized even though there is little data on it.

Mr. Love expressed his displeasure that there were no Gulf War clinics, programs, environmental coordinator, or kiosk at his VA facility in Temple, Texas. He stated that this facility had more Gulf War veterans than any other VA facility in the country. He has brought this issue to the attention of VA Public Affairs, all the way to the senior coordinator at VA's Central Office in Washington, DC. Mr. Love stated that he was part of the effort that put in place the laws for these programs and was disappointed that VA had not been able to properly diagnose his condition. He is now seeking treatment, but it may be too late. He stated that short-term, not long-term, programs needed to be pursued, because veterans like him have no place to go right now. He stated that it had been announced that there would be a clinic with the UTSW program. However, VA has managed to turn it into something else. Every time veterans almost have a place to go for help, they are robbed of it. He said that the only reason he was alive was that he was conducting his own dietary trials and living in extreme measures. Medications didn't work for him and actually resulted in adverse reactions. The best he can do now is to do the dietary trials, e.g., dark chocolate. He has had to do these trials himself because there was no program or place for him to go for help. He indicated that this was not the fault of the Committee, but asked that it consider recommending small, short-term solutions, which could be done in conjunction with brain imaging. He stated that research was needed on real-time imaging, as well as long-term functional imaging. There were a variety of ways to do both short- and long-term research. A two-fold plan was needed.

Ms. Becky Cann, a Gulf War era veteran, spoke to the Committee. Ms. Cann did not actually deploy to theater because she became ill from the vaccines administered in preparation for deployment. She stated that she was sicker than many of the troops who were deployed. She received her vaccines in November 1990 and became ill almost immediately. She tried to deploy for several weeks, but was finally told that she would never be able to and would not recover. She said that she had found a treatment, thanks to an anti-aging physician. It involved IV therapy and sub-lingual medications, most of which are hormones. Oral medications did not work. She stated that she had been exposed to uranium too. If you lived in a

mining town or served in the Gulf, you were going to get sick. She stated that there were nine uranium mines in South Texas and the Rio Grande area. She has been forced into retirement, but is not eligible for Social Security. She stated that she had the same infections, chronic fatigue and cognitive function problems that affect deployed Gulf veterans. Their brains have changed. There are days that she can not drive, prepare her meals or even shower. She has had to seek this treatment on her own. The VA has diagnosed her as a "psych case." Anti-depressants cause people to commit suicide and go into rages. Their adrenal glands don't fit the description of people who are depressed. There is a need for tests, like brain scans, to show that there is a cascade of physiological events that have changed these veterans' DNA, hormonal system, adrenal glands, and brains. Veterans need treatments today because they were looking down the barrel of death.

Ms. Lauren Billings, a Gulf War veteran who was a navigator on an Air Force KC-135 air refueler, spoke to the Committee. She stated that to be on an air crew, you have to be one of the healthiest of the healthy. She served in the military from 1989 to 1996. Before she was deployed to the Gulf, she would become sick from her vaccines, which was dismissed by the medic. When she returned from the Gulf, she began experiencing extreme fatigue. She asked the physician if she had mononucleosis, chronic fatigue syndrome, etc. She began researching thyroid and immune issues. In the fall of 1998, she developed vision problems, which included sensitivity to light. After having a MRI and spinal tap, she was confirmed to have MS. She indicated that she was part of a minority among Gulf veterans, having received an actual MS diagnosis. She is trying to hold down a job which can be difficult because of the fatigue and cognitive problems. This has been particularly difficult because she has received a graduate degree, but no longer can remember and learn things like she used to. She also has two young sons that she is not able to interact with like she would like. She is sensitive to extreme heat and cold and can't be outside with them much. She does take Copaxone, but this is only slowing down the process. She recently found out that she has a family history of severe reactions to vaccines. Because she has been sensitive to all of her vaccines, she has not vaccinated her children. She expressed reservations about taking a good immune system and "revving" it up with "stuff," including metals.

Ms. Denise Nichols, a Gulf War veteran, spoke to the Committee. She noted that the Committee had reviewed oxidative stress, mitochondrial damage, and a broad range of other topics at its last several meetings. She was thrilled to see this progression. She wanted to keep pushing for all specialties and concerns to be included in the discussions. There should not be a single focus on neurological concerns. She stated that there appeared to be some bias against anti-aging and environmental doctors. She wanted the Committee to create a round table approach and invite all these parties and specialties to join in the discussions. She noted that there were at least three anti-aging and environmental physicians in Dallas, but none were invited to speak to the Committee. She indicated that they have treated Gulf War veterans and should be allowed to speak to the group. Ms. Nichols indicated that she loved Chairman Binns' charge to UTSW, as well as Dr. Kerr's presentation. Despite all of the ups and downs, she had a lot of hope. She asked that handouts of the meeting presentations be provided to the audience so that it would be easier for them to follow along. She indicated that it was difficult for the veterans to multi-task now. She also noted that there were social / interpersonal relationship problems among Gulf War veterans. Many were working to compensate, but were also dealing with fatigue and neurocognitive problems, which lead to these problems. She asked Dr. Haley if there were measures for these social and behavioral problems. She stated that they were not like this before the war, and they were fighting not to be so now. It has led to problems with their families. She also noted that Gulf veterans became tired faster, had noise sensitivity problems, and sexual dysfunction for both male and female veterans. She noted that she had a few suggestions that she would like to make for the UTSW program. There was a lot of money and it needs to be used in manner that "works." Testing for pituitary function and thyroid hormones should be done on all the individuals brought in for the clinical phase of the study. There are things that we can do to help these veterans.

Chairman Binns thanked the veterans who spoke.

The meeting recessed at 5:48 p.m. for the day.

Day 2

The meeting reconvened on Thursday, July 19, 2007, at 8:33 a.m. at the Hilton Anatole, 2201 Stemmons Freeway, Dallas, Texas. Dr. Nettleman was not present for the second day of the meeting.

MRI Reveals Evidence of Structural Brain Differences Among Veterans Deployed to the first Gulf War

Roberta White, PhD
Chair, Department of Environmental Health
Boston University School of Public Health

Dr. White gave an overview of her research team's preliminary findings on structural brain differences that distinguished Gulf War veterans with high levels of symptoms from those who were less symptomatic. ([See Appendix – Presentation 12.](#)) These findings had previously been presented at a scientific meeting, and had been reported in the press. Analyses were not yet complete, but Dr. White indicated that she was confident about the findings because they had also found a relationship with function.

Ms. Knox asked Dr. White if she thought her findings indicated brain atrophy in these Gulf War veterans. Dr. White said that it was unclear. It could be brain atrophy but it could be their brains were always smaller. She commented that the press releases about the study suggesting a “shrinking” of the brain, but she was not sure this was the case. She added that the issue of causation would be clearer when she was able to look at the exposure-related outcomes. If she found clear relationships between brain measures and exposure to sarin and cyclosarin or pesticides, she would be more comfortable saying the brain change was related to some causative factor. However, it could have been a risk factor. That is, individuals who have smaller total cortical brain areas might have been more susceptible. This would be incredibly important to know because it would tell us who to worry about and who might be particularly vulnerable to an experience like the Gulf War theater. She was not able at this point, however, to say if the differences were due to shrinkage or a pre-existing structural difference. Ms. Knox asked if any of these veterans had had MRIs prior to serving in the Gulf War. Dr. White stated that none had, but they did have scans from one or two from the 1990s. She has been advocating that predeployment testing include imaging, but to her knowledge this is not happening.

Dr. Meggs asked if the study participants had been asked to donate their brains to medical science upon their deaths. Dr. White stated that they had considered asking for several types of tissues to bank. They had made a big effort to bank blood, but VA would not allow it. If they had the bloods from these veterans, they could look for new genetic information and perhaps biomarkers. Brain banking is a good idea, but it was far beyond what she was funded to do. She indicated that one study participant had called her recently asking how to donate their body to the medical school.

Dr. Golomb noted a recent study looking at magnetic resonance imaging in patients who had self-reported cognitive loss and found that these patients had, on average, greater brain atrophy than control patients, despite having normal neuropsychological test scores. This is another reason to listen to one's patients

when they have something for which you have not yet identified a measure. Dr. White agreed and characterized her findings as preclinical. Since the New York Times article came out, she had spoken with many Gulf veterans who had white matter lesions. But she didn't think it was just matter of brain lesions, but the small differences in volume. It was similar to the situation with neuropsychological test measures differences that are often not considered clinically significant. For example, one would not diagnose amnesia from the differences identified in the California Verbal Learning Test. What subclinical and preclinical findings tell us is that it is important to listen to patients' complaints when they don't meet diagnostic criteria for something. Exposure to chemicals and other things can result in symptoms and changes in brain function that aren't "big" enough for us to see clinically.

Dr. Golomb noted that the normal range for these cognitive tests encompass a wide range of people and levels of ability. A person can have marked cognitive losses that affect their daily lives and job performance and still fall in the normal range. Sensitive pretesting, followed by post-testing, was needed to determine the variation, but this was difficult to establish in an individual. Dr. White commented that this was not case with neuropsychological testing, since the baseline was not set at "average," if average is what you call "normal." The baseline used a model of what people were like before a brain insult. Many CEOs get early MS and no longer can be a CEO. They may obtain a normal test score, but it is still a standard deviation or two from their baseline.

Dr. Barlow asked if other brain areas were examined, and if so was this area the only one in which abnormalities were found. Dr. White stated that that they examined about 15 brain areas and total volumes during the preliminary analyses. These were the targeted areas. They are now looking at everything, as well as all the white matter measures.

Dr. Haley stated that this was an important question for anybody doing neuroimaging studies. He frequently gets calls from veterans who have had a brain scan, asking for his thoughts on the results. Many times the lesions seen in the white matter are probably the unidentified bright objects (UBOs) that neuroradiologists see. In his previous studies, SPECT scans and MRIs were conducted on cases and controls. They found that the UBOs were the same in the sick and well subjects. This is true in neuroradiology in general. These UBOs are bright specks that appear to be defects in the white matter. However, they are really nonspecific findings and may have no clinical significance. This is controversial. Some people may say they do have significance. But he believed that they don't appear to be related to disease and symptoms. He added that his group had conducted SPECT scans because of the growing research using this technique on people with unidentified illness. They had done a study where three or four radiologists read the scans of cases and controls blinded. They found that there was not one lesion that more than one radiologist identified, and these findings were the same in the cases and controls. Quantitative comparisons were needed. And there also needs to be a very good control group or good series of "normals" to which one is comparing values, e.g., volumes, lesions, etc. He thought that things that radiologists see visually are not related to this class of illness.

Dr. White questioned this, and noted that there was a way to take digitized measurements of white matter lesions. There also was a lot of evidence that having more white matter lesions was associated with mild cognitive impairment. There are also studies showing dose effect relationships between the amount of white matter and cognitive change. She agreed that it was controversial. If you talked to a clinical radiologist or neurologist versus a neuropsychologist or a vascular dementia expert, you would get differing opinions. Dr. Haley thought that they agreed. If one digitized lesions or volumes and compared them to normal values, this was reasonable and should be done. But they shouldn't rely on a visual interpretation of a neuroimaging scan, which are the main source of questions from veterans. Dr. White agreed, but noted that they can do these automated readings without doing a special kind of scan. There are two reasons she started using neuroimaging in the 1990s. First, brain scans deliver a strong public

health message. When she conducted neuropsychological testing, she might believe there was an exposure/outcome relationship and changes in the brain of the patient. But she knew that these findings did not have the same impact as pictures showing a brain difference related to sarin exposure. The other reason is that post-processing techniques are improving every day. They can take old scans and do new processing and find amazing things.

Chairman Binns stated that he had found Dr. White's studies very persuasive because they were imaging studies. One didn't have to go through an extra layer of interpretation, which may be easy for well-informed scientists to understand, but was less obvious to lay people. Similarly, he understood neuroimaging better than the functional tests, e.g., moving pegs around on a board. He asked Dr. Haley if straightforward volumetric imaging that could be matched with comparable psych tests was included in the proposed research at UTSW. Dr. Haley indicated that it was.

Dr. Steele commended Dr. White for her research approach, and specifically for the parallel studies that correlated imaging findings with studies of function. She also pointed out that Dr. White had symptom data on this cohort at repeated intervals since just after the Gulf War. On the question of whether individuals with smaller brain volumes had been more susceptible to exposures, she wondered whether this was testable in animals. Dr. White stated that it could be tested depending on the animal model. She wasn't sure whether mouse models would be sufficient. She is using a primate model looking at the effect of mercury on white matter. This provides a better comparison of brain changes but it is very expensive.

Dr. Bloom commented that there were a lot of data on mouse models of human neurodegenerative diseases. One could do high resolution tests, e.g., 9 Tesla MRI, that bring the resolution down to 100 microns volumetrically. A transgenic mouse line has been established for Alzheimer's disease. Changes can be seen in a matter of 4-5 weeks. Generally, the problem is not tissue degeneration but rather failure to proliferate and achieve adult status. These mice start out with smaller hippocampi, for example. This suggests that the genes that cause human neurodegenerative disease may strike a lot earlier than the pathological findings that are observed when symptoms present. So these animals enter an exposure period with a smaller than normal brain. Similar studies have been done on mouse models of ALS. One can spot, with high resolution, early changes that precede the motor weakness that occurs. However, he was not sure there had been a study done across mice strains with sarin exposure for long-term chronic effects. It would not be a cheap study to do. He had a contract with CalTech, who had a 9.4 Tesla machine, to do a similar study. It cost him about \$5,000 per mouse. However, it was an approach that didn't require the removal or dissection of the brain. It allowed him to see gray matter and white matter boundaries and could segment and show findings for selected brain regions. The key was to have good hypotheses before conducting this type of study. Dr. Steele expressed surprise that it cost so much to study animals. Dr. Bloom noted that these animals were dead and could be scanned over nine hours. A human could never lie still enough for that period of time. Also, the heartbeat and respiratory rate of a mouse are such that one loses resolution if the animal is alive during the scan. It "jiggles" the brain and causes the boundaries between grey and white matter to be blurred. Because these animals are clones of each other, one doesn't have to follow an individual animal. The next generation will be exactly the same.

Dr. Barlow commented that we don't know if these structural differences in Gulf veterans predisposed them to developing the symptoms or were the cause of it. When one tries to model this in an animal, one has to figure out how to create a model that is predisposed. We don't know what this would be so you would need to begin with a range of animals with different brain types. But since we don't know what causes differences in brain types, you might not pick the right reasons for the brain types. Until we better

understand the genetics that give rise to differences in brain size, it would be very difficult to study this in an animal model.

Dr. Golomb commented that to assume that the smaller brain volume predisposed one to the injury, one would also have to posit that individuals with smaller brain volumes were also selectively exposed to more sarin. Dr. Barlow stated that one would have an increased risk for damage from the same level of exposure. Dr. Golomb understood this, but thought Dr. White had also found that people with higher quantitative exposures had more brain atrophy. Dr. White said that they had found a dose-effect relationship in the white matter volumetric findings. She believed this provided support for suggesting that sarin might be a causative factor for the brain volume differences.

Dr. Steele asked if there was any literature on what it means clinically to have reduced brain volume in the areas described by Dr. White. For example, does reduced cortical volume correlate with a specific condition or problems? Dr. White stated that there was quite a bit of literature on the relationship between structure and function. This was part of the neurocognitive field discussed during the previous day. There is considerable literature on individual diseases as well. Dr. Steele asked what other diseases or conditions might be associated with findings similar to the reduced brain areas identified by Dr. White. Dr. White indicated that one disease would be MS. She thought MS was an interesting example because there were a number of neurotoxicant exposures that have been related to the development of MS. Another example might be some forms of epilepsy.

Ms. Knox asked Dr. White if any of the veterans in her study had been diagnosed with MS or if MS had been ruled out as a cause for their symptoms. If they had atrophy and lesions, did any have optic neuritis or spinal fluid testing? Dr. White replied that the patients she had described did not have, by definition, lesions. One study participant did have MS and lesions but his data were not part of the analyses that she had presented. Ms. Knox asked how they had differentiated the lesions from the UBOs. Dr. White indicated that they had quantified them and that she didn't have all of these data yet. There was a total white matter lesion volume measure. But none of the patients from the data shown that day had clinically abnormal scans. Two independent radiologists found the scans to be normal. They did this in order to inform participants about whether or not they had abnormal scans. These individuals did not have lesions, but rather had differences in specific structural areas. This is what she meant by examining the subclinical or preclinical picture.

Dr. O'Callaghan stated that he had been impressed with their finding of a decrease in the cortical volume. If this was viewed as an atrophy that had started at a certain point, this was a larger decrease than he had ever seen with other neurotoxicant exposures, including a host of demyelinating agents. He asked if there was age-related loss of myelin volume that could be detected with MRI. Dr. White said that there was and that they had adjusted for this. Dr. O'Callaghan asked if there was a gender difference. Dr. White stated that some researchers thought there was, but others didn't so they had been looking at it both ways.

Chairman Binns opened the floor to the public for brief questions on the presentation.

Mr. Hood asked if Dr. White had been able to distinguish the veterans based on the areas to which they were deployed in the Gulf War. Dr. White stated that they had self-reported veteran location data, unit information, and some GIS-coded data related to where the veterans were at various times during the war. Mr. Hood asked if Dr. White was aware that there were other areas besides Khamisiyah that were sites of possible chemical and biological exposures, for example, Al Nasiriyah and Tallil Air Base.

Ms. Nichols noted that neurocognitive testing was an element of the Gulf War registry exams. She asked Dr. White if any of her study participants had had one of these exams and if so, would she be able to

repeat this testing and would it be an effective measure. She also wondered if a veteran had a predeployment IQ measurement, whether (1) new IQ measures should be obtained, and (2) would those measures have been adequate. Dr. White said that she avoided using IQ measures, except as a sort of control measure. She indicated that they did have previous neuropsychological data for many of these participants from previous study visits. The point of doing the California Verbal Learning Test and peg board was to look at function. These two tests showed consistent effects that were related to self-reported and other exposure measures.

Chairman Binns thanked Dr. White.

Chairman Binns introduced Dr. Bill Meggs, a Committee member and Chief of Toxicology at East Carolina University School of Medicine.

Environmental Medicine and Gulf War Illnesses: Does the map fit the territory?

William J. Meggs, MD, PhD

Chief, Division of Toxicology

East Carolina School of Medicine, Greenville, NC

Dr. Meggs gave an overview of environmental medicine, including discussion of diagnostic techniques and treatment, and how this area may inform the diagnosis and treatment of ill Gulf War veterans. ([See Appendix – Presentation 13.](#))

Following Dr. Meggs' presentation, Dr. Steele inquired whether the pupillometry testing was used for people who were routinely exposed to organophosphates or other pesticides, and also whether it could be informative only near the time of exposure, or even years after exposure. Dr. Meggs stated that the Ishikawa study participants had acute organophosphate poisoning, then recovered and were tested at a later point. It was not acute exposure testing. The occupational studies brought in individuals who were exposed every day to organophosphates, who tolerated the exposure and were still working. Using the control group, they were able to show these exposed workers had abnormalities. Dr. Steele asked if Dr. Rea had used this type of testing in his patients who are long removed from their exposures. Dr. Meggs indicated that Dr. Rea did use it. He indicated that the testing did not have value for treatment, but did document subtle, subclinical brain damage.

Dr. Steele noted Dr. Meggs' discussion about parallels between sinusitis and rhinitis symptoms and chemical sensitivity. She asked whether successful treatment of the upper airway symptoms had any benefit for other chemical sensitivity symptoms or systemic symptoms. Dr. Meggs said that he had prescribed nasal steroids and antihistamine decongestants for these patients, but many could not tolerate the nasal spray due to irritation. He had found Nasalcort AQ, which is an aqueous solution, to be better tolerated. The really severe patients, the ones who had chronic fatigue, neurocognitive problems, etc., did not seem to be helped by these treatments. From his clinical impressions, individuals who were compliant with creating a clean environment and avoiding chemicals did get better in time and became more tolerant. However, they never lose their chemical sensitivity. He was only aware of two instances where an individual was reported to have been cured. One was reported in a religious book that discussed medical healing. The other case reported a cure resulting from hypnotism. If it is really a neurological pathway set up to cause severe localized reactions to stimuli, which are acquired via learned behavior, this might explain these outcomes. However, his experience was that most people get better over time using avoidance techniques and limiting their chemical exposures, but they were not cured.

Dr. Bloom noted that Gibson's study did find that prayer was the third most effective treatment. Dr. Meggs indicated that was correct.

Dr. Golomb said that her clinical experience with chemical sensitivity patients mirrored Dr. Meggs' experience. She indicated that she had a couple of patients who went to another country and upon return had severe reactions. She stated that there was evidence that in conditions involving oxidizing stressors, the body upregulates antioxidants, but not necessarily at levels sufficient to return to normal. She discussed research at the University of California at San Diego's that looked at sinus irrigation as a treatment. Many of her patients who have used this technique have given up nasal inhalers, which was good considering their chemical intolerance.

Dr. Steele noted that there had been a VA physician, Dr. Myra Shayevitz, who was familiar with multiple chemical sensitivities, and had a clinic for Gulf War veterans in a VA hospital that incorporated environmental controls. Dr. Shayevitz never did a formal study, but reported to Congress that she had treated 25 patients and had some positive results. Several of these patients wrote letters to Congress about the success of their treatment. Dr. Shayevitz believed that this type of study should be done on a larger scale for Gulf War veterans. Dr. Meggs commented that it would be easy to create one of these environmental control units in a VA facility. Because the facilities are typically of older construction, simple modifications and bans on chemicals on the ward would allow for the creation of a reasonably controlled environment. Dr. Steele said that Dr. Shayevitz's unit did not require construction, simply the banning of chemicals and education of patients on how to avoid chemicals. Dr. Meggs stated that this would be easy to do, i.e., creating a relatively clean environment compared to the living environment of the average person.

Mr. Hardie related his own experience with multiple chemical sensitivities, sinusitis, and lung problems. He indicated that he had sinus surgery 10 years ago, involving the removal of bones and mucous membranes. He found that until swelling returned eighteen months later, he had some of the worst sensitivities in his life. He wondered if Dr. Meggs had heard similar complaints from others. Dr. Meggs indicated that he had. A parallel would be the observation that bronchodilators increased mortality from asthma. One reason is that the bronchospasm is being treated but the inflammation is not. Inflammation is what individuals die from. Bronchospasm is actually a protective reflex. It is triggered by sensory C-fibers in the upper airway. When a noxious stimuli enters the airway, a neural reflex creates a bronchospasm to protect the lung and a burning sensation to prompt flight. Dr. Golomb said that another issue was that beta-agonists cause down regulation of beta receptors in the airway. So when one experiences a bad exposure and goes to use his or her inhaler, it is no longer as effective. Dr. Meggs added that asthmatics were more likely to die from mucous plugging and other inflammatory response than bronchospasm. He acknowledged that it was a multifactorial situation. He noted that one of the effects of corticosteroids was to upregulate the beta-receptors so that bronchodilators work. But the point was that bronchospasm was only one component of asthma, which is an environmentally-induced, pathological alteration/inflammation of the airway.

Chairman Binns noted that many members of the audience had experiences related to these conditions and treatments and he would like to hear about them. However, due to time constraints, he could offer them the opportunity to speak at this point of the meeting or at the scheduled public comment period later in the day, but not both.

Mr. Hood spoke about his experiences with multiple chemical sensitivities and other health conditions. He learned on his own over time how to avoid bad environments and exposures. Many Gulf War veterans are self-reporting similar symptoms, but VA has "shut the door" to them. He noted that Gulf

War studies exclude those veterans who served in the Gulf but not during the 1990-1991 war itself. He is working to get Gulf War veterans involved in addressing this issue.

Dr. Ruth McGill, a physician and audience member, spoke to the Committee about her personal experiences in an environmental control unit. She indicated that, in reference to Dr. Haley's and Dr. White's studies, her neuroimaging results had been positive. In her own case, she was able to establish the connection between environmental exposures and her condition. She stated that the nervous system was a two-way street. The nervous system "talks" to all of the other body systems, especially the immune system, and will raise alarms. One of the things that an environmental control unit does is minimize the stimulation and makes it possible to clarify what the actual stimulants are. This provides relief for the patient who enters one of these units. However, when the patient leaves the unit, the suffering starts all over again. Dr. McGill indicated that she created an isolated environment for herself at one point, living in a "ceramic box" in the desert with care by a visiting nurse. She indicated that she had a lot to share about the treatment of multiple chemical sensitivities. She was happy to answer any questions that the Committee might have, providing more details than had been presented by Dr. Meggs. She indicated that she could be contacted through her website.

Chairman Binns thanked Ms. Nichols for suggesting that this topic be discussed at a Committee meeting. She indicated that she would comment later during the scheduled public comment period.

Mr. Hardie noted that many present in the room had tried several of the treatments listed in Dr. Meggs' presentation. He noted that use of alcohol nasal spray on mucous membranes was an experience that would not be soon forgotten.

Chairman Binns thanked Dr. Meggs and said he believed that a lot could be learned from these experiences. If nothing else, it seemed to him that pupilography testing was an inexpensive way to test the autonomic nervous system. Dr. Haley indicated that the method was included in the UTSW research protocol. Chairman Binns was glad to hear this. He noted that it would be difficult for many VA facilities to adopt some of the more exotic and expensive imaging techniques.

The meeting recessed for a break at 10:54 a.m.

The meeting reconvened at 11:08 a.m.

Dr. Ferree gave a brief explanation about a handout he had brought with him to explain UTSW's decision to use EEG, rather than MEG, testing in their Gulf War research program.

Chairman Binns thanked Dr. Ferree.

Update on Research in Persian Gulf War Veterans Illnesses

Beatrice A. Golomb, MD, PhD

Associate Professor, University of California at San Diego

Dr. Golomb gave an overview of published research related to the health of Gulf War veterans that had emerged since the Committee's last update in November 2006. ([See Appendix – Presentation 14.](#))

Chairman Binns thanked Dr. Golomb and asked Dr. Steele to proceed with the discussion about the Committee's report that was being prepared.

2007 RAC Report: Discussion of Recommendations

Lea Steele, PhD

Scientific Director, Research Advisory Committee on Gulf War Veterans' Illnesses

Dr. Steele reviewed the comments and the types of changes and additions that had been recommended by Committee members in relation to the draft report discussed at the Committee's April 2007 meeting. ([See Appendix – Presentation 15.](#)) She asked Committee members for their opinions and input on additional types of recommendations that had been raised by members.

Dr. Golomb wondered if it would be useful for the Committee to recommend that veterans avoid exposure to chemicals. Dr. Steele stated that this was implied to some extent by some of the information in the report, but that since these were research recommendations, the focus should be on collection of data. She said that anecdotal reports suggest that chemical avoidance is a good thing. But it would be nice to establish scientifically whether this was helpful to veterans or not. Such findings could also provide a basis to make a formal recommendation for a clinical trial of chemical avoidance. Dr. Golomb indicated that there was evidence to support this type of recommendation.

In the discussion of the need for additional follow-up of the large national epidemiologic study conducted by Dr. Kang, Dr. Melling asked if any gaps had been identified in Dr. Haley's and Dr. Kang's epidemiologic studies. If so, he wondered if the Committee should suggest that work be done to develop a study or studies to cover these gaps. Dr. Steele said that Dr. Haley indicated he had incorporated some of the questions that had not been answered by Dr. Kang's original study into the UTSW National Survey. But if Dr. Kang did a follow-up study again, it would be good for him to address some of these questions. Dr. Steele added that Dr. Kang's initial follow-up study had not originally asked about multisymptom illness or changes in symptoms over time. But he had accommodated a request by the Committee to incorporate this information into his study.

Dr. Haley commented that it was important to think separately about Gulf War illness/multisymptom illness and rare neurological disorders like Parkinson's disease and ALS. This is because no survey will capture these disorders. The VA has a huge clinical database that could be utilized. Dr. Haley noted that Dr. Kang did some preliminary analyses and presented them a few years ago, but they were unsatisfying and incomplete. Dr. Haley suggested that the VA conduct surveillance for these conditions. Dr. Steele noted that this recommendation had been made previously. However, it had been suggested that most veterans who have these conditions are not being treated at VA. Due to the delayed onset of some of these diseases, many veterans do not connect the condition with their service. Dr. Steele added that there would also be a need for a comparison group of nondeployed veterans to determine if there was an increased disease rate in deployed Gulf War veterans. Dr. Haley thought such surveillance could be done for those with ALS using mortality data because of the short period of time between onset and death. So the incidence rate was about the same as the mortality rate. Dr. Haley stated that surveillance of brain cancer should be done as well.

Dr. Haley asked about the status of the ALS registry at Duke University. Dr. Steele noted that this was a passive registry that had identified only 50 cases of ALS among Gulf War veterans, and this number was dwarfed by the large number of registry participants from other eras. Dr. Haley reiterated that he still thought there was a need to conduct surveillance of the VA database for these neurological conditions. Dr. Steele stated that there was a general recommendation to monitor for increased cancer and serious neurological disease rates. The Veterans Health Administration database could be included as an example of a source of information to monitor. Dr. Haley agreed that such a suggestion should be made.

He noted that when one was first considering such a study, he or she could probably think of five different reasons why it shouldn't be done. However, a good epidemiologist can think about the question/problem carefully and can probably figure out a way to make the findings meaningful. It is a surveillance tool. It is not an accurate measurement of incidence. However, through surveillance, one might be able to detect if case numbers appeared to be "passing the threshold." Dr. Haley noted that MS was a fairly common disease with a known age distribution. He thought that creative analyses could be done with the data in the VA's databases to see if the rate of MS was above an accepted threshold. Dr. Steele said that this approach might raise a red flag.

Aside from using this approach for rare diseases, Dr. Steele asked Dr. Haley for his thoughts on reassessing disease rates longitudinally at specified intervals. Dr. Haley agreed that this would be good to do too, noting that consideration had to be given to optimal intervals, funding available, new research discoveries that might inform about new treatments, etc. He suggested 5-10 year intervals with ongoing discussions about when specifically to do it and which data collections should be repeated. Dr. Steele noted that with the data from Dr. Haley's and Dr Kang's samples, along with mortality data collected down the road, they would have self-reported symptom and exposure data on a large sample that could be related to health outcomes and mortality. Dr. Haley agreed.

Dr. Steele asked the other Committee members if a recommendation should be made for additional longitudinal evaluations to follow-up Dr. Kang's original study. The general consensus was "yes." Dr. Meggs stated that it should be done at least every 10 years, but the interval may change if case reports suggest an increase in any particular condition, e.g., MS. Chairman Binns commented that he believed that additional epidemiologic study of neurodegenerative diseases, including MS, had been covered by a recommendation in the Committee's 2004 report. Based on this recommendation, the Senate Veterans' Affairs committee had written a directive into the VA authorization bill for FY2008 that this study be conducted. Other high risk illnesses might also be addressed by this mechanism.

In relation to the discussion of the potential for chemical exposures after the war to have precipitated or exacerbated illness in Gulf War veterans, the Committee indicated its consensus for a recommendation that Gulf War epidemiologic studies collect data on onset and/or exacerbation of Gulf War illness and other conditions in relation to exposure to hazardous substances subsequent to Gulf War service.

Dr. Steele then provided background information on issues that had been raised in relation to the Institute of Medicine's (IOM) Gulf War and Health series of reports. With regard to the update report on sarin exposure that was part of this series, Mr. Smithson noted that the IOM report had not reflected the reason it had been commissioned to reexamine effects of sarin. He noted that the reason for the request was to consider animal study data, but the IOM did not seem to acknowledge this. Chairman Binns stated that the letter from former Secretary Principi was very clear in saying why he was requesting that IOM reconsider the evidence of health effects related to sarin exposure. The disconnect between the report and the reason for the report had happened further downstream in the organization.

Dr. Golomb commented that her father was in the National Academy, and he had commented that National Academy reports are known to be reports "for hire." Often, individuals who are not in the National Academy prepare the reports with conclusions in favor of whoever funded the report. She said that there has also been criticism of the fact that IOM committees sometimes have members with known conflicts of interest. She noted that GAO (U.S. Government Accountability Office) reports seemed to be more balanced. She wondered if there was room to suggest that VA commission a GAO report instead. Dr. Steele stated that the statute says if an agreement with IOM to conduct this type of review can not be reached, the Secretary may contract with another organization of similar stature and expertise. She was not sure what organization might fit this description.

Dr. Steele commented that, in addition to the issues discussed regarding the use of animal studies, the IOM reports had also been selective in which studies had been considered and presented. One clear example was its failure to incorporate information from epidemiologic studies of Gulf War veterans. For example, in Volume 4, the IOM reported on the rate of multisymptom illness in Gulf War veterans. In RAC-GWVI reports, the Committee has listed figures from seven studies with findings in both deployed and nondeployed veterans. Six out of the seven studies show an excess of between 25 and 30 percent of Gulf War veterans are affected by multisymptom illness, in comparison to nondeployed veterans. One study reported that excess to be in the range of 13 to 15 percent. The IOM report only provides figures from this one study, with no mention of other studies' findings. There were many other examples that could be provided.

Dr. Steele indicated that one positive aspect of the IOM reports was that their focus on occupational exposure research in other populations made them a good resource for this information. However, IOM had fallen short in considering all of the other areas of information related to Gulf War illness, the health of Gulf War veterans, and effects of exposures in the Gulf War.

Dr. Golomb questioned the quality and evidence reviewed by IOM and stated that she wasn't sure if the Committee should even recommend IOM prepare another report. She indicated that in a study of the anthrax vaccine, the IOM had found the vaccine to be inherently effective against all forms of anthrax. This was based on the fact that the vaccine targeted protective antigen, which was present in every form of anthrax. But Dr. Golomb noted that there was mouse data that directly contradicted this conclusion. The mice present an antibody response to protective antigen, but are completely unprotected to future anthrax exposures. There are no data in humans to support that the vaccine is effective against different forms of anthrax. In light of the fact that there was directly contradictory evidence on effectiveness but no supporting evidence, Dr. Golomb expressed her reservations about advising another report be prepared.

Dr. Steele indicated that she thought it would be possible to address Dr. Golomb's concerns in the recommendations. She then outlined several possible recommendations that were detailed in her slides and asked for discussion of the different options. Mr. Smithson commented that, if the Committee recommended that another organization produce a new report, it should identify this other organization. Dr. Steele noted that it was difficult to identify such an organization. Dr. Melling stated that the great advantage of staying with IOM was that it was identified in the statute. He suggested that a powerful recommendation would be to acknowledge the law and asked that it be properly applied. If the study is then done properly, it would be even more powerful because the IOM, in effect, would have to reverse itself. Chairman Binns agreed with Dr. Melling. He commented that Dr. Golomb's first point may be the "telling one." If IOM is a business for hire by government agencies, it is known that if you hire a consultant, they will produce a report that says what you want.

Dr. Bloom disagreed, stating that this was not true. As a co-chairman of the National Academy's report committee, he sees all IOM reports designated for review. The report committee goes to great lengths in selecting reviewers and monitors the reviews to ensure they have no conflict of interest in relation to the outcome of the report. There may have been problems with biased reports in the past. However, for the past four years while he has served as report committee co-chair, he has strictly scrutinized the reports for potential bias. In cases where it has been identified, he has advised that it be made explicit that certain members of the committee in question may benefit from the outcomes of the report.

Chairman Binns stated that he was pleased to hear this and expressed his appreciation for Dr. Bloom's effort to resolve this issue. Scientists who have served on IOM committees have certainly been honorable scientists. To the extent to which there has been this type of influence, he stated his belief that it was at

the staff level. He thought the statute did not envision that there could be another organization suitable for this process. And he did not view it as IOM's fault that this has happened.

Mr. Smithson commented that the proposed recommendations 1 and 2 were reasonable, as they simply require asking IOM to redo the studies based upon the requirements of the original public law passed by Congress. He indicated that recommendation 3 was open to debate.

Dr. Bloom stated that the text that followed these recommendation bullets would have to state the problems related to VA's commissioning the reports in a way that did not match the requirements of the public law. Dr. Steele indicated this was addressed in the text of the chapter. That text laid out the facts described in her presentation, and was followed by the recommendation bullets. Chairman Binns stated that he thought it could be made clearer that VA, in contracting with IOM, did not commission reports that were in accord with the statute. Dr. Bloom stated that there was great discussion about the statement of task whenever a proposal comes to the IOM. These statements of tasks are listed against the recommendations made by the committees. If the recommendations don't match the statement of task, the report can not pass review.

From her review of the list of panelists and reviewers on these reports, Dr. Steele indicated that she was stricken by their lack of involvement in, and probably lack of familiarity with, the Gulf War illness research literature. She wondered if this was done on purpose. The reports appear impressive at first glance, owing to the volume of information described. So even reviewers who are great scientists, but know little about the information not considered, might conclude that the findings were "kosher." Dr. Bloom stated that while they are not specialists in this area, the reviewers should be wise enough to appreciate the facts.

Dr. Bill Goldberg, the Committee's designated federal officer (DFO) was asked for his thoughts on a possible recommendation to reassign responsibility for commissioning these reports away from VA's Office of Public Health and Environmental Hazards (OPHEH) to VA's Office of Research and Development (ORD). Dr. Goldberg stated that his reading of the statute was that the intent of these reports was to advise the Secretary on issues such as clinical care, benefits, and service connection. These issues are clearly outside the purview of ORD. ORD also would not have the funds to commission these reports, and the funds could not be transferred as they were part of the clinical appropriation. He stated that there were legal, contracting, and appropriation reasons why this transfer could not happen. Dr. Steele asked if it could happen if the funds were appropriated to ORD. Dr. Goldberg stated that it was a benefits issue, and the monies for benefits and clinical care could never be moved to ORD. He stated that the law would have to be rewritten to provide for this transfer and change in purpose. Dr. Steele commented that, in reality, the IOM reports were used for much broader purposes, and noted the fact sheet prepared by OPHEH for Senators Murray, Rockefeller, and Bond.

Chairman Binns commented that Dr. Goldberg's point was very interesting. He stated that one of the central problems was that OPHEH, on its own initiative, had begun to usurp the role of ORD and treat these reports as something to be used much more broadly than advice related to benefits. For example, the Secretary had recently been asked by several senators about the recent studies done by Dr. White and her team in Boston. The response, which was drafted by OPHEH, indicated that they were going to refer these questions to IOM, "which is the body that reviews Gulf War health studies for VA on a biannual basis." Chairman Binns stated this letter basically said that VA was going to use IOM, and didn't acknowledge that Congress had already established a body, i.e., the Committee, to advise on Gulf War research. He appreciated that Dr. Goldberg and ORD were not able to act on this. However, if the Committee did not address this situation, it might as well say it was wasting its time here. Somebody at VA had decided to use IOM, instead of the Committee, to advise on Gulf War research. This was not

right, nor what Congress intended. He thought, therefore, that the last recommendation should be included, with careful wording.

Dr. Haley asked if it could be worded so that when OPHEH issued these contracts for research reviews, it was with the concurrence of ORD. Dr. Steele commented that she wasn't sure why this process could not be removed from OPHEH. The statute may state the purpose is to advise on benefits. However, the information being reviewed is research. Chairman Binns indicated that he thought Dr. Goldberg's understanding of how VA budgeting operated was accurate. He thought that, in the worst case, the language could advise to move the contracting responsibilities out of OPHEH and suggest that the process should be concurred by ORD.

Dr. Haley thought there could be a distinction between contracting for the reports and the task of creating the charge to IOM. The contracting authority could stay in OPHEH. However, the charge could be written by ORD and given to OPHEH to go into the contract. Dr. Goldberg stated that ORD reports to the Secretary. OPHEH does as well. Each of the offices' charges come from "on high." ORD could not tell another office how to operate their shop. And OPHEH could not tell ORD what it should be funding in research. If OPHEH gets questions, they might request input from ORD on what research was being funded and occurring. They could get as much or as little input from ORD as they requested in drafting the Secretary's response. Dr. Goldberg recalled the inquiry by Senators Murray, Rockefeller, and Bond. He stated that input was requested from ORD related to what was happening in research. OPHEH's role in the organization was to write the response for the Secretary's signature.

Chairman Binns noted that, at the very least, the Committee could recommend that this role be taken away from OPHEH. Mr. Smithson stated that if this recommendation was made, the Committee should recommend the office to which it would be reassigned. Chairman Binns stated that the most that could perhaps be done was require the concurrence of ORD, but this might not be enough.

Dr. Golomb asked if it would be better to have no reports from IOM, rather than have a report that leads people astray. Chairman Binns stated that he believed the IOM would do a proper job if properly tasked.

Dr. Melling stated that a recommendation to move the study out of IOM would leave the door open for bureaucratic haggling and lack of progress. It would be better to stay within the envelope of the law. He wondered if it would be appropriate, as the Committee reports to the Secretary, to offer the Committee's service to review the charge made to IOM and then advise the Secretary whether or not the charge fulfills the requirements of those public laws. Chairman Binns indicated that this offer had already been made. When it was convenient for OPHEH to say this wasn't research, they were perfectly happy to say "we don't advise on your work." However, OPHEH will then take the position that they are the final word on research. Chairman Binns thought it would be great if such a provision could be made because it was certainly research, at least research that would be used for evaluating benefits. Mr. Hardie noted that was certainly the case because both Congressional directives, the one establishing the Committee and the one directing the IOM reviews, were created under the same law. Dr. Bloom asked why the Committee did not stipulate the statement of task for the next IOM study in the Committee's report. Chairman Binns stated that it was not clear what the next study was and noted that task statements were not trivial documents.

Dr. Steele asked what the consensus of the Committee was in relation to the contracting of future IOM studies. Mr. Smithson stated that if it was removed from OPHEH, there should be a recommendation as to where this authority should be transferred. Dr. Steele asked what would happen then if a suggestion to move it to a particular office was not possible. Mr. Smithson understood this, but thought a specific recommendation would be helpful in order for the Secretary to make it happen. Chairman Binns thought

it could be recommended to the Secretary that the responsibility should be removed from OPHEH and reassigned. Dr. Steele asked if he meant that the reassignment be made “as determined by the Secretary.” Chairman Binns said the language could be fine-tuned, but just needed to make clear that the responsibility be removed from OPHEH. He would also support the idea of adding language that would allow the Committee to review the task statement.

Dr. Meggs asked if the Committee should be a little bit stronger in its explanation as to why, that is, because OPHEH did not properly charge the IOM with regards to the requirements set forth by Congress. Chairman Binns stated that he thought Dr. Bloom had made this point and agreed that the Committee needs to be clear that the fault lies with VA.

Mr. Hardie stated that he found it unacceptable that the Committee was not involved in the contracting with IOM, since the Committee was supposed to be determining and evaluating Gulf War research and was created under the same law. He hoped that this language was strong and forceful with regard to that message and that the Committee should be active in the process of creating future task statements. Mr. Smithson stated that the specific examples of what had been done should be included to remind them of this.

Dr. Steele asked if other members would like to address the questions raised, but none had additional comments. Mr. Smithson asked for clarification about whether the second recommendation was that the previous IOM reports be redone. Dr. Steele indicated that the general consensus had been yes, that this was the case. Dr. Golomb reiterated her reservations about reassigning it back to IOM. Even if one removed individuals with overt bias, the previous work will still influence the outcome. Dr. Bloom agreed that there was some truth to this. Chairman Binns stated that, between the awareness of this issue within IOM and a true change in policy at VA, he thought this was a solvable problem. Nothing has been solved to date, however. But for the recent letter drafted by OPHEH, he would have hoped it had been.

Dr. Melling asked to be reminded if there was a recommendation with respect to treatment issues. He acknowledged Dr. Haley’s statements during the previous day’s meeting that there was little point to pursuing serendipitous work in his program with the hope that some treatment will emerge. However, we know that good things happen by accident. The Committee should consider a recommendation that would improve the chances of capturing something good that does happen. Dr. Steele noted that the report discusses the two avenues of finding treatments. One is tied to physiology. The other one, which she did not view as being serendipitous, related to identifying and evaluating treatments in use for Gulf War illness or conditions with similar features. Overall, the draft report recommends that research leading to treatments receive the highest priority and that both approaches be utilized in identifying treatments.

Chairman Binns asked to return to the discussion about Dr. Golomb’s recommendation to include advice that Gulf War veterans avoid pesticides. It is better to avoid pesticides, given what is now known versus what is not known. While the Committee has recommended that studies should be done on this and it has been explained in the text, it had never been included in a recommendation. Dr. Steele asked about the type of recommendation that might be made. For example, would the Committee recommend that VA advise their clinicians to advise ill veterans to stay away from chemicals? This was not a research recommendation and there were no data to support that clinicians do this. Dr. Golomb stated that there was data in an Australian study linking pesticides to ALS, and Gulf War veterans have an increased chance of getting ALS. Dr. Steele noted that there might be a lot of diseases that could be related to a lot of exposures that Gulf War veterans may have. She didn’t disagree that this could be true, but there weren’t data to support any of them in particular. Dr. Golomb understood, but noted that there was no expected health benefit from pesticide exposure but there were potential health harms. Even in the

absence of the anecdotal information where people say exposures make things worse for them, one could say that strong evidence is pending, but avoidance might be prudent. Dr. Golomb added, however, that she did not feel strongly that such a recommendation should be made, since she understood that the Committee was tasked to make research recommendations. But she indicated that if she was a sick veteran, she would want to know this.

Mr. Hardie stated that he was disappointed that OPHEH had failed to provide real information to Gulf War veterans. The information that has been provided has been a whitewash and/or contains nothing of substance. The coverage of the Committee's activities was limited. He noted that the most recent coverage only noted, in a paragraph, that new members had been appointed. It would be helpful if a real publication, one that did not imply that there was nothing wrong with Gulf War veterans, was produced by some other entity, a publication that veterans could take to their physicians. It didn't have to make judgments about the research. It just needed to present it. Why not have research summaries and citations for the studies? Why can't the Committee advise VA on what to do with the research that the Committee is reviewing?

Chairman Binns commented that there was a Committee recommendation that the clinical guidelines be revised and updated in light of research. He wondered if the Committee should restate this in the report. Mr. Hardie stated that he was thinking of a recurrent publication. Dr. Steele stated that she had never heard positive comments from veterans on the Gulf War Review or indications that it helped with their knowledge of Gulf War illness. She noted that only one edition had been published in the past year, and it had been online, and few knew how to find it. She wondered if the suggestion should be made that VA have a publication that does provide this service to veterans and does disseminate research. She asked how other committee members felt about this. Mr. Smithson stated that this would fall under outreach, and he had no problem with making such a recommendation. Chairman Binns stated that if the guidelines were revised, the veterans would be advised as well. Dr. Steele noted that the Committee's website provides summaries of the most current Gulf War research, and is regularly updated. This had been how the Committee had provided this information to the public. She hoped that the Committee's report would help in providing a comprehensive view of the subject in a way that a newsletter can't.

Mr. Hardie thought it was important to disseminate this information to treatment providers and veterans. The Secretary could determine how this dissemination should occur. Chairman Binns asked if Mr. Hardie thought revised treatment guidelines would take care of this and would provide an even more emphatic statement than a newsletter. Dr. Steele noted that there were also continuing education instruction materials on Gulf War health issues for VA healthcare providers, and the Committee had recommended that these be revised too. Mr. Hardie noted that the VA's webpage on Gulf War illness was poor, containing many broken links and a lot of information about the current conflict veterans and depleted uranium. There was little information that could inform a treatment provider. Dr. Steele said that she agreed that these types of improvements were needed, but the question was what the best way was to make this happen. Mr. Hardie indicated that the Committee should think about what would be the best approach to achieving this goal.

Dr. Steele asked the Committee to make note of any objections, additions, or other suggestions related to restructuring or rewriting the draft report that would be distributed in hard copy for review.

Chairman Binns stated that he had summarized the previous day's discussions of the UTSW program after the meeting. He said that there were some conflicting comments and his summary was not in the form or nature of recommendations. But there might be some value in presenting a summary of what individuals thought had been the most important points. This would provide comments in some official form to UTSW. He indicated that he would send these notes around for the Committee to review. If they

were accurate, they could be included as cover comments, along with individual comments provided by each Committee member.

Update on VA Gulf War research programs

William J. Goldberg, PhD

VA Office of Research and Development Gulf War Research Portfolio Manager

Dr. Goldberg gave the Committee an update on the Gulf War tissue biorepository. Dr. Louis Fiore, the principal investigator on the biorepository project, reported to Dr. Goldberg that ten brains of veterans with ALS had been “captured” from the ALS registry. Dr. Goldberg stated that he had asked Dr. Timothy O’Leary, Director of ORD’s Clinical Science and Biomedical Laboratory Research and Development services, whether the program was in a position to begin accepting consents for brains and other tissues from Gulf War veterans. Dr. Fiore had indicated that they were ready, noting that the project had received institutional review board approval. Dr. O’Leary had requested the Committee’s advice on systematic approaches to the identification of veterans and veterans’ families that were willing to participate in this program and how to contact these individuals. This would be the specific recruitment of ill Gulf War veterans.

Dr. Steele noted Mr. Hardie’s suggestion of a newsletter that is distributed periodically to Gulf War veterans.

Dr. Haley suggested going back and calling all of the veterans who participated in their national survey. There would be prospective data, collected over time, along with veterans’ profiles. Dr. Goldberg asked if it was possible to incorporate this inquiry into the UTSW survey. Dr. Haley thought it was, considering the consent issues had been worked out. Dr. Goldberg stated that there would have to be care to ensure that the proper actions or links were in place to obtain the tissues once the veteran died.

Mr. Hardie asked if there was a national healthcare provider organization that could help identify veterans at the hospital level. Dr. Goldberg stated that this was difficult because most would probably not die at a VA hospital, so it wouldn’t be a matter of having this consent in their VA medical records.

Dr. Haley stated it had to be a veteran and family issue. These veterans often die unexpectedly so there is no one at the hospital to coordinate this donation. It has to be the veterans and their families who work out a plan to contact the registry when the veteran dies. It would be like carrying a tissue donation card in their wallet. Dr. Goldberg stated that he would also speak to Dr. Fiore about the possibility of including the question in Dr. Haley’s survey. Dr. Haley stated that this did need to be discussed because the highest yield would be those who had been in a survey. They had systematic health information about each veteran. Dr. Haley noted that there were potentially thousands of participants with 10,000 in his study, 10,000 in Dr. Kang’s study, as well as Dr. White’s Fort Devens’ group.

Dr. Steele suggested contacting all of the veterans enrolled in the VA’s Gulf War registry.

Dr. White commented that there were questions about whether institutional review board approval would allow her to go back to the Fort Devens’ cohort for contact information. This action would probably require approval because they would be re-accessing names. The other issue was that contacting individuals about this type of donation is very tricky. This project involved the entire country and required a carefully thought-out program in place that specified how to approach individuals and what instructions would be given to the donors. Dr. Goldberg stated that the collection procedures had been worked out for the entire country. Dr. White was glad to hear this.

Dr. Steele asked if an announcement could be sent to the registry participants in the Gulf War Review and/or another type of publication. This would potentially reach 150,000 Gulf War veterans. Mr. Smithson noted that mailings were not being sent at this time. Dr. Steele commented that it could be done for this specific purpose. Dr. Goldberg stated that it was his understanding that the Gulf War Review would be sent out in paper and electronic format in the future. Dr. Steele said that Dr. Mark Brown had told her that the Gulf War Review would remain an online publication. Mr. Smithson asked Dr. Goldberg if he knew when it was slated to be mailed out to veterans. Dr. Goldberg stated that he would have to check when he returned to Washington, D.C. Dr. Steele noted that this would be a reason to mail out the newsletter, which could include updates on other issues.

Mr. Hardie commented that DoD had an excellent mailing list, noting that it had been used to notify many Gulf War veterans of their possible exposure to the debris plume from the demolition of the Khamisiyah ammunition depot.

Chairman Binns invited veterans to comment on possible ways to notify the veteran population of this opportunity.

Ms. Nichols suggested that the VA put this information on its website and issue a public service announcement and press release about the program. She also suggested asking the veteran service organizations to include this announcement in their magazines. This would at least reach those veterans who have access to the Internet.

Mr. Hood stated that veterans had an organization called Dignity Memorial that could distribute this message. Notices could be included in medical journals to notify civilian physicians of the program. Public service announcement also could be made by veterans service organizations and the Department of Health and Human Services. There are three categories of veterans to contact, both active and inactive: Reserves, National Guard, and Active Duty.

Dr. Goldberg indicated that he would take these suggestions back to Dr. O'Leary and would report at the next meeting on this effort's progress.

Dr. Steele asked Dr. Haley for clarification about his tissue bank. Dr. Haley stated that it would be a blood and DNA bank, not a brain bank. There would be no overlap with the Gulf War veteran biorepository.

Dr. Steele asked Dr. Goldberg for an update on funding of Gulf War research proposals. While there was no longer a specific Gulf War funding announcement, she wondered how many proposals were being submitted via the normal funding routes. Dr. Goldberg stated that no newly submitted projects had been included on the portfolio lists that the Committee received. He stated that there were a couple of studies that would begin this year, but that they had been included on the previous year's funding list. Most of the proposals being received were focused on OIF/OEF. A significant portion of VA's research budget had been appropriated to the UTSW program. There was also significant pressure from Congress and the Secretary's office to address OIF/OEF issues. There was a need for VA to move into this realm.

Dr. Steele asked about the progress in listing Gulf War studies on NIH's website: www.clinicaltrials.gov. Dr. Goldberg stated that other work had sidetracked him from this project. However, he would take steps to "put it back on his plate." It wasn't an issue of whether studies other than clinical trials could be included on the website. Any studies that involved human subjects could register and use the website as a source of recruitment. Dr. Steele noted that the Committee hears from veterans all the time that they

would like to participate in studies. She said that there were three clinical trials involving Gulf War veterans currently listed on the website. One involved cognitive behavioral therapy administered using a telemedicine approach. Another was a clinical trial of treatment for irritable bowel syndrome. The last one was an evaluation of the use of continuous positive airway pressure machines to treat sleep irregularities in Gulf War veterans. Dr. Goldberg stated that there were several other studies that involve human subjects, but were not trials. Imaging projects fall into this category. They are not required to be registered, but can be.

Chairman Binns thanked Dr. Goldberg.

Public Comment – Day 2

Chairman Binns explained to those present that he had limited earlier discussion of the recommendations to Committee members because this was a particular Committee function. He indicated that the Committee now would like to hear comments from the recommendations or other matters. He asked how many individuals wished to speak and noted that comments should be limited to five minutes.

Dr. McGill spoke to the Committee. She discussed her website honorthenames.com. One of the purposes of the website was to use it as a research tool. She requested help in making it complete. They have the names of 4,500 deceased veterans. This also raised the issue of surveillance. She noted that the life expectancy of Vietnam veterans was 57 years. One of her reasons for starting the website was to try and determine the life expectancy of Gulf War veterans, as well as their causes of death. They were still working on this and would be for the rest of their lives. She recommended that there be “cross-talk” between this website and the Committee’s website. She indicated that she would ask her webmaster to include a link to the Committee’s website. She requested that the Committee do the same. With regards to the IOM study, Dr. McGill stated that the IOM aimed their reports toward their customer’s request. She asked that an ill veteran be placed on the IOM committee to help correct the problems that were made in the IOM’s first six volumes on Gulf War health.

Chairman Binns thanked Dr. McGill.

Mr. Mark Anderson, whose brother-in-law served in the first Gulf War, spoke to the Committee. He thought that the Committee was generally doing a good thing, but asked it to not lose sight of the issue of depleted uranium. It was the one constant in the war, which was arguably among the most brutal wars in history, waged against third world nations with little military to speak of and killing over one million Iraqis in the most inhumane fashion. Most in the United States can not even imagine what is happening there. Mr. Anderson quoted Mr. Mitchel Cohen’s statement that “300 tons of depleted uranium from spent rounds lay scattered in various sizes and states of decay across the battlefields of Iraq and Kuwait. Welcome to the wave of the future: ‘low intensity’ nuclear war, inaugurated in the Gulf War by the United States.”

Mr. Anderson noted that in a survey of 10,000+ Gulf War veterans, 82% had entered captured Iraqi tanks that were disabled by depleted uranium rounds. Quoting Mr. Cohen again, Mr. Anderson stated: “Leaving more than 600,000 pounds of depleted uranium scattered throughout the region, by war’s end the US had turned the Gulf area into a deadly radioactive grid, affecting not only US soldiers but hundreds of thousands, perhaps millions, of people who live and work in the Gulf. . . . Is it any wonder that many symptoms of Gulf War Syndrome are so similar to radiation sickness? . . . A secret report by the British government estimated that the use of depleted uranium weapons in the Gulf could alone account for 500,000 deaths in the region. That report was based on estimates that 25 tons of depleted

uranium munitions had been used; in actuality, the Department of Defense now estimates that the US fired more than 12 times that amount.” Mr. Anderson stated that we were in a unique situation because we now live in perpetual warfare. There appears to be no resolution in sight. We have been using these munitions in the Middle East for close to two decades, in varying degrees. Mr. Anderson’s point was that sick and injured veterans would keep coming. This will cause the cost of the war to “balloon.” Every dollar spent on the ongoing war will deplete the funds that might be available for research. Mr. Anderson suggested that Committee members think as citizens, not in their specialized roles as scientists. Do we as American citizens like this kind of policy? Ultimately, to stop Gulf War syndrome, we must stop the Gulf War.

Chairman Binns thanked Mr. Anderson.

Mr. Hood commented that his occupations while serving in the Gulf were the same ones he had stateside, that is, he had been an air surveillance technician, combat plan technician and computer technician. When he deployed, he deployed as a one man team as an operations control technician. He described his service in the Gulf and health conditions following this service. He learned during his time in the hospital how to do post-deployment interviews and began to work with a South Texas group that operated out of the Veterans of Foreign Wars office in San Antonio. He spent his time checking on his comrades during this time and learning about the various exposures that they had been subjected to. Mr. Hood said that Mr. Kirt Love had given him ideas that he incorporated into his questionnaire. They also hand out maps of biological and chemical weapons sites, SCUD and nuclear reactor sites, as well as areas where depleted uranium was known to be used. He noted that, like in the movie “Hidalgo”, the desert moves like a rolling carpet. So, when one starts talking about Gulf War illness, one must consider 970 nuclear, chemical, and biological sites that were hit during the first 45 days of the war. Those who moved in during the ground war were “slammed.” They moved up into the toxic zone. After the ground war, 994 additional sites were demolished during the cease-fire phase with troops in place. Khamisiyah represents one of those 994 sites. There were 40 warehouses and 100 bunkers, approximately the size of Wal-Mart. Mr. Hood asked if anyone would like something like this blown up in their backyard.

Chairman Binns thanked Mr. Hood.

Ms. Lauren Billings, an Air Force Gulf War veteran, spoke to the Committee. She stated that there were 90 aviators within her unit. Within one year of their return from the Gulf, there were four cases of cancer: prostate (1), bone (1), breast (1), and cervical (1). This amounted to four individuals out of 90 within the first year. Ms. Billings questioned whether these statistics were the same as the general population.

Chairman Binns thanked Ms. Billings.

Ms. Denise Nichols spoke to the Committee. She stated that the diagnosed illness data were not being collected. She recalled the 1991-1994 cancer information that she had submitted to the Committee in May 2006. She stated that she had asked the Committee to request the data on Gulf War veteran cancer deaths. The only way to get compensation like Agent Orange veterans is with a presumption of illness. Gulf War illness is separate from diagnosed illnesses. However, some Gulf War veterans have both. The only Committee that Gulf War veterans have is this one. VA didn’t follow the Committee’s recommendation to create another committee to address clinical and benefits issues. She hoped that this recommendation could be carried forward in the report. The Gulf War veterans are feeling the same as Vietnam veterans did. Every time one opens their paper or e-mail, there is another benefit for the OEF/OIF veterans. Ms. Nichols stated that she receives calls from Gulf War veterans asking for a progress status report and indicating to her that they still need help. She keeps standing up, even though she is told to shut up, about this issue. She had received an e-mail that General Downing, who

commanded the American Special Operations forces during Desert Storm, passed away the previous day from multiple myeloma and bacterial meningitis. She noted that a Gulf War veteran with ALS recently passed away too. With regards to environmental medicine, she did not receive answers from VA and sought her own answers and testing so that she could pass this knowledge onto others. She discussed the various types of testing and treatments that she had undergone. These involved nontraditional medicine and IVs of vitamins and supplements, including glutathione and CoQ10. It wasn't a whole lot to ask that these treatments be considered. It helped her. It wasn't a cure, but it did help with cognitive function.

Ms. Nichols also commented that she received calls from veterans whose health had stabilized, but then moved and began having problems. Some were exposed to agricultural chemicals and became unstable. She can only tell them that there is no treatment, but she tries to help them figure out the triggers for their new health concerns. And the only option is to try and get away from it. She uses this as a complementary medical approach. Lastly, Ms. Nichols wanted to ask the Committee to remember to suggest investigations of blood hormones—pituitary and adrenal hormone levels in Gulf War veterans. If abnormal values are found, the veteran should receive treatments. Many veterans are on hormones and it helps them.

Dr. Steele said that she understood that Ms. Nichols was frustrated about not getting information on rates of cancer and diagnosed illnesses. Dr. Steele noted that one of the recommendations presented at the Committee's last meeting was to monitor cancer rates. The Committee's report quotes the rates that have been reported from different studies and notes that these rates are pretty dated and are not complete. But the rates are probably more complete than those that could be obtained from VA hospital data. However, it is still not good enough. The Committee continues to recommend that more comprehensive data collection be done to monitor cancer rates in Gulf War veteran. A few questions have been raised by results from the state cancer registry study, which is ongoing. Dr. Steele noted that this issue hasn't been ignored, but more needs to be done.

With respect to the other diagnosed illnesses, Dr. Steele stated that the Committee has emphasized the need to identify rates of neurological diseases. However, the hope is that the large surveys will help identify any problems that have not yet been identified, perhaps with regards to autoimmune diseases, etc. If a "red flag" is raised, the Committee could then make more specific recommendations. This will require an epidemiological study to ascertain whether there is really a problem. Monitoring hospital or benefits data is inadequate because it would only tell us if there was a "huge" rate of illness, and maybe not even then. For example, if one looked at the benefits data for MS, one would find no difference between deployed and nondeployed Gulf War era veterans. But this does not really tell us if there is an excess rate, since we have no idea whether those who have separated from the military and later developed MS would have applied for VA benefits. This is why an epidemiologic study is needed. Dr. Steele stated that her Kansas study had identified a number of Gulf War veterans who had been diagnosed with lupus since the war. But it was not enough cases to evaluate statistically to determine if there was an excess.

Dr. Haley commented that his group would be looking at adrenal and pituitary hormone levels in its Gulf War study.

Ms. Nichols asked that the Committee's report highlight the need to look at oxidative stress and autoimmune disorders. Dr. Steele stated that the recommendation is to look at all medical conditions, including those.

Mr. Hood asked if any of the researchers present had utilized the Armed Forces Institute of Pathology (AFIP) tissue and blood bank samples. He stated that he was registered in this system and that this would be a good resource for study.

Chairman Binns thanked the veterans present. He expressed his appreciation for what many of the veterans were doing to try to make their own bodies and tissues available for research, as well as their participation in meetings like this. He knew it was difficult to stand up and talk about it, but the Committee did appreciate it.

Chairman Binns expressed his appreciation for the Committee's participation and the hospitality of UTSW. He noted that there was considerable talent and attendance at the previous day's meeting and this was a sign of the UTSW program's commitment to do the job that they have assumed.

The meeting adjourned at 1:47 p.m.

Appendix

Presentation 1 – Jonathan Kerr



Chronic Fatigue Syndrome / Myalgic Encephalomyelitis
(CFS/ME): a disease characterised by
neuro-immune features and virus infection

Dr Jonathan R Kerr MD, PhD
St George's University of London

Chronic Fatigue Syndrome (CFS)

Fatigue

unexplained
new onset
lasting over 6 months
not related to exercise
not relieved by rest

Exclusion

Physical causes
Psychiatric causes

Associated symptoms

Four or more of the following:

Impaired short term memory or concentration
Sore throat
Tender lymphadenopathy
Muscle pain
Multijoint pain w/o swelling or redness
New headache
Unrefreshing sleep
Post-exertional malaise

No laboratory test

CDC criteria – Fukuda et al., Ann Intern Med 1994;121:953-9.

Recommended additional characterisation – Reeves et al., BMC Health Serv Res 2003; 3:25.

Chronic Fatigue Syndrome (CFS)

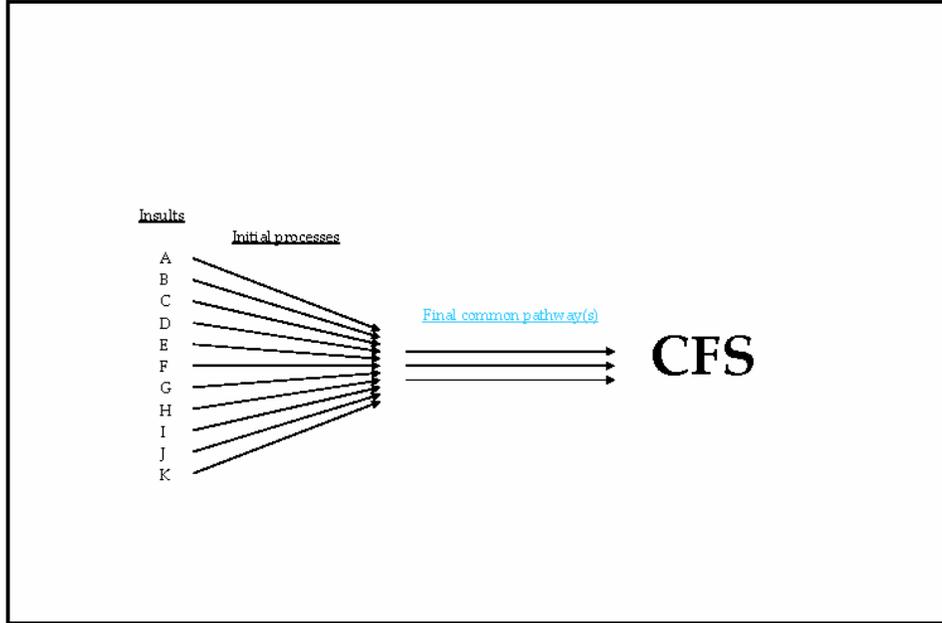
Epidemiology

- Prevalence of 0.5%
- More common in females (6:1)
- Sudden onset
- Preceding virus infection (‘flu-like illness, outbreaks, specific viruses)
- Exposure to toxins, chemicals, pesticides, vaccination
- Pre-existing emotional stress

Chronic Fatigue Syndrome (CFS)

Studies of Pathogenesis

- Immune system - \uparrow IC's, \uparrow IgG, \uparrow B cells, \downarrow NK
Th2 phenotype
cytokine dysregulation / chronic immune activation
- Infection - virus, bacterium
- Nervous system - paresis, visual loss, ataxia, confusion
abnormal metabolism of 5-HIAA, A-V, 5-HT, PRL
brain scan abnormalities
- Endocrine system - slight \downarrow HPA axis
- Cardiovascular system - vasodilatation
- Psychological function - depression & anxiety
- Genetic predisposition - deduced from twin studies



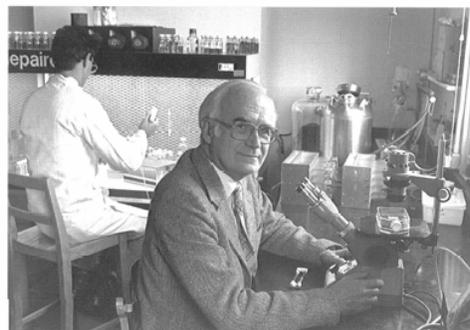
Our Research Strategy

Gene expression signature
Viruses
Protein biomarkers
(Treatments)

How did we develop this strategy?

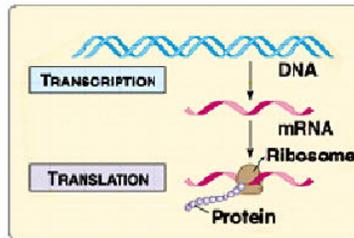
Recognition of need to understand pathogenesis
(human / virus gene expression is important)
(gene screening techniques)

Recognition of need for a diagnostic test
(detection of protein biomarkers)

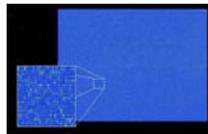


Dr David AJ Tyrrell CBE, FRS

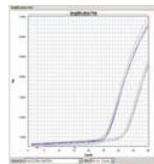
Basic cell processes



Microarray / PCR study

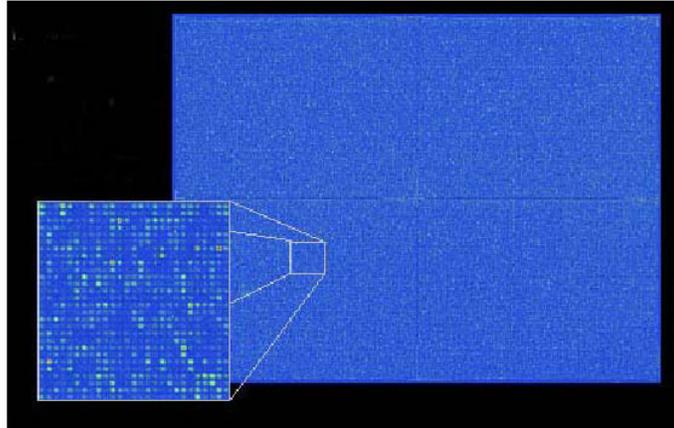


Microarray (~23,000 genes)
27 CFS patients / 54 normal blood donors



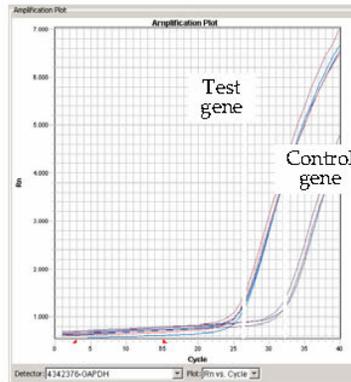
Real-time PCR (182 genes)
57 CFS patients / 60 normal blood donors

83 genes confirmed



Affymetrix U133+2 gene array
47,000 human genes

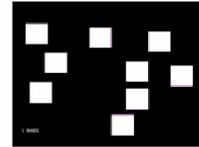
Real-time PCR



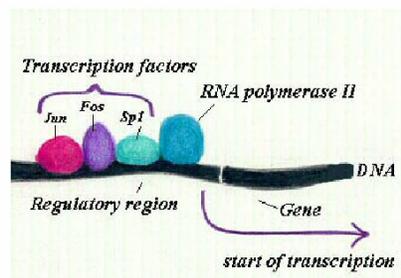
Phase-1
cont.

Phase-1 continued Study Clinical aspects

1. Diagnosis according to CDC criteria
(Fukuda et al, 1994)
2. Assessment of health & associated symptoms:
 - CIDI
 - Cantab
 - McGill
 - Chalder
 - MOS-SF36
 - SPHERE
 - Pittsburgh



Gene regulation

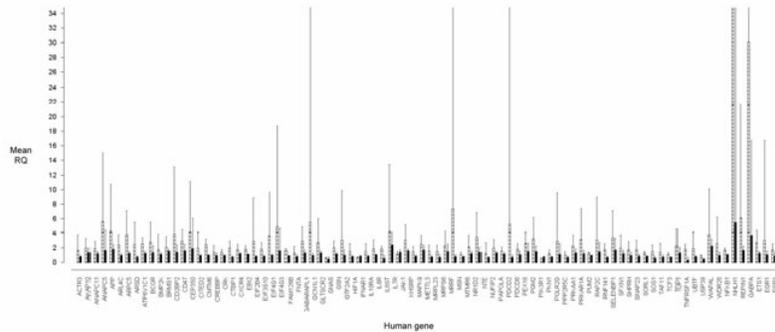


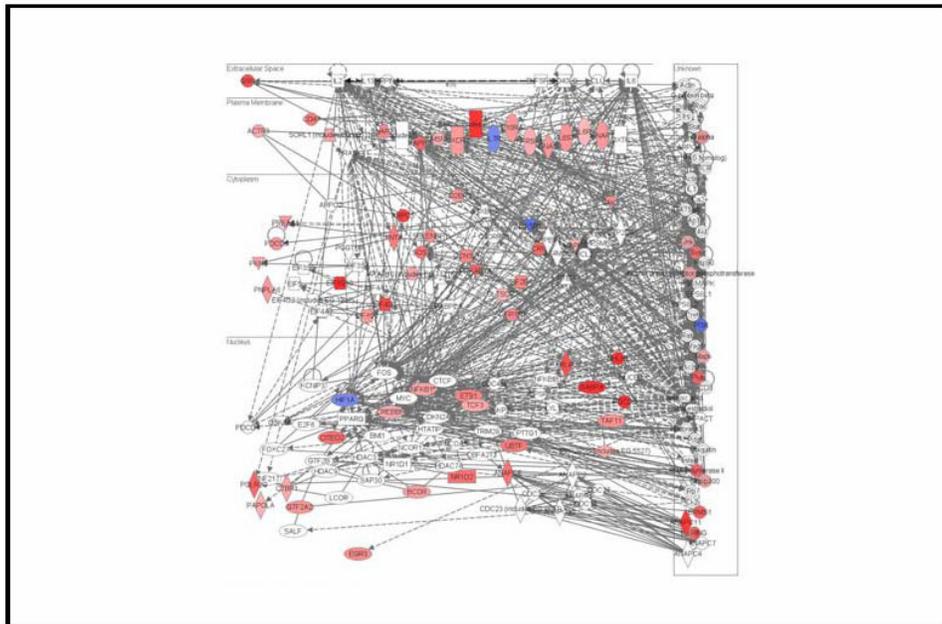
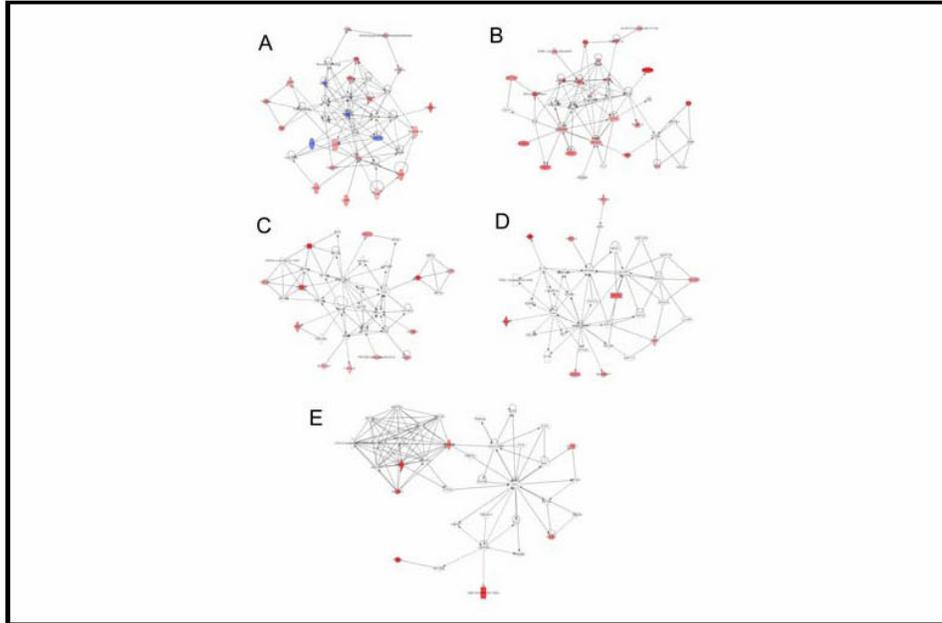
13 transcription factors over-represented

Transcription factors

EGR-1	2.82	0.01480
EGR-3	1.92	0.01690
ETS1	2.11	0.00001
GABPA	8.06	0.00032
NHLH1	11.51	0.00074
REPIN1	3.62	0.00001
NFKB1	1.59	0.00004
EGR-2	2.26	0.09934
GTF3A	1.27	0.18480
SPI1	1.37	0.10086
Egr-4	x	x
REST	x	X
BRLF1		

89 CFS/ME-associated genes





Diseases and disorders

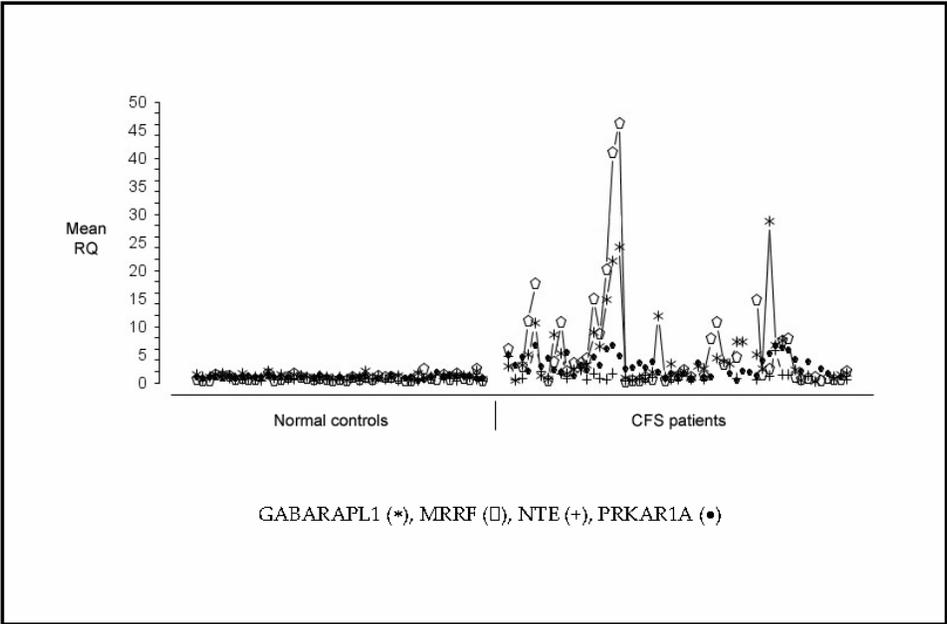
Haematological disease
Immunological disease
Cancer
Dermatological disease
Neurological disease

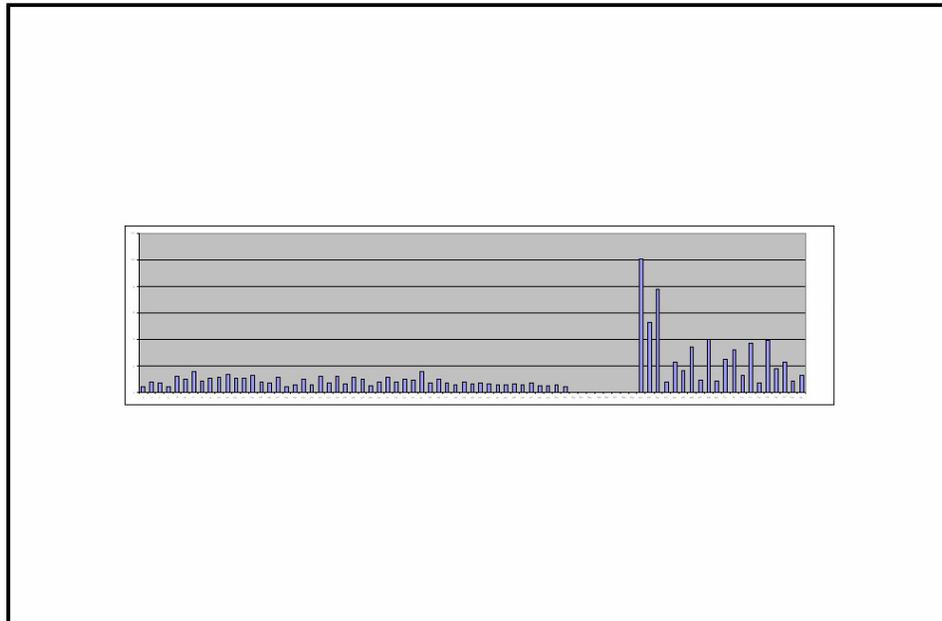
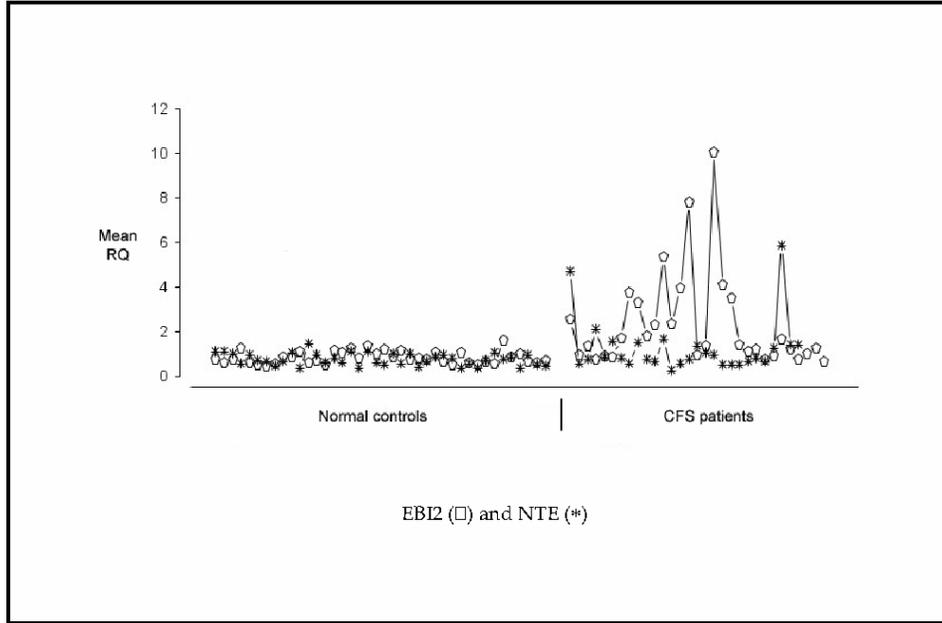
Molecular and cellular functions

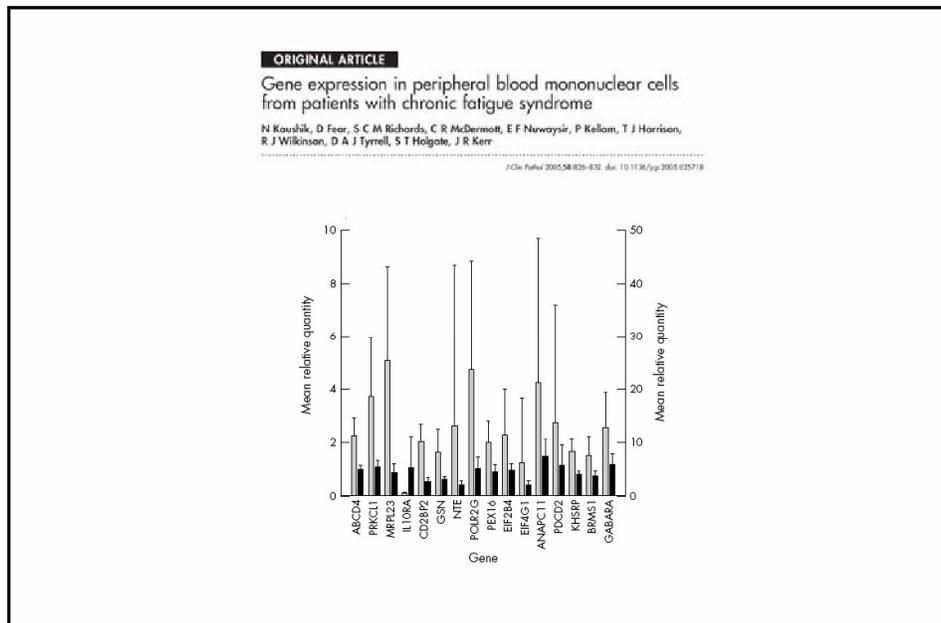
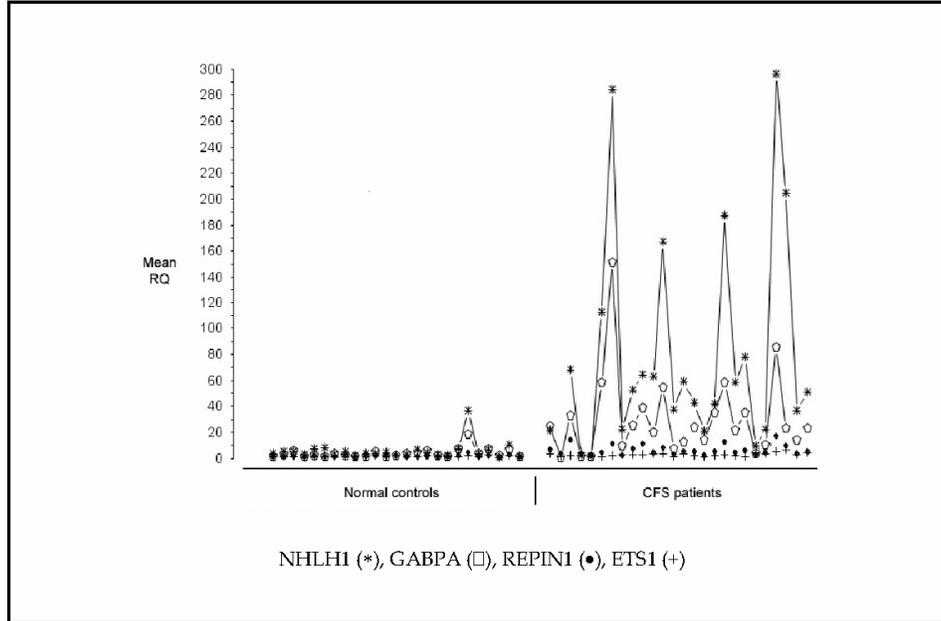
Cellular development
Cell death
Gene expression
Cellular growth and proliferation
Cellular assembly and organisation

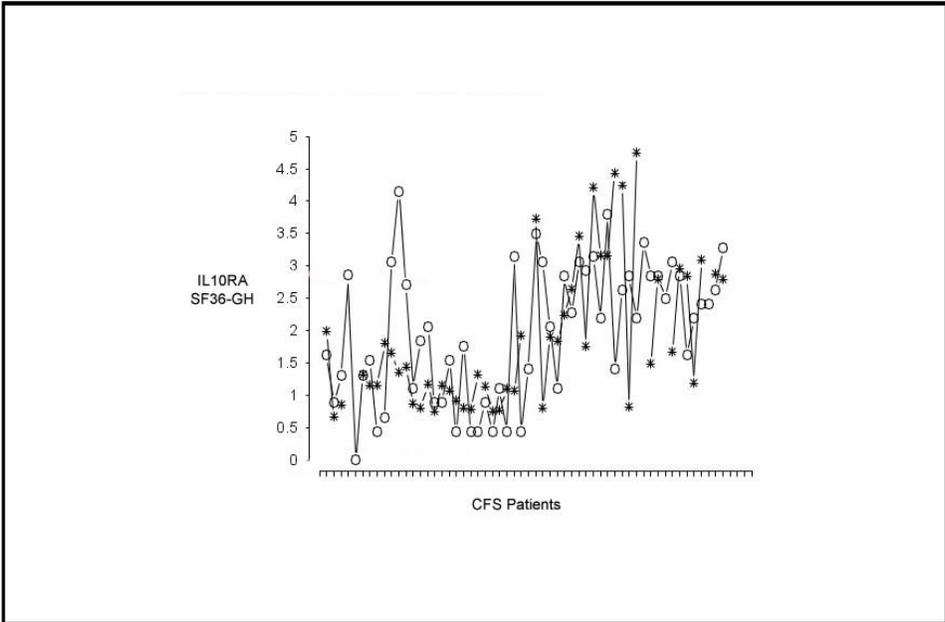
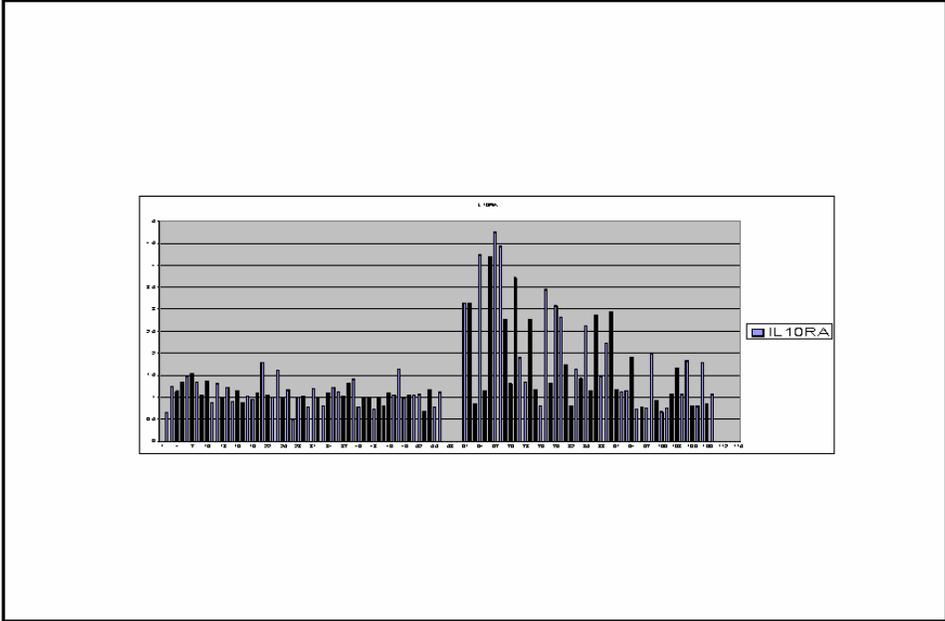
Physiological system development and function

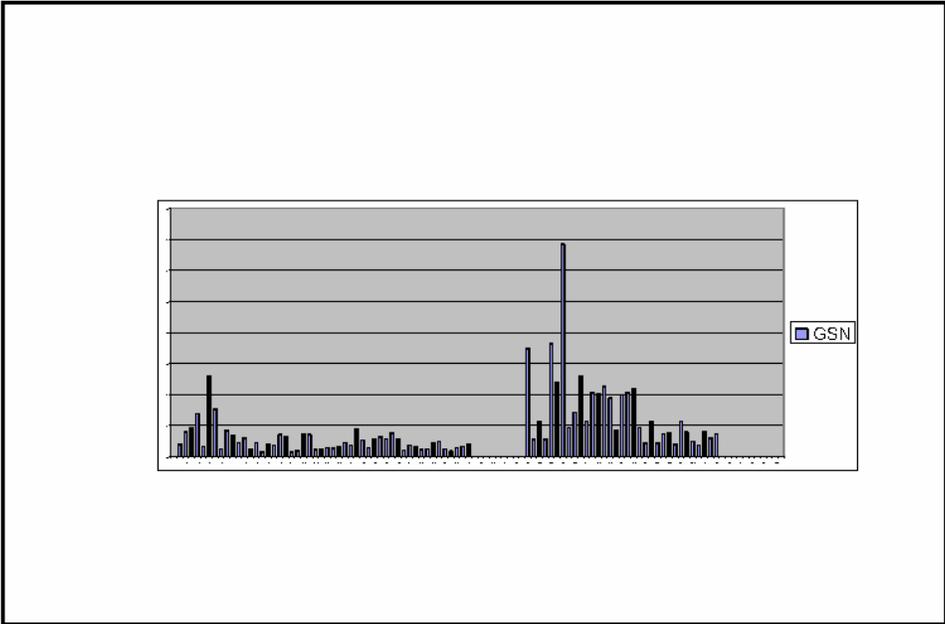
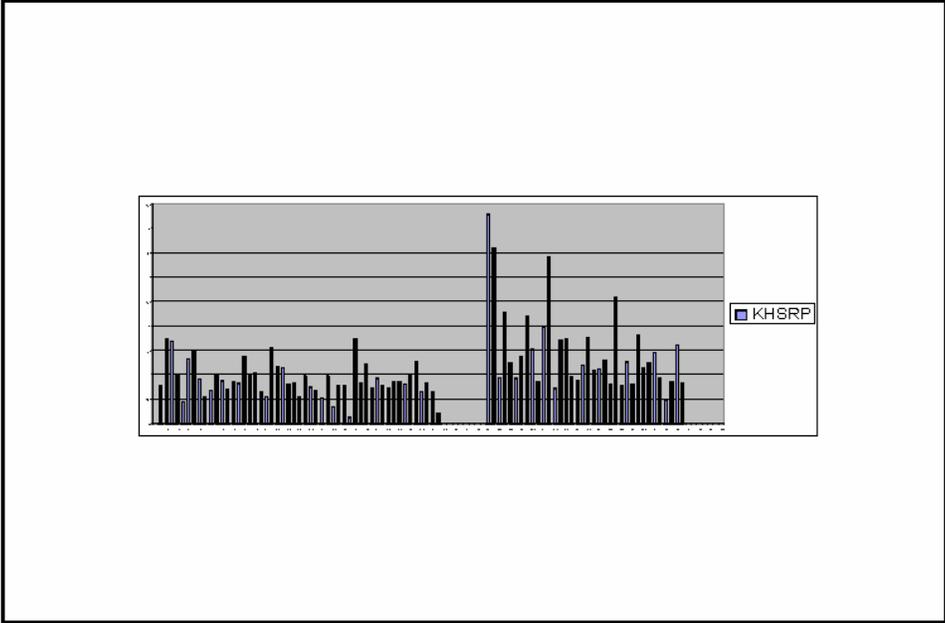
- Haematological system development and function
- Immune and lymphatic system development and function
- Tissue morphology
- Organismal survival
- Immune response

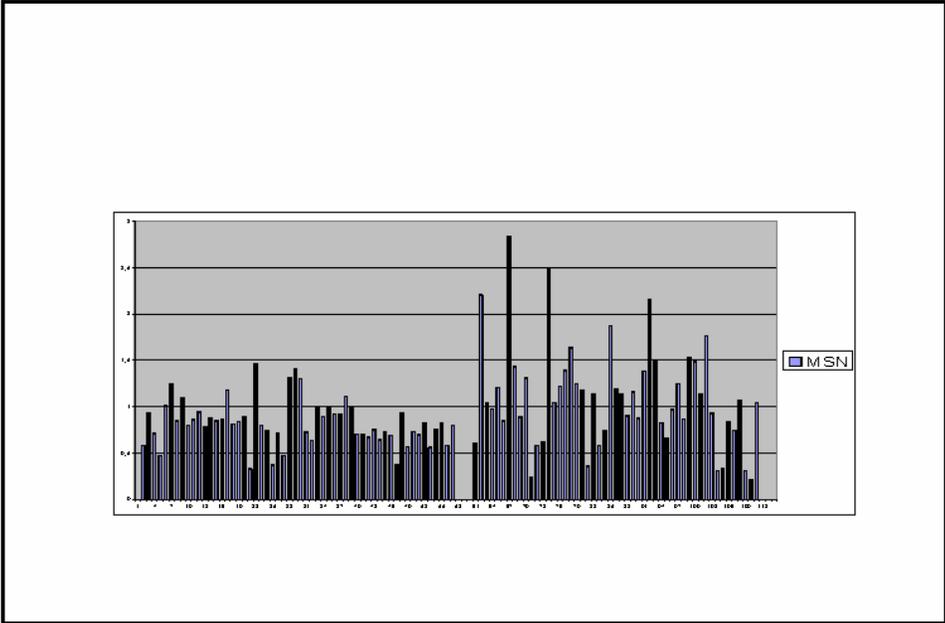




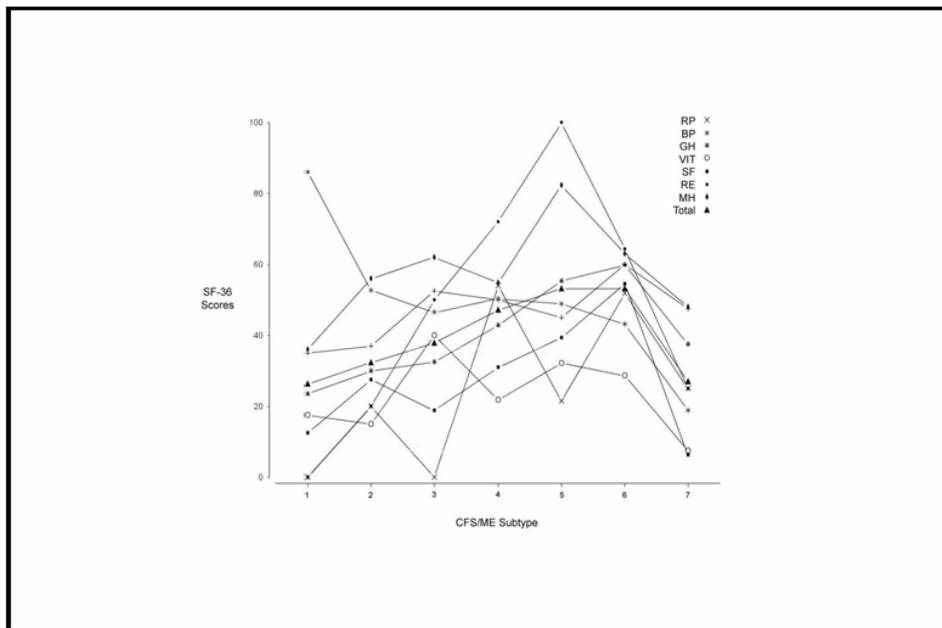
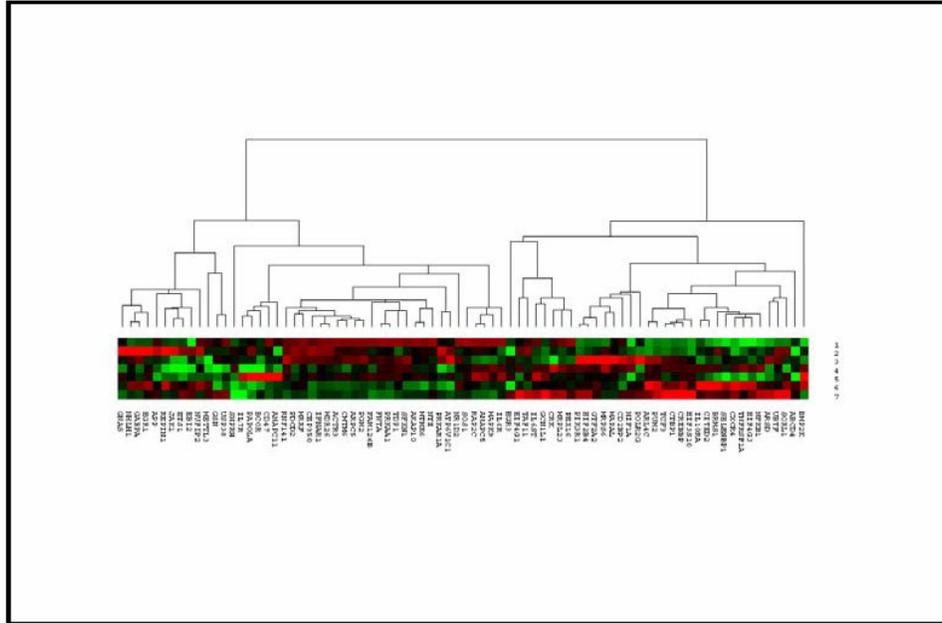


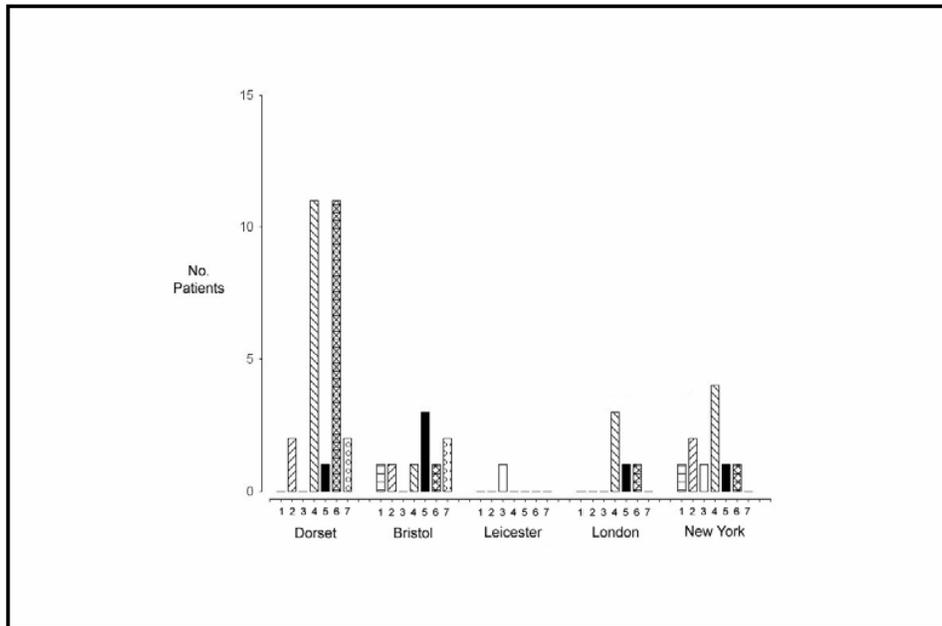
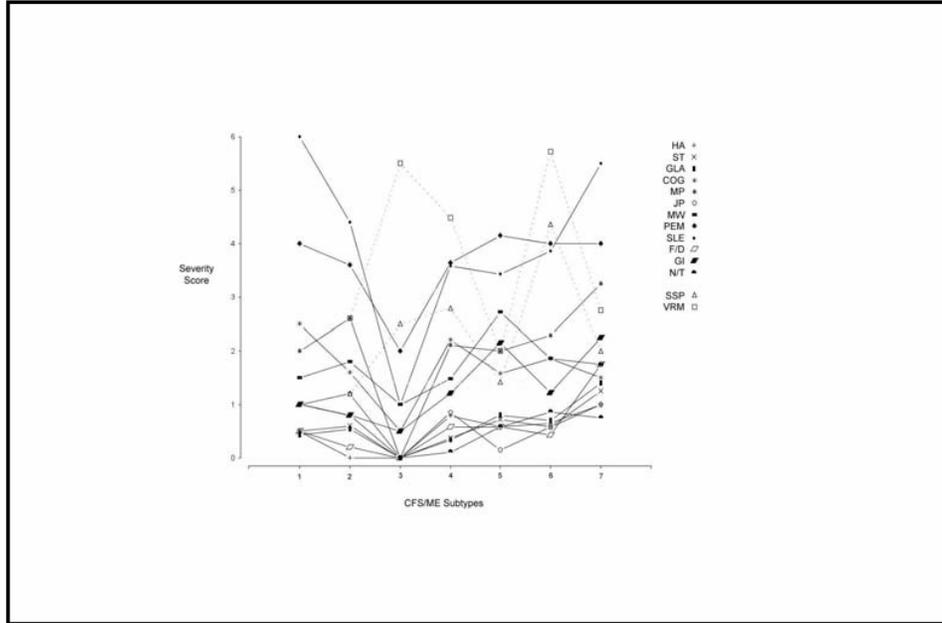






CFS/ME-associated gene	EBV gene	Mechanism
NFKB1	LMP1	Upregulation
EGR1	BRLF1 BZLF1	Upregulation, EGR1 required for reactivation
ETS1	LMP2A	Upregulation
GABPA	LMP2A	ETS1 upregulation leads to GABPA upregulation
CREBBP	BRLF1 BZLF1	BRLF1 and BZLF1 interact with CREBBP
CXCR4	EBNA2 LMP1	Downregulation and reduced CXCR4-dependent migration
EBI2	?	Upregulated 200 fold in EBV infected cells
HIF1A	LMP1	Upregulation
JAK1	?	JAK-STAT activation in PTLD
IL6R	?	Upregulation
IL7R	?	Downregulation
PIK3R1	EBNA2A	Upregulation
BRLF1	BRLF1	**

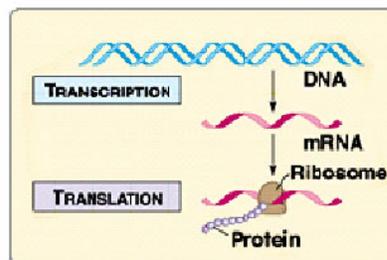




Gene signature of CFS:
current priorities

Subtype confirmation
Variation with time
Specificity
? Overlap with GWI
Expression in different WBC subsets

microRNAs



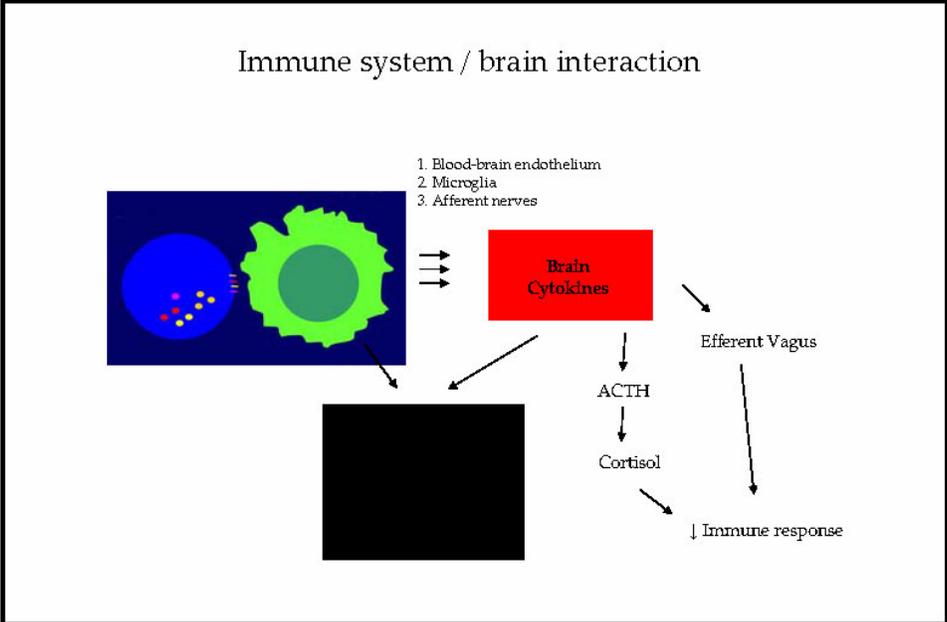
Viruses in CFS

1. Acute / chronic
2. Reactivation

Study of viral gene expression in CFS

Massive
Parallel
Signature
Sequencing
(MPSS)

Virus genome	MPSS TPM CFS	MPSS TPM Normal	P value
1	24	0	4.22E-03
2	161	59	9.38E-05
3	342	128	1.14E-08
4	342	128	1.14E-08
5	35	12	4.00E-02
6	42	0	1.80E-04
7	926	643	3.90E-05
8	48	10	5.68E-03



Proteins

Increased prolactin, HGH, IL-6, TNF- α , IFN- γ , TGF- β 1, B-microglobulin

Changes in DHEA, DHEA-S, Cortisol, ACTH, prolactin, serum metals, oxidative stress markers, plasma-free tryptophan, melatonin

CSF Corticotropin-releasing factor (CRF) in FM (McLean, 2006)

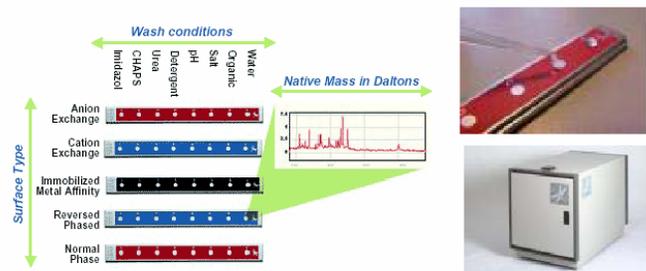
Increased b-alanine secretion in subgroup of CFS pts (Hannestad, 2006)

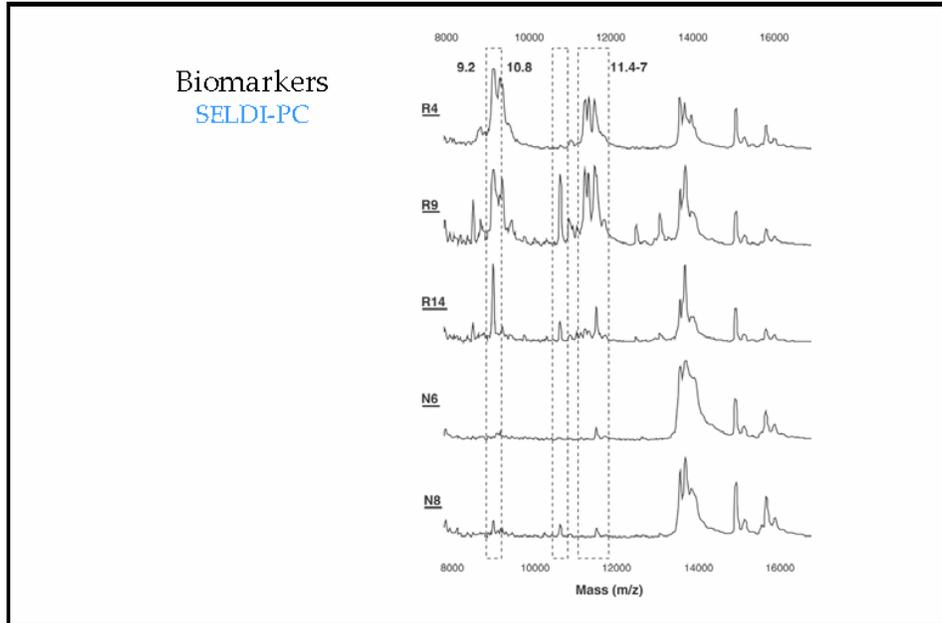
Vis-NIR spectroscopy differentiates CFS vs normal (Sakudo, 2006)

CFS-related proteome in human CSF (alpha-1-macroglobulin, amyloid precursor-like protein-1, keratin 16, gelsolin, orosomucoid 2, pigment epithelium derived factor) (Baraniuk, 2005)

Serum protein biomarkers of CFS

Surface-enhanced laser desorption and ionisation – time of flight
SELDI-TOF





Proteins

15 protein biomarkers

Identification by 2D gel electrophoresis and mass spectrometry

Further CFS patients, Normal persons, and disease controls
(specificity)

Select combination which provides best sensitivity and specificity

Take Home Points

Gene signature in CFS - subtypes
Protein biomarkers
Novel viruses
(Novel approaches to specific therapy)

Acknowledgements

CLINICAL COLLABORATORS

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Dr Paul Langford, Imperial College London
Prof Tony Komaroff, Harvard University, USA
Dr Dan Peterson, Nevada, USA
Annette Whittemore, Nevada, USA
Dr David Bell, NY, USA

FUNDING

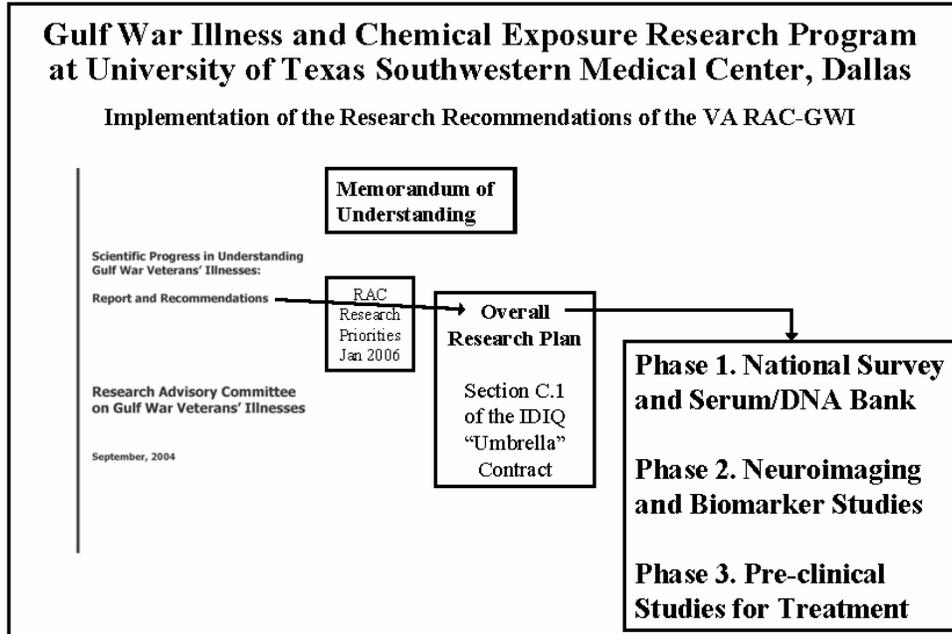
CFS Research Foundation, Hertfordshire, UK
ME Research UK

STUDY DESIGN & LABORATORY WORK

Deepika Devanur, St George's University of London
Robert Petty, St George's University of London
Beverley Burke, St George's University of London
Joanne Hunt, St George's University of London
John Gough, St George's University of London
David Christmas, University of Bristol
Clare McDermott, Dorset CFS Service
Jane Montgomery, Dorset CFS Service
David Fear, Kings College London
Tim Harrison, UCL
Paul Kellam, UCL
David AJ Tyrrell, CFS Research Foundation
Stephen T Holgate, University of Southampton
Emile Nuwaysir, Nimblegen Inc, USA.
Don Baldwin, University of Pennsylvania, USA
Frank Boulton, NBS
Dr Judy Mikovits, Nevada, USA



Presentation 2 – Robert Haley



**Gulf War Illness and Chemical Exposure Research Program
at University of Texas Southwestern Medical Center, Dallas**

- Congressional mandate
 - FY 2006 budget—announced November 2005
 - Establish a Gulf War illness research center at UT Southwestern Medical Center in Dallas
 - In collaboration with a VA medical center
 - Funded at \$15 million per year for 5 years
 - Through the Department of Veterans Affairs

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 - In collaboration with a VA medical center
 - Funded at \$15 million per year for 5 years
 - Through the Department of Veterans Affairs
- **Funding mechanism set up by VA**
 - Indefinite Delivery, Indefinite Quantity (IDIQ) contract
 - Individual projects funded through task orders under the IDIQ “umbrella” contract

**Gulf War Illness and Chemical Exposure Research Program
at University of Texas Southwestern Medical Center, Dallas**

- **The IDIQ “Umbrella” Contract**
 - \$15 M received in the middle of each fiscal year FY’06 through FY’10
 - 2 fiscal years to obligate the funds in a task order which can run for 5 years.
 - Contract administered by Dallas VA contracting office
 - Contract officer
 - Contracting officer’s technical representative (COTR)
 - Federal Acquisition Regulations (FAR) and VA regulations and policies for Research Funds
 - Subject to audit by the VA OIG

Gulf War Illness and Chemical Exposure Research Program at University of Texas Southwestern Medical Center, Dallas

- **The IDIQ “Umbrella” Contract**
 - Section C: Merit Review Process
 - Projects reviewed by UT Southwestern Merit Review Group, chaired by Dean Al Gilman
 - MRG approves an *Overall Research Plan*
 - Projects must implement the *Overall Research Plan*
 - Human subjects protection and animal use governed by:
 - UT Southwestern IRB and IACUC if performed at UT Southwestern
 - UT Southwestern and VA IRBs/IACUC if a VAMC involved
 - All data and samples owned by VA but possession ceded to UT Southwestern indefinitely
 - Data storage subject to VA IT Security Requirements
 - Serum/DNA storage subject to VA Tissue Banking Requirements

Members of the Merit Review Group

Al Gilman, M.D., MRG chair, UT Southwestern Dean/Provost

Eric Nestler, M.D., Ph.D., chair, Dept. of Psychiatry

Stephen Cannon, M.D., Ph.D., chair, Dept. of Neurology

James Stull, Ph.D., chair, Dept. of Physiology

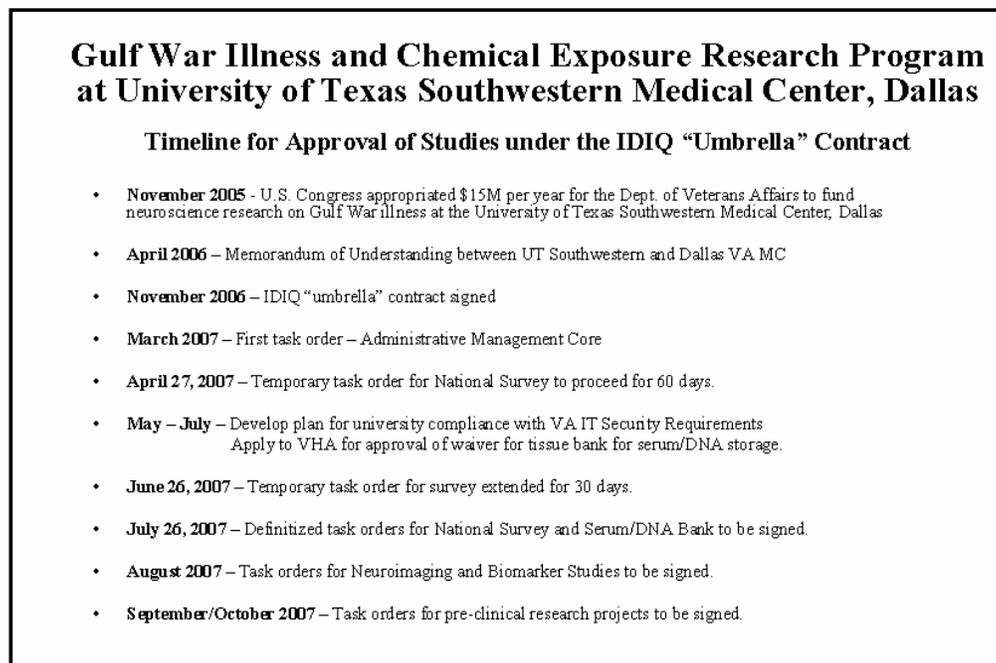
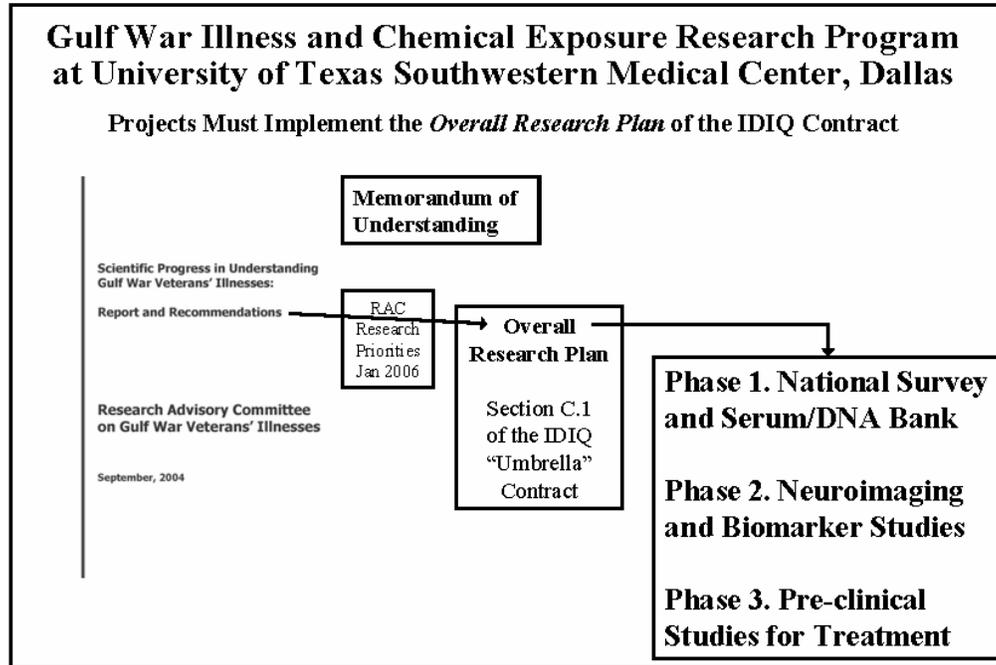
Milton Packer, M.D., chair, Dept. of Clinical Sciences

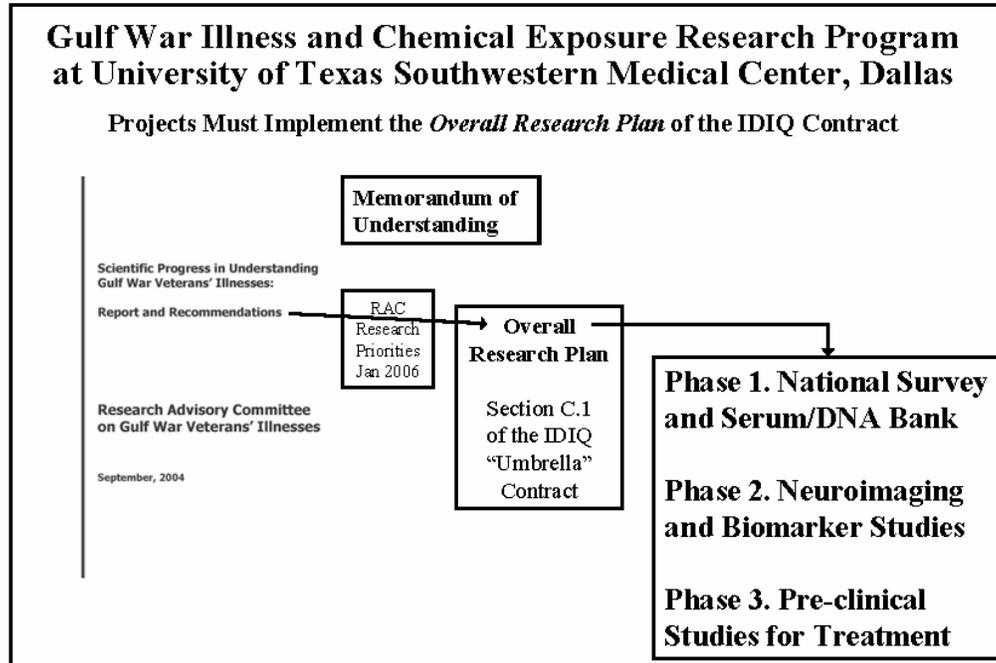
Craig Malloy, M.D., medical director, Advanced Imaging Research Center

James O’Callaghan, Ph.D., head, Molecular Toxicology Laboratory, CDC

Ex officio member

Perrie Adams, Ph.D., Vice President for Research Administration

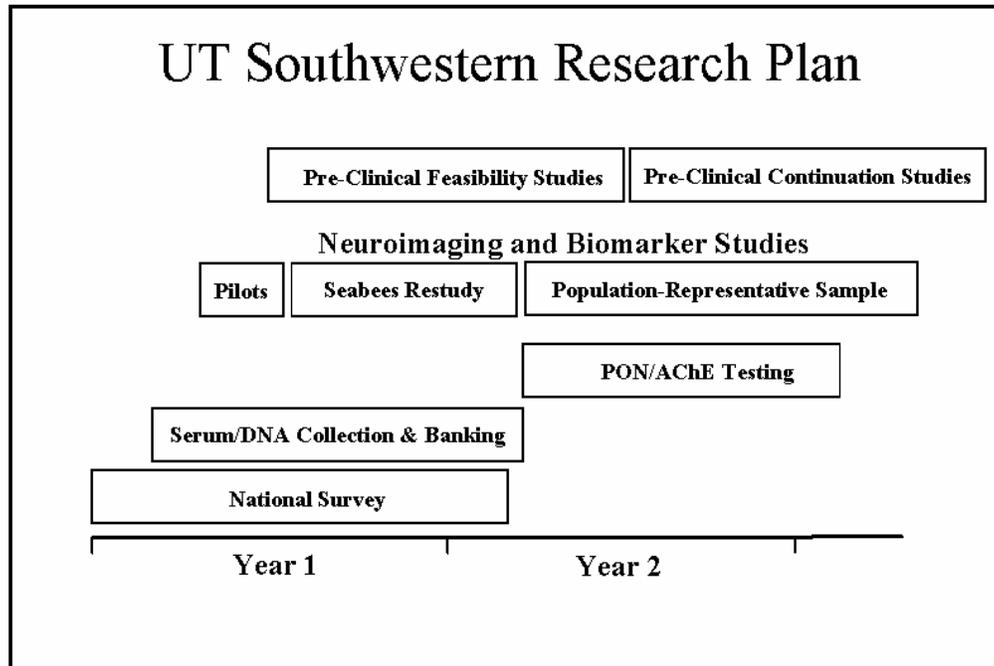




- Overall Research Plan
Approved by the MRG on 9 Nov 2006**
- **Specific Research Objective #1:
National Survey and Serum/DNA Bank**

 - **Specific Research Objective #2:
Sensitive Brain Imaging Procedures and
Biomarker Studies**

 - **Specific Research Objective #3:
Pre-clinical Studies of Effects of Gulf War
Exposures on Cells**



VA Research Advisory Committee *Research Priorities –January 2006*

Gulf War Research: General Principles (6)

Highest Priority Areas of Interest for Gulf War Illness Research (9)

Other Topics of Importance (8)

Gulf War Research: General Principles

1. Evaluate epidemiologic, clinical, and laboratory parameters in Gulf War veterans stratified into subgroups defined according to exposures, locations, units, or other characteristics potentially associated with the outcome of interest, as opposed to evaluation of all deployed veterans as a single group
2. Identify measurable differences between symptomatic and healthy Gulf War veterans, particularly specific markers that distinguish individual GWI cases from controls

Overall Research Plan (ORP) Objective #1: National Survey and Serum/DNA Bank

- Telephone interview survey in a random sample of Gulf War-era veterans (N = 14,754)
 - **Stratification**
 - Age, sex, race/ethnicity, active/reserve status, deployment, sarin exposure risk zones
 - Stratified random sample of deployed and nondeployed era veterans (N = 10,077)
 - Deployed to high risk zone (N = 4,609) "High risk zone" = Near Kuwaiti border on 20 Jan 91
 - Deployed elsewhere in KTO (N = 3,502) Also in Khanusiyah plume
 - Deployable nondeployed (N = 1,757)
 - Medically nondeployable (N = 209) Separated out to control of "healthy warrior effect"
 - Special strata (N = 4,677)
 - 10 year followup of the 24th Reserve Naval Mobile Construction Battalion (Seabees, N = 235)
 - Twins discordant on deployment to theater and high risk areas (N = 1,238)
 - Air Force pilots and ground crews (N = 1,817)
 - Units exposed to ammunition dump explosions at Camp Doha (N = 736)
 - All Gulf War-era veterans with postwar Goldenhar birth defect child (N = 53)
 - **Content**
 - Case definitions: Haley, Steele, Fukuda, Kang (?), CFS, FM, MCS, Diagnosable Conditions, SF-12, etc.
 - Stratification measures, exposure measures, confounding variables, birth denominator data
- Tissue bank for serum, plasma and DNA from sample (N = 2,064)
 - Sample characteristics:
 - All seabees and twins, all Haley or Steele syndromic, sample of the subsyndromic, sample of the non-syndromic
 - High priority tests
 - Paraoxonase & butyryl-cholinesterase isoenzyme activity and genotyping
 - Genomic screening of SNP array (being planned)

Overall Research Plan (ORP) Objective #2: Sensitive Brain Imaging Procedures and Biomarker Studies

- The following groups will be admitted to UT Southwestern GCRC for 5-day neuroimaging and biomarker study:
 - Pilot study samples
 - 20 ill and 20 well members of 24th Seabees studied by similar tests in 1998
 - 80 randomly selected from U.S. Military Health Survey (20 ea from syndromes 1, 2 and 3 and 20 healthy controls)

- The testing protocol includes:
 - MR spectroscopy, MRI for volumetrics, DTI, Connectivity, high res. EEG, ESL, SPECT with cholinergic challenge, and fMRI paradigms probing regions/functions thought to be impaired.
 - Neuropsychological testing, brain dopamine turnover, dexamethasone suppression test, autonomic evaluation, quantitative sensory, and audiovestibular testing

- Past and ongoing statistical research has identified a new approach to the analysis of brain imaging and EEG data that greatly increases the power to detect subtle group differences in brain structure and function.

Clinical Case-Control Study Testing Schedule

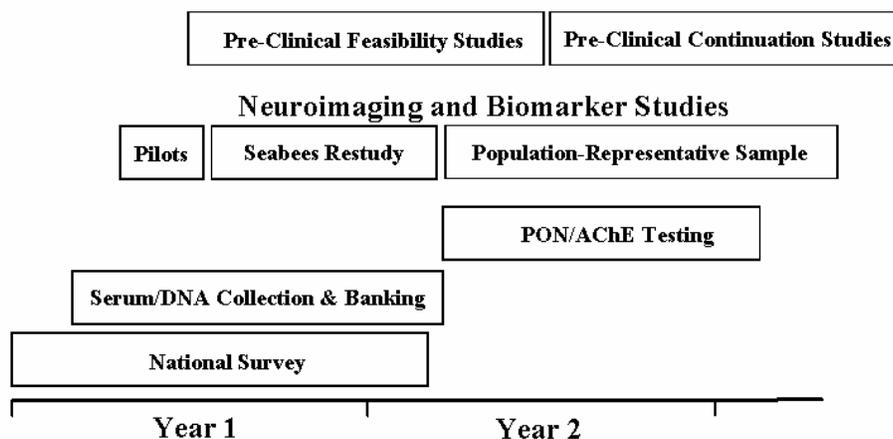
[Dates]	Sun	Mon	Tues	Wed	Thur	Fri	Sat
7:00							
7:15		BFAS	BFAS	BFAS	BFAS	BLOOD	BLOOD
7:30			MRI Instruct		MRI Instruct	BFAS	BFAS
7:45							
8:00		Autonomic	MRI Viscer/flat	NP Testing	MRI Conjoint	NP Testing	
8:15							
8:30							
8:45			BREAK				
9:00			MRI Emotiv		BREAK		
9:15							
9:30							
9:45							
10:00							
10:15		MRI Instruct			MRI Comp/Vis		
10:30			QuantSens				
10:45							
11:00		MRI - MTL		LUNCH		SCID	
11:15					BREAK		
11:30					DTI, FXL CON		
11:45				EEO			
12:00		LUNCH	LUNCH		LUNCH	LIQ LUNCH	LUNCH
12:15							
12:30							
12:45							
1:00		Neuro/Ataxia Exam	INFUSION saline only		INFUSION saline + physio	Audio/veib	DC GCRC
1:15							
1:30							
1:45			HSPAC (r)		HSPAC (r)		
2:00			ASL		ASL		
2:15			AbnTest		AbnTest		
2:30							
2:45		MRI Instruct					
3:00							
3:15		MRI - FSSD		MRI Instruct			
3:30			SPECT PMH	MRI Cerebellum	SPECT PMH		
3:45							
4:00			SPECT EG		SPECT EG		
4:15	Admt GCRC						
4:30	CONSENT	BREAK		BREAK			
4:45		MRS 1		MRS 2			
5:00	MED EXAM						
5:15			DINNER		DINNER		
5:30			Language NP Tests		Language NP Tests		
5:45							
6:00							
6:15	DINNER					DINNER	
6:30	Qs	DINNER		DINNER		Qs	DEX @ 8

Version 6 12-9-2006

Measurement Technologies Capable of Demonstrating Subtle Brain Differences

- **Clinical measurements**
 - Neuropsychological testing
 - Autonomic—High frequency heart rate variability, clinical autonomic battery
 - Quantitative sensory testing (cooling, heat pain and vibratory thresholds)
 - Brainstem evaluation tests—ENG, brainstem evoked potentials
 - HPA axis—Dexamethasone suppression test
 - Brain neurotransmitter production—Brain dopamine (plasma HVA/MHPG ratio)
- **Biomarkers for organophosphate exposure**
 - Paraoxonase (PON1) isoenzyme activity and genotype
 - Butyryl-cholinesterase (BChE) activity and variant genotypes
- **Magnetic resonance scanning (new 3T magnets at UT Southwestern and Dallas VA)**
 - MR Spectroscopy (MRS scanning)
 - Volumetric analysis of MRI images (brain volume changes)
 - Functional MRI (fMRI), Functional Connectivity and simultaneous fMRI/EEG
 - Diffusion Tensor Imaging (DTI, tractography)
- **Nuclear tracer scanning**
 - Single photon-emission computed tomography (SPECT with cholinergic challenge)
 - Positron-emission tomography (PET, ¹¹C-R-PK11195 radioligand, PBR receptors)
- **Analysis with new *Spatial Modeling* statistical approach**
 - To increase power to detect subtle group differences

UT Southwestern Research Plan



Gulf War Research: General Principles

3. Advance efforts to identify beneficial treatments for Gulf War veterans' illnesses either directly by evaluating specific treatments or indirectly by identifying pathophysiological processes potentially amenable to treatments

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ORP Objective #1: National Survey

- Survey includes battery of questions on what medications veterans have tried and whether each has been beneficial, ineffective or harmful for reducing symptoms.

ORP Objective #2: Sensitive Brain Imaging Procedures and Biomarker Studies

- Will test previously framed hypotheses about pathophysiology potentially amenable to treatment.

3. Advance efforts to identify beneficial treatments for Gulf War veterans' illnesses either directly by evaluating specific treatments or indirectly by identifying pathophysiological processes potentially amenable to treatments

ORP Objective #3: Preclinical Studies of Effects of Gulf War Exposures on Cells

- Currently proposed (but not yet approved) experimental studies will explore mechanistic questions about the effects of pesticides, sarin nerve agent, and pyridostigmine on the following cellular processes in mice:
 - Immune system
 - Neuro-inflammation
 - Cholinergic signaling
 - Mitochondrial health
 - Intracellular calcium signaling
 - The ubiquitin-proteasome intracellular complex
 - Autonomic nervous system function
 - Hippocampal function
 - Fear conditioning
 - A mouse model of motor neuron disease
 - A mouse model of glioblastoma brain cancer
 - Effects of in-utero exposure on post-natal brain development

Gulf War Research: General Principles

4. Integrate findings from experimental studies that characterize effects of Gulf War-related exposures with human studies of Gulf War veterans

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ORP Objective #3: Preclinical Studies of Effects of Gulf War Exposures on Cells

- A whole-animal mouse model of delayed effects of repetitive low-dose exposure of pesticide, sarin and pyridostigmine will assess the following at 12 weeks and one year post exposure:
 - Behavioral tests
 - Sleep patterns
 - 24 hour patterns of heart rate variability
 - Auditory evoked potentials (audiovestibular tests)
 - High field (12.5 T) MR spectroscopy for NAA concentrations
 - SPECT before and after cholinergic challenge
 - Other neuroimaging parameters found to be abnormal in GW veterans

Gulf War Research: General Principles

5. Studies of Gulf War illnesses should use well-constructed and clearly-described case definitions for Gulf War-associated multisymptom conditions and illness subsets.

Gulf War Research: General Principles

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ORP Objective #1: National Survey

- **Case definitions of Haley, Steele, Fukuda, Kang, SF-12, CFS, FM(s), MCS, etc.**
- **If Seabees longitudinal study shows substantial change in the illness profile, a new case definition may be developed with validation in split halves of the national sample and twins sample.**

ORP Objective #2: Sensitive Brain Imaging Procedures and Biomarker Studies

- **The final sample will be population representative.**
- **The neuroimaging protocols will be tested in pilot studies and in the Seabees sample before study of the population-representative sample.**

Gulf War Research: General Principles

6. Proposals whose principal focus is on psychological stress or psychiatric conditions as the primary cause of Gulf War illnesses should not be considered under this RFP.

Gulf War Research: General Principles

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ORP Objective #3: Pre-clinical Studies of Effects of Gulf War Exposures on Cells

- **One planned study will assess possible alterations of fear conditioning *caused by* exposure to pesticides, sarin and/or pyridostigmine and combinations.**

Highest Priority Areas of Interest for Gulf War Illness Research (9)

1. Epidemiologic studies of neurological diseases
2. Neuroimaging
3. Biological and genetic predisposition to GW exposures
4. Molecular differences between ill and healthy groups
5. Autonomic function
6. Animal models of effects of GW exposures
7. Inflammatory effects on GW veterans
8. Animal models of effects of GW exposures on inflammatory processes
9. Identification of retained markers of GW exposures

Interest Area 1: Epidemiologic studies of neurological diseases

Epidemiologic studies of rates of diagnosed neurological diseases (e.g., multiple sclerosis, Parkinson's Disease, amyotrophic lateral sclerosis, brain cancer)—as well as CNS abnormalities that are difficult to precisely diagnose—in Gulf War veterans and appropriate comparison groups

ORP Objective #1: National Survey

- The survey is powered to study the rates of GW case definitions (difficult to diagnose conditions) and the effects of risk factors within the defined strata.
- The sample will be inadequate to estimate population rates of the diagnosable neurological conditions, but significant relative risks might be obtainable if rates of any of these conditions occur at high rates in certain exposure comparison groups or GW illness subgroups.
- If rates of self-report neurological conditions show epidemiologically important group differences, the diagnoses will be confirmed by medical record review upon recontacting veterans who have given permission to be recontacted.

Interest Area 2: Neuroimaging

Use of state-of-the art neuroimaging and electroencephalography technologies to characterize aspects of brain structure and function that may distinguish ill Gulf War veterans (including illness/exposure subgroups) from healthy veterans

ORP Objective #2: Sensitive Brain Imaging Procedures and Biomarker Studies

- The testing protocol includes:
 - MR spectroscopy, MRI for volumetrics, DTI, Connectivity, high res. EEG, ESL, SPECT with cholinergic challenge, and fMRI paradigms probing regions/functions thought to be impaired.
 - Neuropsychological testing, brain dopamine turnover, dexamethasone suppression test, autonomic evaluation, quantitative sensory, audiovestibular testing
- Past and ongoing statistical research has identified a new approach to the analysis of brain imaging and EEG data that greatly increases the power to detect subtle group differences in brain structure and function.

Interest Area 3: Biological and genetic predisposition to GW exposures
Studies that investigate biological and genetic variability potentially linked to differences in vulnerability to Gulf War exposures, for example, associations between Gulf War illnesses and genotype/activity levels of enzymes (e.g. paraoxonase, butyrylcholinesterase, acetylcholinesterase) responsible for uptake and metabolism of Gulf War-related neurotoxic exposures

Interest Area 4: Molecular differences between ill and healthy groups
Studies that utilize new technologies (e.g., proteomic, genomic, and metabolomic methods) capable of characterizing molecular differences between ill Gulf War veterans and healthy comparison groups

ORP Objective #1: National Survey and Serum/DNA Bank

- Blood for banking serum, plasma and DNA collected from all meeting Haley or Steele, random sample of healthy, and seabees and twins (N = 2,064).
 - Paraoxonase and butyryl-cholinesterase serum activity and genotyping
 - (Genomic screening of SNP array being planned)

Interest Area 5: Autonomic function

Comprehensive evaluation of autonomic nervous system function in Gulf War veterans with multisymptom conditions and in illness and/or exposure subgroups

ORP Objective #2: Sensitive Brain Imaging Procedures and Biomarker Studies

- The testing protocol for the seabees study and the population-representative cases and controls includes:
 - Autonomic evaluation including 24-hour measurement of heart rate variability and the Mayo Clinical battery of clinical neurology tests of autonomic function.

Interest Area 6: Animal models of effects of GW exposures

Studies that characterize molecular, cellular, systemic, and behavioral effects of individual and combined exposures to neurotoxic substances to which Gulf war veterans were exposed during deployment (e.g., pyridostigmine bromide, low-dose chemical agents, pesticides, insect repellants)

ORP Objective #3: Preclinical Studies of Effects of Gulf War Exposures on Cells

- Currently proposed (but not yet approved) experimental studies will explore the mechanistic questions about the effects of pesticides, sarin nerve agent, and pyridostigmine on the following cellular processes in mice:
 - Immune system
 - Neuro-inflammation
 - Cholinergic signaling
 - Mitochondrial health
 - Intracellular calcium signaling
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- A whole-animal mouse model of delayed effects of repetitive low-dose exposure of pesticide, sarin and pyridostigmine will assess the following at 12 weeks and one year post exposure:
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 - Auditory evoked potentials (audiovestibular tests)
 - High field (12.5 T) MR spectroscopy for NAA concentrations
 - SPECT before and after cholinergic challenge
 - Other neuroimaging parameters found to be abnormal in GW veterans

Interest Area 7: Inflammatory effects on GW veterans

Evaluation of alterations in inflammatory processes in Gulf War veterans affected by multisymptom conditions . . .

- A pilot study of PET study of PK11195 uptake (peripheral dibenzodiazepin receptors) in brain is being conducted in a pair of twins discordant for GW deployment and illness in collaboration with the Johns Hopkins Neuroimaging Center. Since this objective is not yet covered in the Overall Research Plan, this pilot study is being funded by private funds of the UT Southwestern Epidemiology Division.

Interest Area 8: Animal models of effects of GW exposures on inflammatory processes

Experimental studies that characterize persistent effects of Gulf war-related exposures on inflammatory processes and their biological mediators in the central nervous system and other target organs

ORP Objective #3: Preclinical Studies of Effects of Gulf War Exposures on Cells

- Currently proposed (but not yet approved) experimental studies will explore the mechanistic questions about the effects of pesticides, sarin nerve agent, and pyridostigmine on the following cellular processes in mice:
 - Neuro-inflammation

**Interest Area 9: Identification of retained markers of GW exposures
Studies that utilize technologies capable of identifying markers (e.g. retention of toxins, secondary metabolites) that persist after exposure to Gulf War-related compounds individually and in combination**

ORP Objective #3: Preclinical Studies of Effects of Gulf War Exposures on Cells

- A study to address this objective is being designed but has not yet been approved.

Other Topics of Importance (8)

1. Studies of effects of depleted uranium
2. Studies of birth defects and other effects in children
3. Multivariate modeling in epidemiologic studies
4. Studies of effects of vaccines
5. Studies of CW-exposed populations
6. Studies of effects on immune system
7. Studies of occult infectious diseases
8. Experimental studies of GW exposure effects

Other Topic 1: Studies of effects of depleted uranium

Epidemiologic research utilizing a sample size sufficient to evaluate health outcomes of interest (e.g., rates of symptoms and multisymptom conditions, cancer, reproductive effects) among Gulf War veterans known to have been exposed to depleted uranium in comparison to veterans not exposed to depleted uranium during deployment

ORP Objective #1: National Survey and Serum/DNA Bank

- The U.S. Military Health Survey is surveying by telephone random samples 14,754 GW-era veterans, stratified by age, sex, race/ethnicity, active/reserve status, deployment.
- The potential effects of depleted uranium exposure is being assessed by including a special stratum in the sample of units present at Camp Doha during the ammunition explosion and fire—a cohort that should have had the highest DU exposure. Questionnaire items provide the Capstone Study's classification of DU exposure for analysis as a risk factor.
- The sample was powered to assess rates of symptoms and multisymptom conditions.
- If cancer and reproductive effects are highly prevalent in certain subgroups defined by exposures or GW case definitions, there may be adequate power to study them.

Other Topic 2: Studies of birth defects and other effects in children

Use of innovative study designs to evaluate risk of specific types of birth defects or other conditions previously suggested to be elevated among children of Gulf war veterans

ORP Objective #1: National Survey and Serum/DNA Bank

- The U.S. Military Health Survey is surveying by telephone random samples 14,754 GW-era veterans, stratified by age, sex, race/ethnicity, active/reserve status, deployment.
- The sample was also powered to study several reproductive effects, including fertility, miscarriage, gender ratios, and learning problems in children, all of which may be prevalent enough to study.
- Information on birth defects is being obtained and will be analyzed in case rates of birth defects are unusually common in certain subgroups defined by exposures or GW case definitions.
- The association of Goldenhar birth defect is being studied by a population-wide case control study, where all Goldenhar cases in era veterans were obtain by a national registry and birth denominators in deployed and nondeployed samples will be estimated from the national survey.

Other Topic 3: Multivariate modeling in epidemiologic studies

Additional utilization of available epidemiologic and clinical data to more clearly characterize associations between illnesses affecting Gulf War veterans and reported or modeled exposures, using analytic methods capable of distinguishing effects of multiple concurrent exposures and combinations of exposures

ORP Objective #1: National Survey and Serum/DNA Bank

- The U.S. Military Health Survey is collecting risk factor measures by self report and by objective collateral data sources such as the Unit Location Database.
- Multivariate statistical modeling techniques will be used to assess the associations of concurrent exposures and combinations of exposures.
- Sample weights reflecting the complex stratification design and effects of sample attrition will be used to obtain population estimates of prevalences and risk factor associations.

Other Topic 4: Studies of effects of vaccines

Studies of chronic symptoms and health characteristics of military personnel known to have received individual and combinations of vaccines administered to 1990-91 Gulf War veterans, particularly studies of Gulf War-era veterans for whom reliable vaccine information is available

ORP Objective #1: National Survey and Serum/DNA Bank

- The immunization question set of U.S. Military Health Survey asks veteran participants to find the immunization (shot) record and have it available during the interview. This will allow separate analysis of immunization effects in the subset with shot records, if the group is large enough.

Other Topic 5: Studies of CW-exposed populations

Studies of chronic symptoms and other health characteristics of populations known to have been exposed to chemical weapons

- This is not yet included in the Overall Research Plan, but a study of pesticide-exposed agricultural workers is being planned. Japanese researchers are conducting similar studies Japanese citizens with chronic illness after documented sarin exposure in the 1995 sarin attacks and have obtained findings similar to neuroimaging findings in ill Gulf War veterans (Yamasue et al. *Ann Neurol* 2007).

Other Topic 6: Studies of effects on immune system

Comprehensive evaluation of humoral and cellular immune parameters among Gulf War veterans with multisymptom conditions, including parameters that may differ among illness and/or exposure subgroups

- This is not yet included in the Overall Research Plan, but pending the outcome of the pre-clinical studies of the effects of GW exposures on immunologic systems in mice, studies will be designed and carried out on the serum, plasma and/or DNA being banked from the national survey.

Other Topic 7: Studies of occult infectious diseases

Use of diverse methods, including serological testing, polymerase chain reaction testing, and lymphocyte challenge tests, to determine whether Gulf War veterans with multisymptom conditions are affected by undetected infectious conditions (e.g. leishmaniasis)

- This is not yet included in the Overall Research Plan, but this is a likely objective for use of serum, plasma and/or DNA being banked from the national survey or future data collection projects (e.g., biomarker study of 80 population-representative sample).

Other Topic 8: Experimental studies of GW exposure effects

Experimental studies that characterize molecular, cellular, systemic, and behavioral effects of compounds to which Gulf war veterans were exposed (e.g., individual and multiple vaccine combinations, depleted uranium, oil fire smoke, jet fuel) individually, and in combination with other exposures of potential concern

ORP Objective #3: Preclinical Studies of Effects of Gulf War Exposures on Cells

- Currently proposed (but not yet approved) experimental studies will explore the mechanistic questions about the effects of pesticides, sarin nerve agent, and pyridostigmine on the following cellular processes in mice:
 - Immune system
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 - Cholinergic signaling
 - Mitochondrial health
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VA Research Advisory Committee ***Research Priorities –January 2006***

Gulf War Research: General Principles

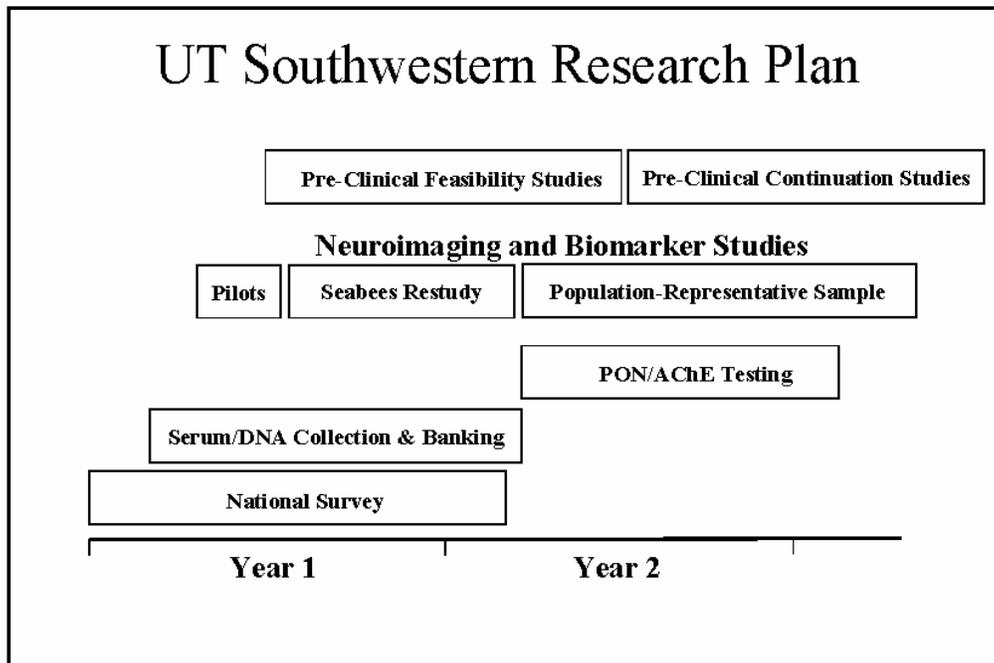
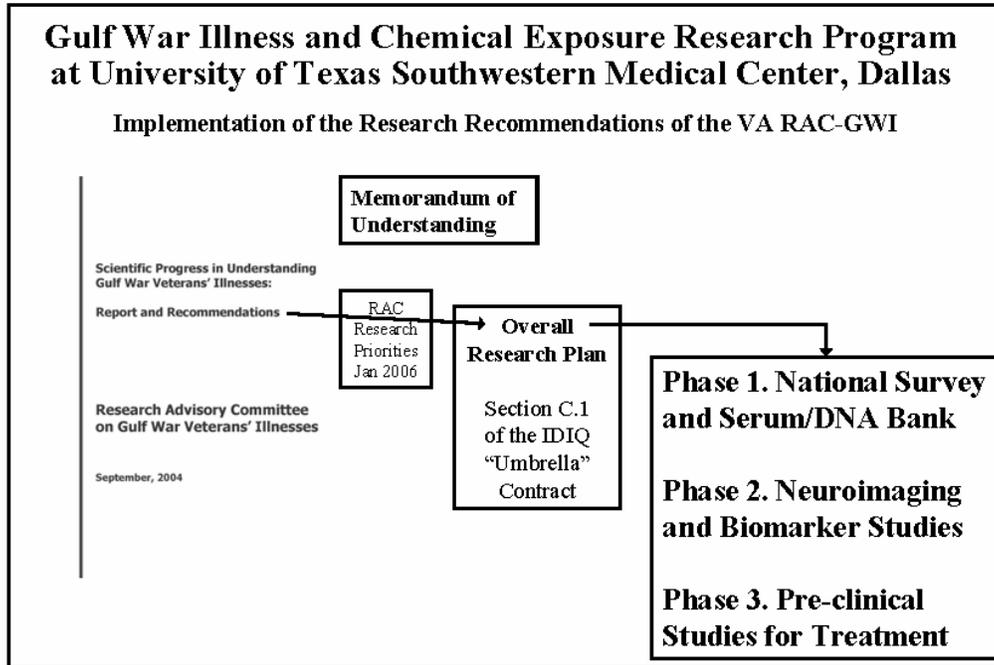
Presently addressing 6 of 6

Highest Priority Areas of Interest for Gulf War Illness Research

Presently addressing 9 of 9

Other Topics of Importance

Presently addressing 5 of 8



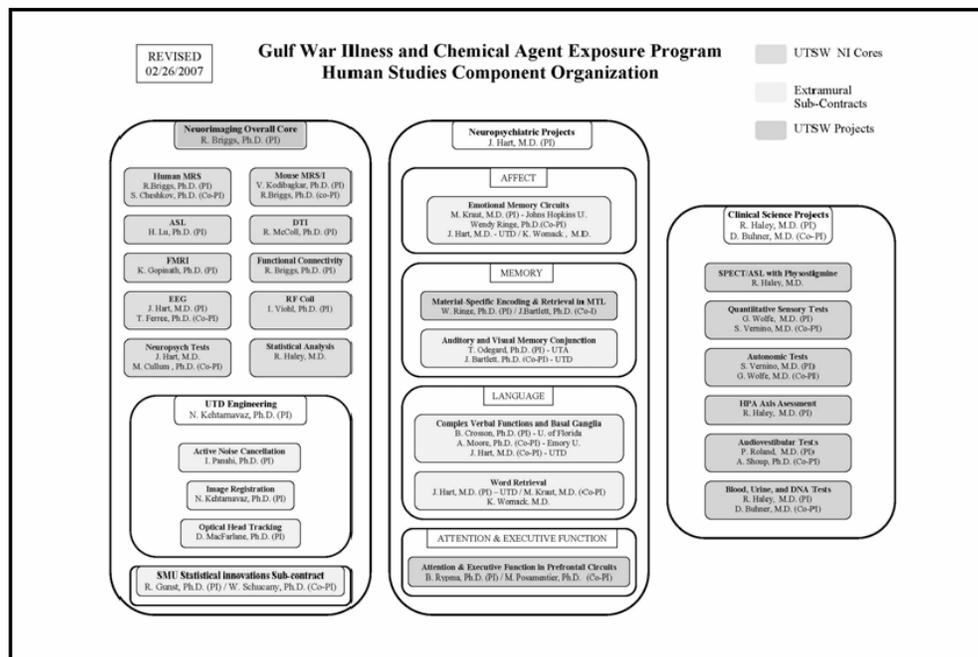
Presentation 3 – Richard Briggs

Neuroimaging Introduction and Overview

Richard W. Briggs, Ph.D.

Department of Radiology, Division of Neuroradiology
Neuroimaging Laboratory
Gulf War Illness and Chemical Agent Exposure Program
University of Texas Southwestern Medical Center
Dallas, Texas

Richard.Briggs@UTSouthwestern.edu



Neuroimaging Sub-Cores and PIs

#	Sub-Core	P.I. (Co-PI)
1	Human MRS	Richard Briggs, Ph.D. (Sergey Cheshkov, Ph.D.)
2	ASL-SPECT CBF	Hanzhang Lu, Ph.D.
3	DTI	Roderick McColl, Ph.D.
4	FMRI	Kaundinya Gopinath, Ph.D.
5	Functional Connectivity	Richard Briggs, Ph.D.
6	EEG	John Hart, M.D. (Tom Ferree, Ph.D.)
7	Neuropsych Tests	John Hart, M.D.
8	Statistics & Analysis	Robert Haley, M.D.
9	Mouse MRS *	Vikram Kodibagkar, Ph.D.

* part of the pre-clinical (animal model and molecular) component task order group

Updates on Neuroimaging Methods and Progress

- EEG (high-density, source localization)
- ¹H Spectroscopy
- Diffusion Tensor Imaging (DTI)
- Perfusion and CBF Imaging (ASL)
- Engineering Innovations (Image Registration, Active Noise Cancellation and Speech Enhancement)

Presentation 4 – John Hart, Jr.

Gulf War Illness Neuroscience Projects Overview

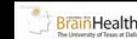
John Hart, Jr.
Professor of Brain and Behavioral Sciences and Neurology
UTD and UTSW

Gulf War Illness Symptoms

- Trouble finding words/speech difficulty
- Attention/concentration
- Slow thinking/processing speed/putting things together
- Memory
 - Short-term (frontal lobe)
 - Semantic object (thalamus and basal ganglia)
 - Learning new material (hippocampus)
- Depression/anxiety/hyperarousal/irritability
- Confusion

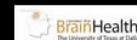
GWV Anatomical Regions Affected

- Basal ganglia
- Thalamus
- Hippocampus
- Amygdala
- Frontal lobes/insula
- White matter
- Brainstem



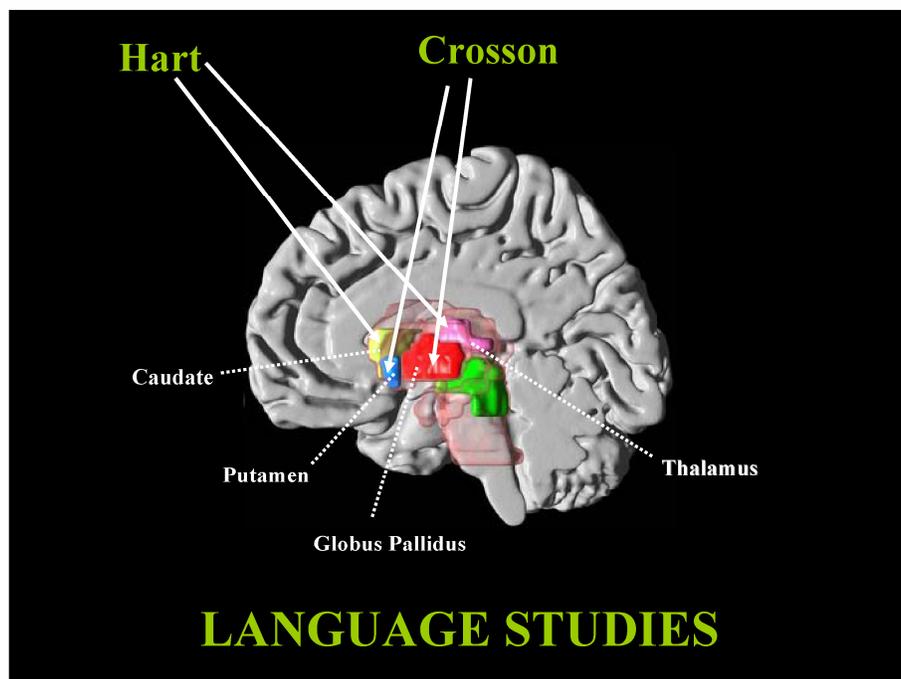
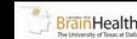
Gulf War Neuroscience Projects

- Word Finding
- Complex Verbal Functions & the Basal Ganglia
- Attention & Executive Function in Prefrontal Circuits
- Auditory Visual Memory Conjunction
- Material Specific Encoding & Recognition in the Medial Temporal Lobes
- Emotional Memory Circuits



Gulf War Neuroscience Projects

- Word Finding (Hart)
- Complex Verbal Functions & the Basal Ganglia (Crosson)
- Attention & Executive Function in Prefrontal Circuits
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- Emotional Memory Circuits

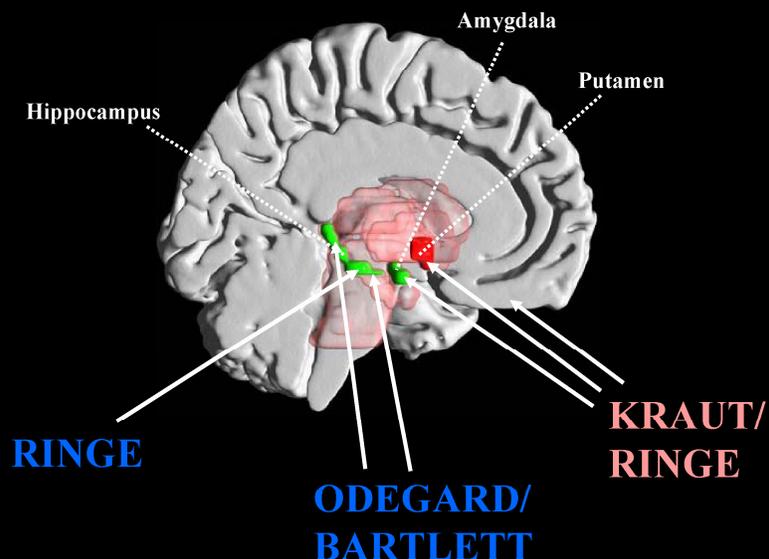


Gulf War Neuroscience Projects

- Word Finding
- Complex Verbal Functions & the Basal Ganglia
- Attention & Executive Function in Prefrontal Circuits
- Auditory Visual Memory Conjunction (Odegard & Bartlett)
- Material Specific Encoding & Recognition in the Medial Temporal Lobes (Ringe)
- Emotional Memory Circuits (Kraut & Ringe)



MEMORY AND AFFECT STUDIES

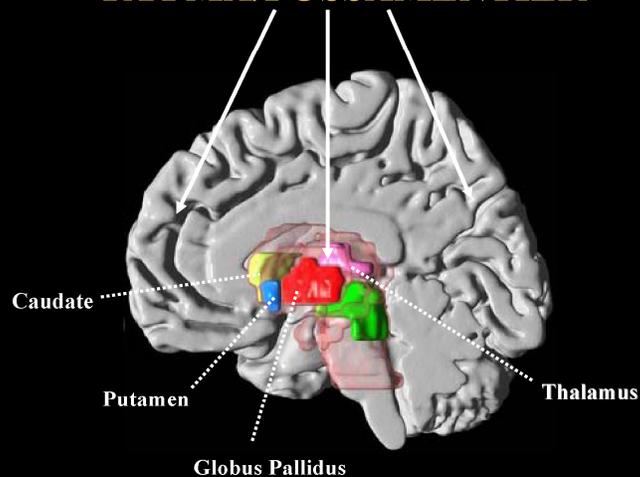


Gulf War Neuroscience Projects

- Word Finding
- Complex Verbal Functions & the Basal Ganglia
- Attention & Executive Function in Prefrontal Circuits (Rypma & Possamentier)
- Auditory Visual Memory Conjunction
- Material Specific Encoding & Recognition in the Medial Temporal Lobes
- Emotional Memory Circuits



RYPMA/POSSAMENTIER



ATTENTION & EXECUTIVE FUNCTION

Gulf War Neuroscience Projects

- TARGETED INTEGRATION OF RESULTS
 - Hypothesis-driven combined analysis
 - Projects
 - Neuroimaging findings
 - Survey
 - Pre-clinical findings
 - Targets
 - Mechanistic understanding
 - Diagnostic toolset
 - Treatment



Gulf War Illness Neuropsychological Sub-Core

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Munro Cullum
Professor of Brain and Behavioral Sciences and Neurology
Professor of Psychiatry
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Neuropsychological Test Battery

- Global cognition
- Attention
- Short-term memory
- New learning (declarative memory)
- Language
- Visuospatial abilities
- Executive functions/reasoning
- Psychomotor speed
- Psychological symptoms
- Motivation/effort

Neuropsychological Testing

- choice of tests based on
 - symptoms expressed by patients
 - tests previously impaired in studies
 - tests administered to the Seabee cohort when last examined

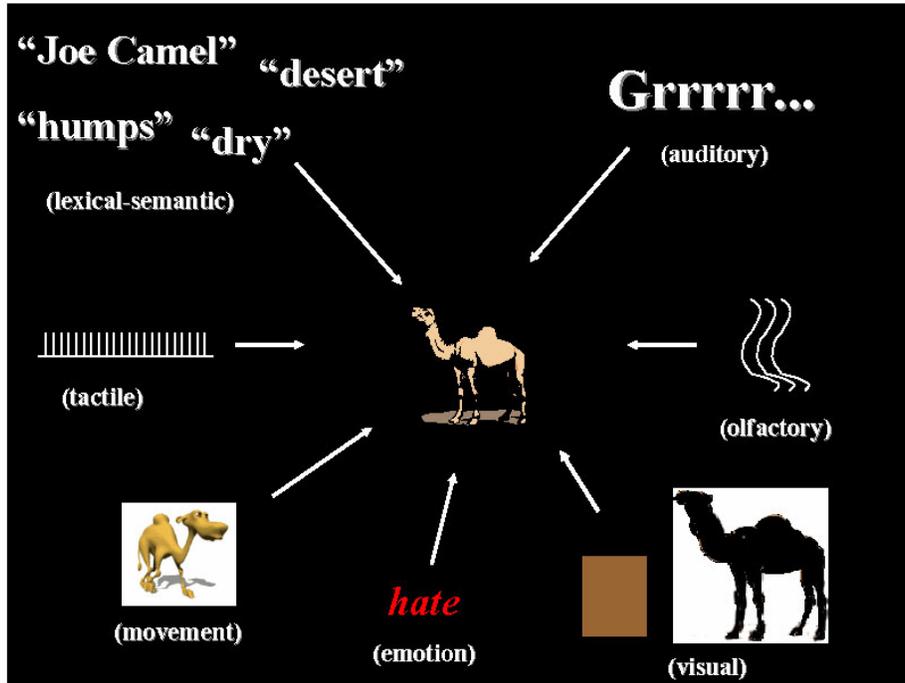
Neuropsychological Testing

- data will provide first longitudinal assessment of cognitive deficits in GWI
 - deficits with aging
 - recovery
 - static
- provide correlates for other studies
 - symptom checklist
 - illness subtypes
 - neuroimaging

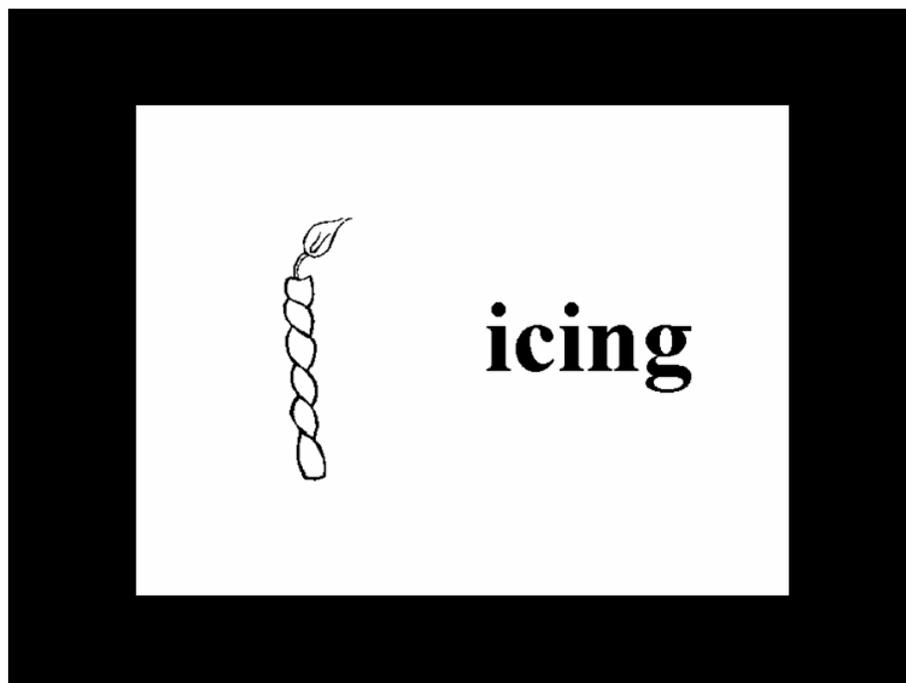
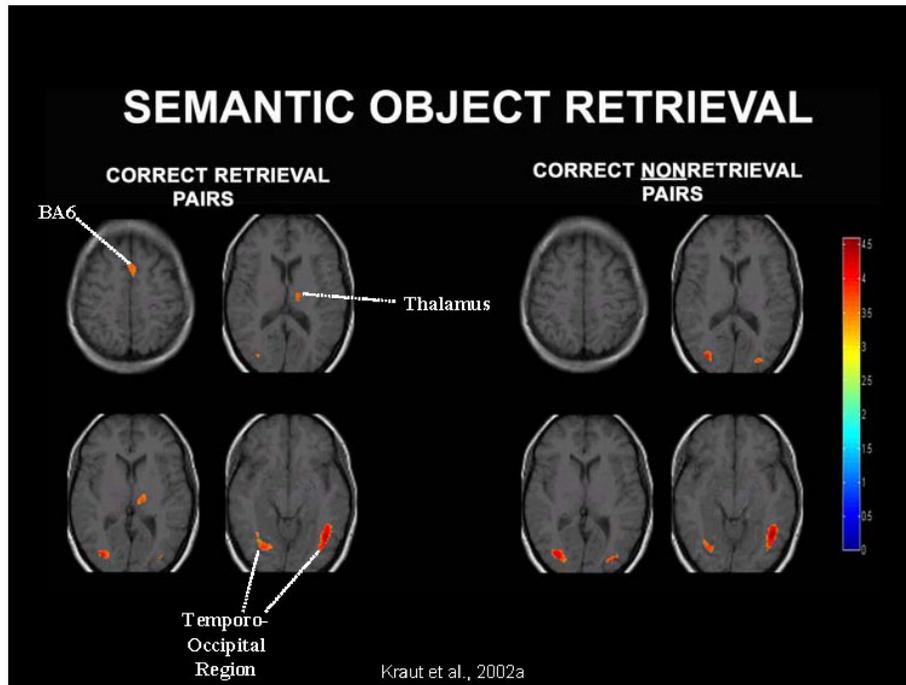


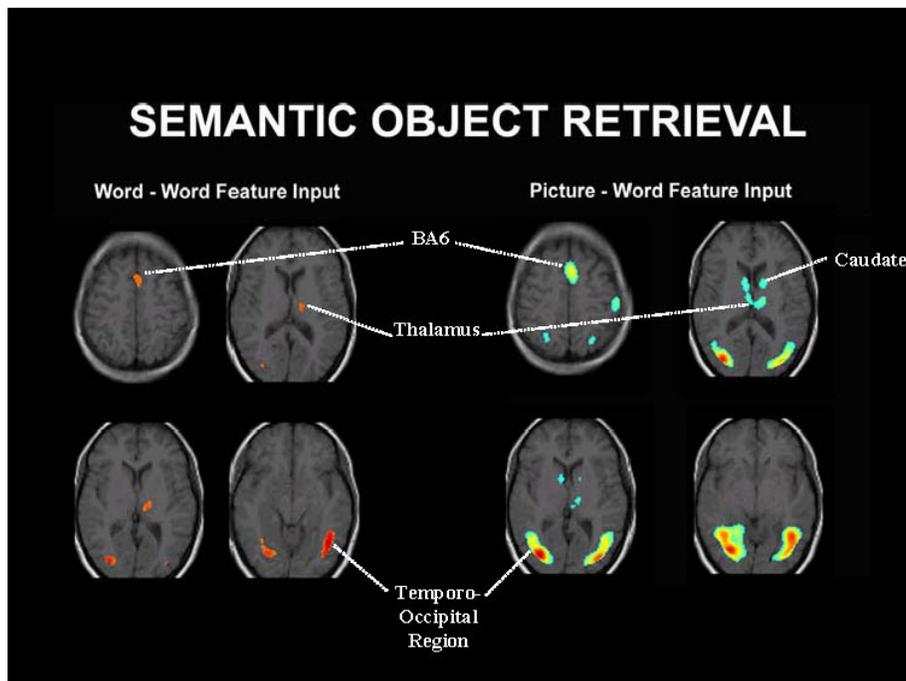
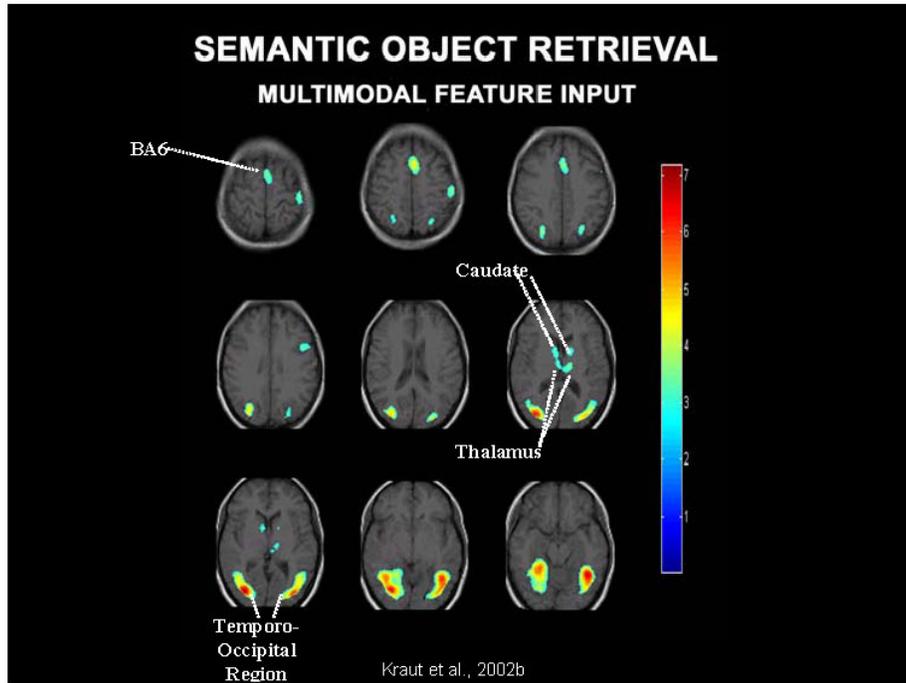
Gulf War Illness Word Finding Project

John Hart, Jr.
Professor of Brain and Behavioral Sciences and Neurology
UTD and UTSW



desert
humps



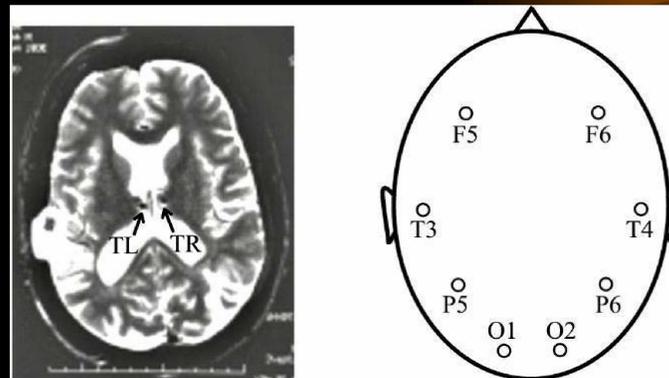


Expected Regions of Activation during fMRI

Cognitive Tests	TO	BA 6	Dorsomedial Nucleus	Pulvinar	Basal Ganglia
SORT (picture-word)	B	B	B	B	B
SORT (word-word)	B	B	L	L	
Object-Category Recall (word-word)	B	B			

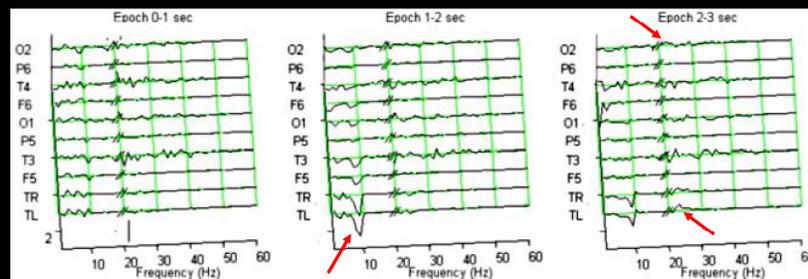
TO=Temporo-occipital; BA6=Brodmann Area 6; B = bilateral; L = left; R = right

Thalamic Depth and Scalp Electrode Placement



Slotnick et al., 2002

Semantic Object Retrieval Test Difference Power Spectra



Slotnick et al., 2002



Semantic Object Memory Retrieval

- EEG alpha power change globally for memory retrieval vs. misses
- EEG gamma power increase in thalamus & occipital for memory retrieval
- synchronized, rhythmical neural firing of regions encoding memory retrieval

Slotnick et al., 2002



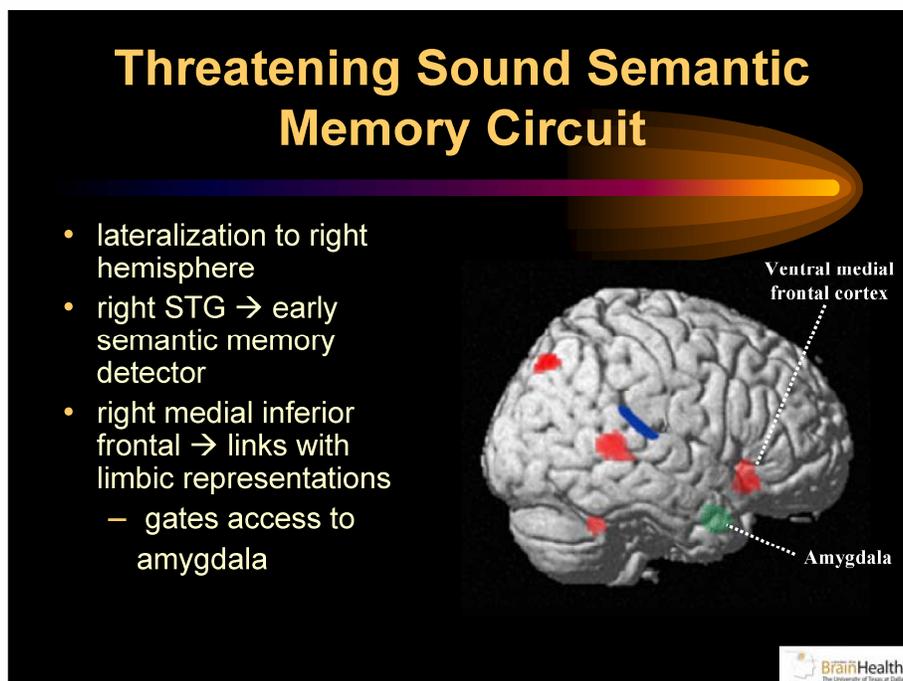
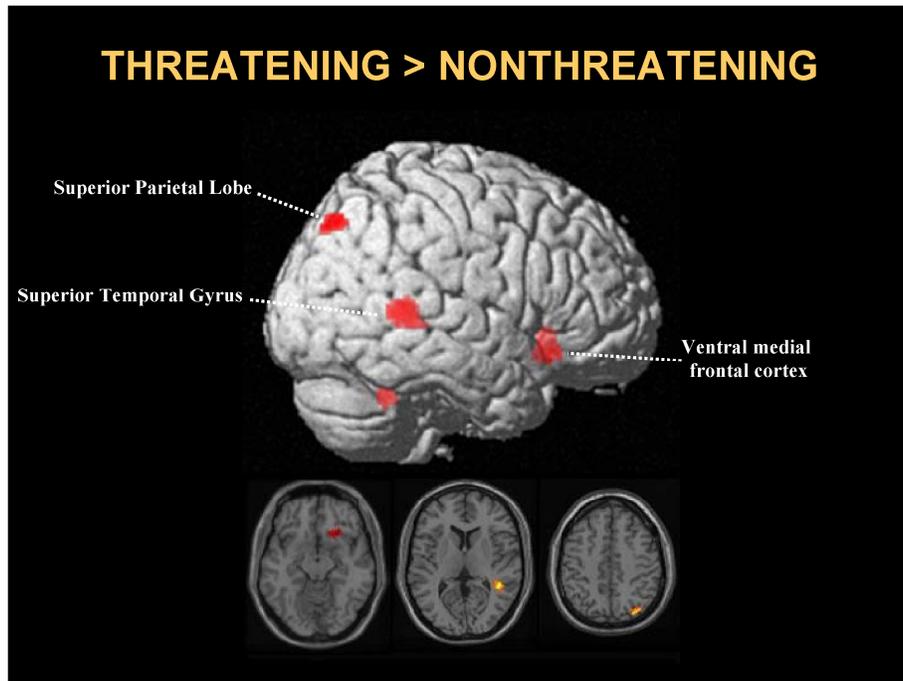
Analysis of Semantic Object Memory Retrieval in GWI

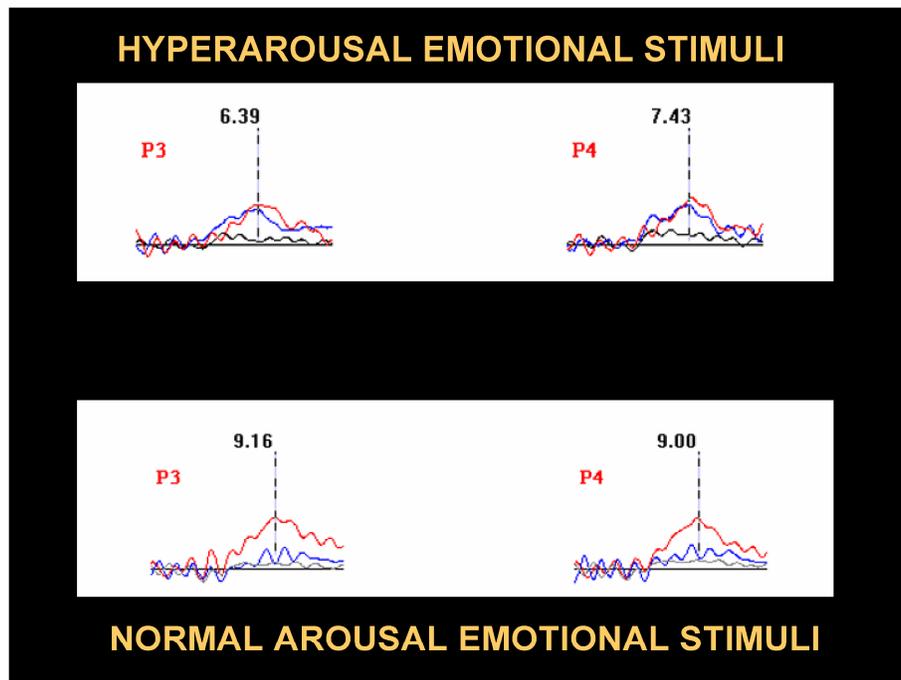
- fMRI detecting if brain regions are normally activated
- EEG alpha and gamma power assessment
 - how and why process impaired
 - if performance intact but task harder to do
 - EEG power and timing of EEG connectivity can detect



Gulf War Illness Emotional Memory Circuit Project

Michael A. Kraut
Associate Professor of Radiology
Johns Hopkins School of Medicine
Wendy Ringe
Assistant Professor of Psychiatry
UTSW





Analysis of Threatening Memory Circuit in GWI

- ERP to see if auditory and/or visual hyperarousal response
- fMRI see if regions encoding visual & auditory threat same in groups
- determine if encoding, gating, or over-responsiveness basis of difficulty
 - relate to cognitive symptoms
 - integrate with targeted neuroimaging markers

Presentation 5 – Michael Motes

Testing Hypotheses of Changes in Prefrontal Function Related to Gulf War Syndrome

Bart Rypma, PhD
Mette Posamentier, PhD
Michael A. Motes, PhD
University of Texas at Dallas

Purpose

- Summarize previous work on neuroimaging age-related cognitive deficits
- Propose model for understanding Gulf War Syndrome-related cognitive deficits

Gulf War Symptoms

Syndrome: "Impaired Cognition"

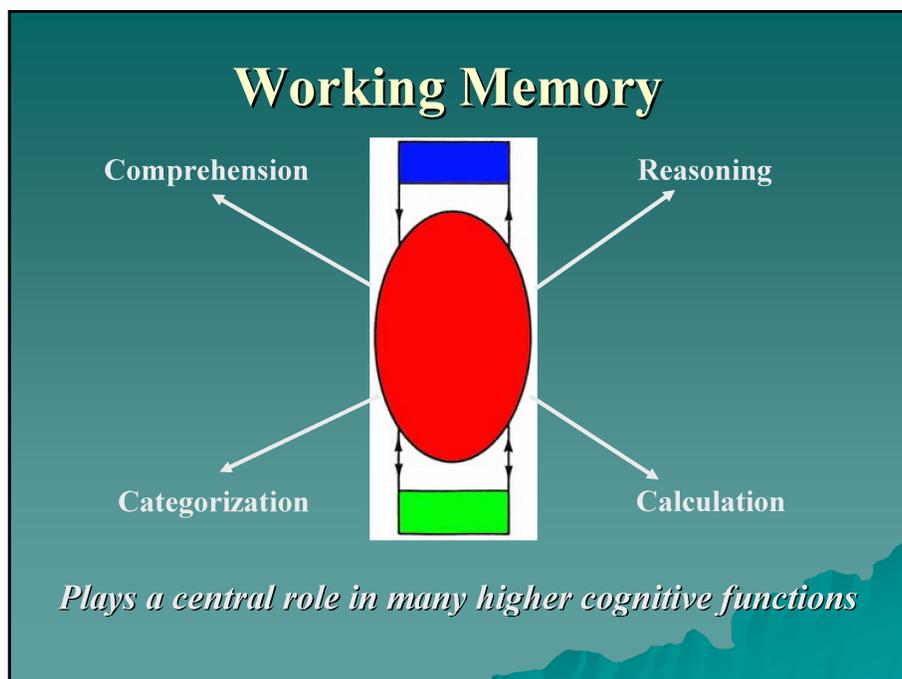
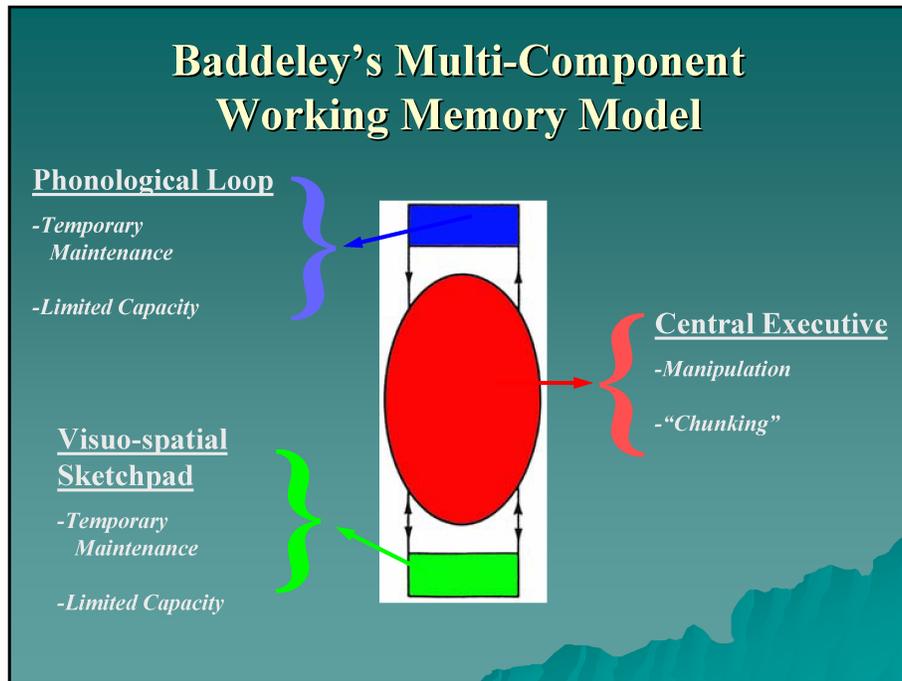
- Memory
 - Impaired short-term memory
- Executive Control
 - Impaired attention/concentration
- Reasoning

Haley, Kurt, & Hom, 1997

What is Working Memory?

Processes that support:

- *short-term retention of information*
- *manipulation of that information*



Neural Underpinnings of Working Memory

The diagram illustrates the neural underpinnings of working memory. On the left, two columns of illustrations show working memory and associative memory tasks. The working memory task involves a monkey in a cage with a tray of food. A hand presents a card with 'Wrong' and 'Right' options. The monkey must choose the correct option to receive food. The associative memory task involves a monkey in a cage with a tray of food. A hand presents a card with 'Wrong' and 'Right' options. The monkey must choose the correct option to receive food. The tasks are shown in three stages: Cue, Delay, and Response. The PFC Lesion diagram shows a brain with the Prefrontal Cortex (PFC) highlighted in purple. Below the brain, the text 'PFC Lesion' is written. Two arrows point from 'PFC Lesion' to 'Working Memory' and 'Long-term Memory'. Below 'Working Memory', an arrow points to 'Impaired'. Below 'Long-term Memory', an arrow points to 'Unimpaired'. The citation 'Goldman-Rakic et al., 1992' is at the bottom left.

Working memory task Associative memory task

Cue Cue and response

Delay Delay

Response Cue and response

PFC Lesion

Working Memory Long-term Memory

Impaired Unimpaired

Goldman-Rakic et al., 1992

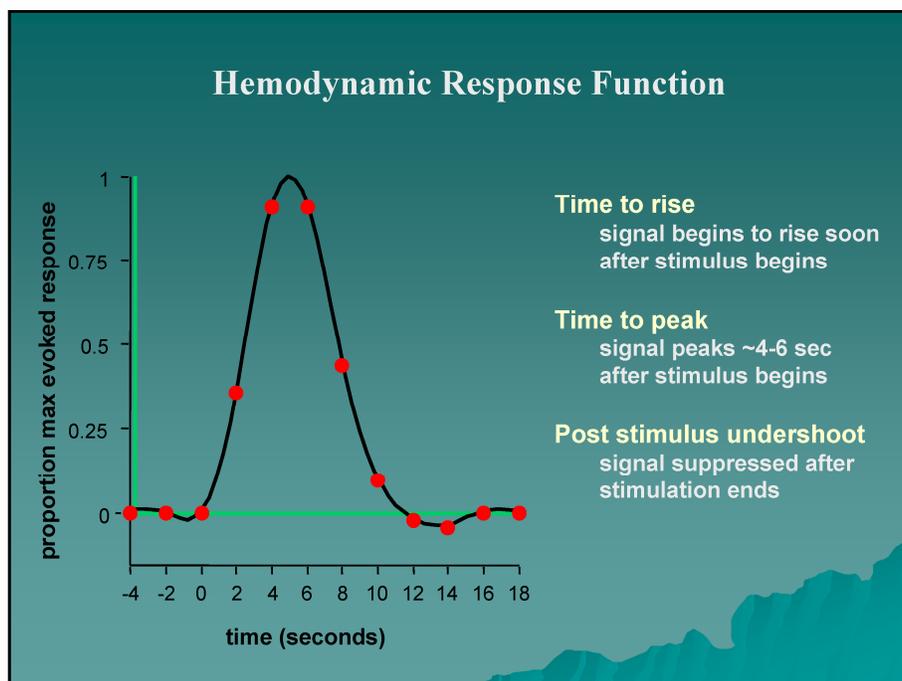
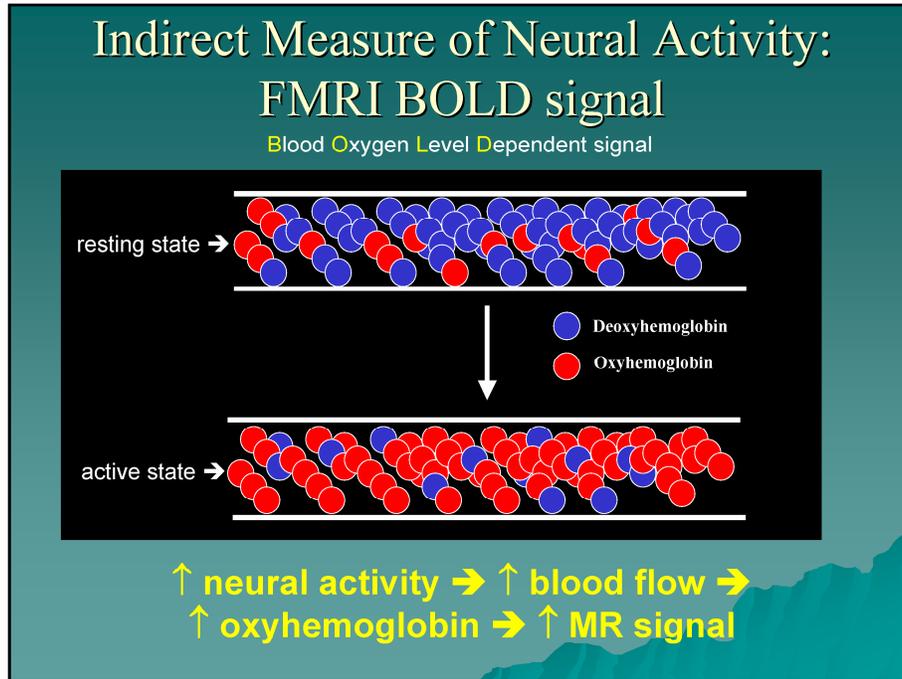
Used fMRI to Examine Functional Subsystems of Prefrontal Cortex

Dorsolateral Prefrontal Cortex
-Manipulation Working Memory Processes
Chunking

The diagram shows a lateral view of the human brain with the Prefrontal Cortex (PFC) highlighted in red and blue. The red area is labeled 'Dorsolateral Prefrontal Cortex' and the blue area is labeled 'Ventrolateral Prefrontal Cortex'. The citation '(Rypma et al. 1999, Neuroimage)' is at the bottom right.

Ventrolateral Prefrontal Cortex
-Maintenance Working Memory Processes
Rehearsal

(Rypma et al. 1999, *Neuroimage*)



Measuring Working Memory: The Delayed Response Task

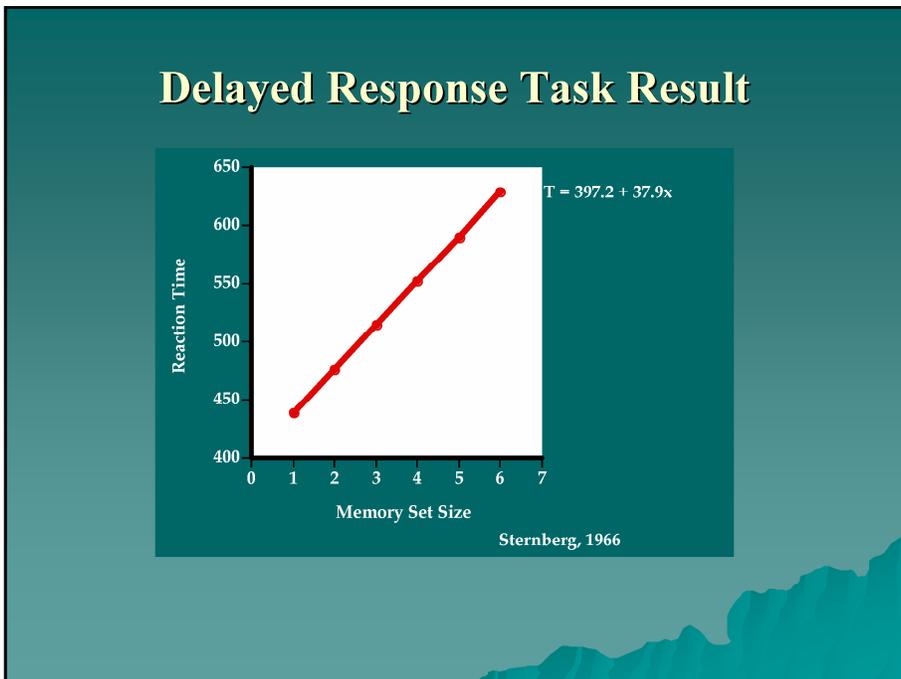
1 - 8 Letters

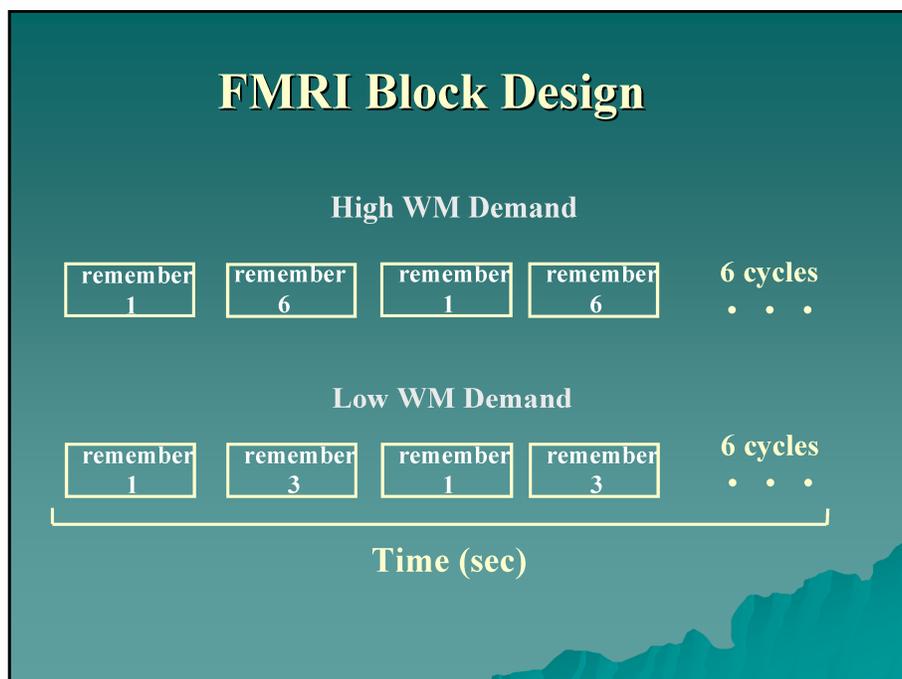
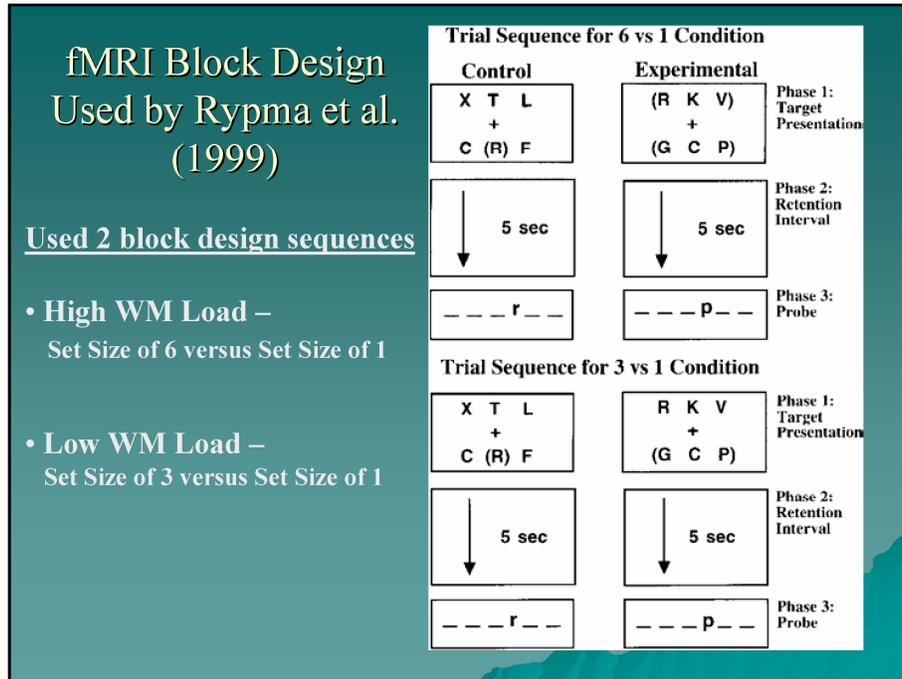
PKJVBNM

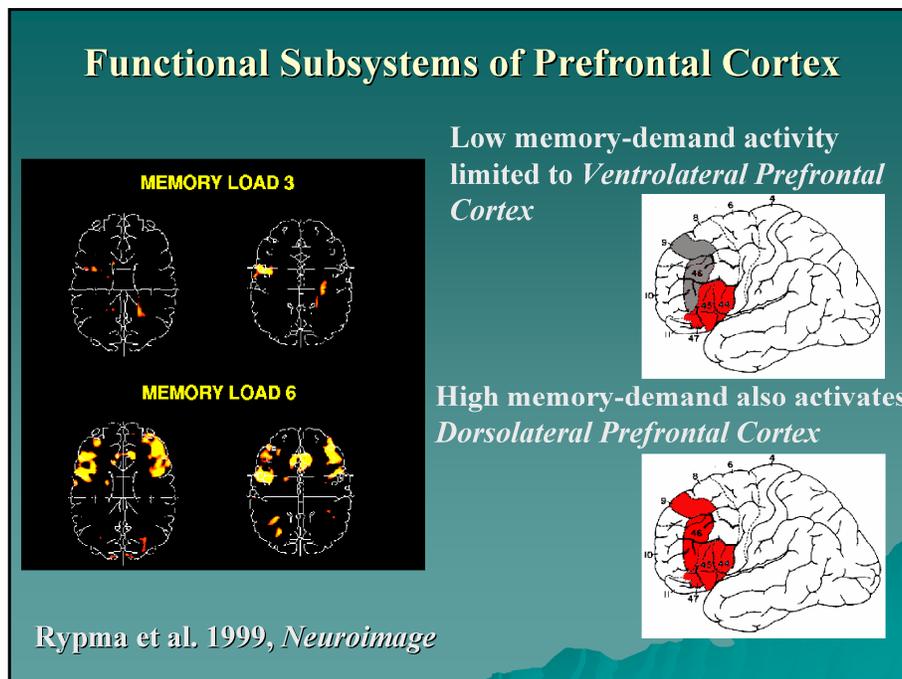
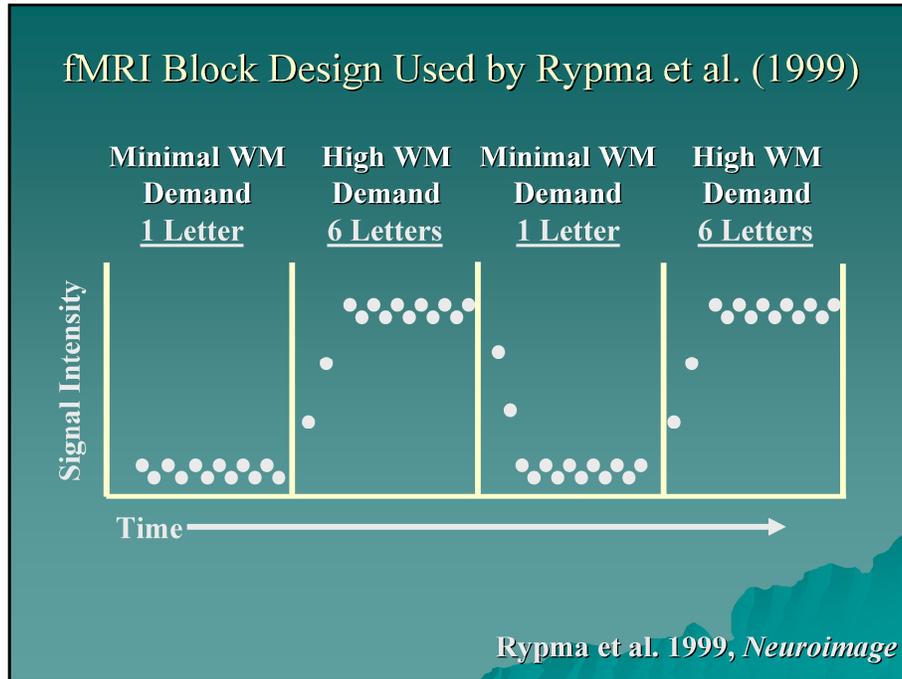
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encoding delay response

Sternberg, 1966

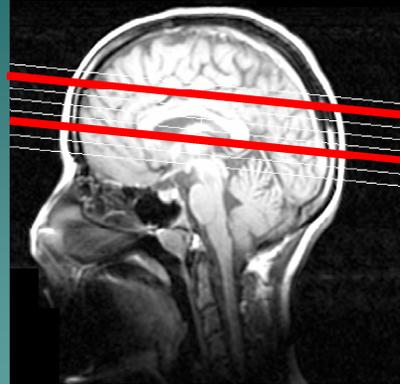






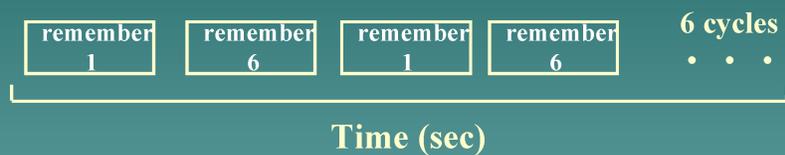
Relationship between PFC Function & Age-Related WM Deficits

- ❖ 6 younger subjects, 6 older subjects
- ❖ Delayed Response WM Task

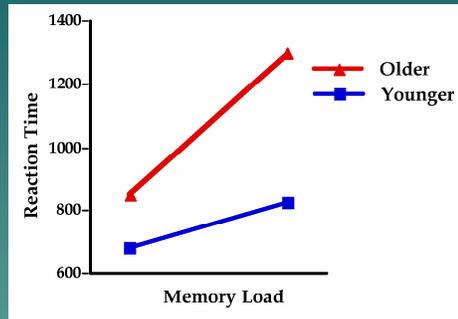


Rypma, Prabhakaran, Desmond, & Gabrieli, 2001
Psychology and Aging

FMRI Block Design



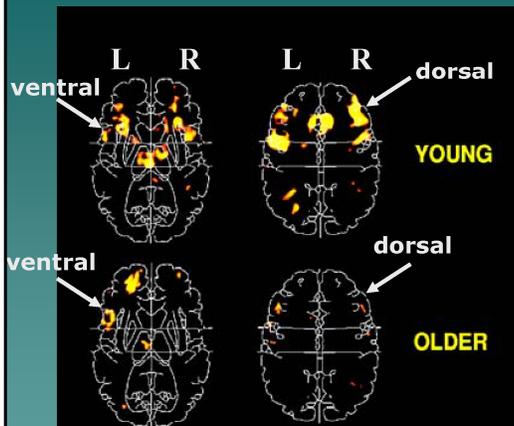
Age Differences in Memory Search Time



(Anders, Fozard & Lillyquist, 1972)

Age differences increase with increasing memory set size

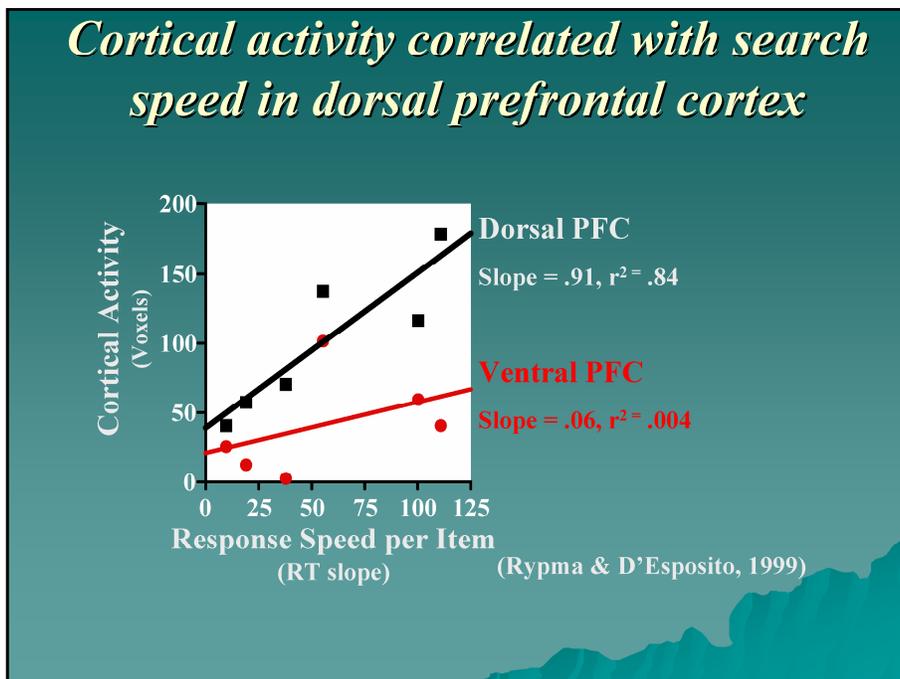
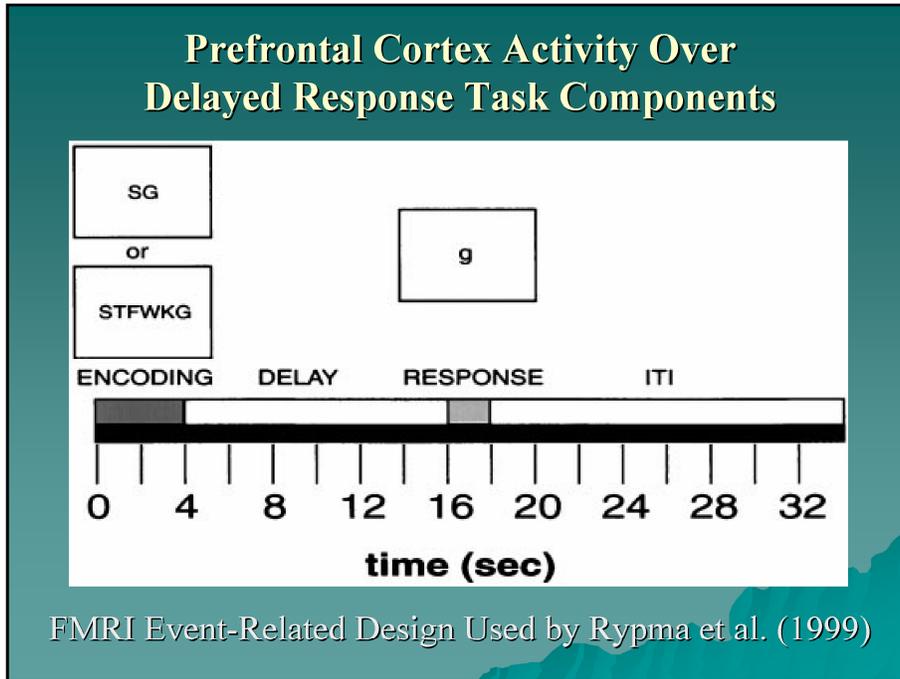
FMRI Results



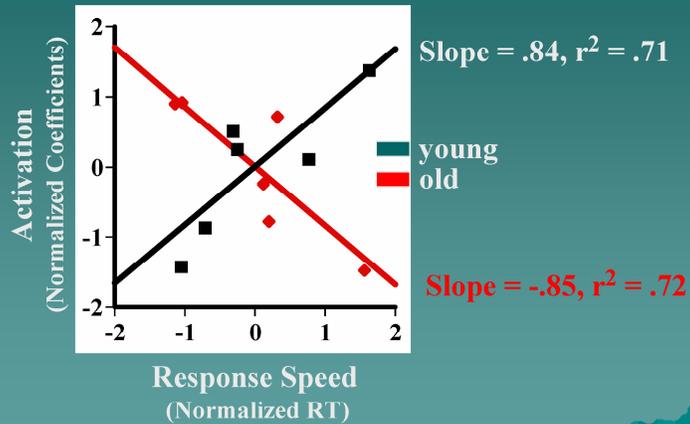
-Decreases in dorsal PFC activation with age

-Equivalent ventral PFC activation with age

Rypma, Prabhakaran, Desmond, & Gabrieli, 2001
Psychology and Aging



Dorsolateral PFC Activity Differentially Related to Search Speed for Young and Old



(Rypma & D'Esposito, 2000
Nature-Neuroscience)

Processing Speed

Digit Symbol Substitution Test

10. DIGIT SYMBOL	1	2	3	4	5	6	7	8	9	SCORE															
	1	2	3	4	5	6	7	8	9																
	-	J	□	L	U	O	△	X	=																
SAMPLES																									
	2	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4	5	6	3	1	4
	1	5	4	2	7	6	3	5	7	2	8	5	4	6	3	7	2	8	1	9	5	8	4	7	3
	6	2	5	1	9	2	8	3	7	4	6	5	9	4	8	3	7	2	6	1	5	4	6	3	7
	9	2	8	1	7	9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

... (90sec)

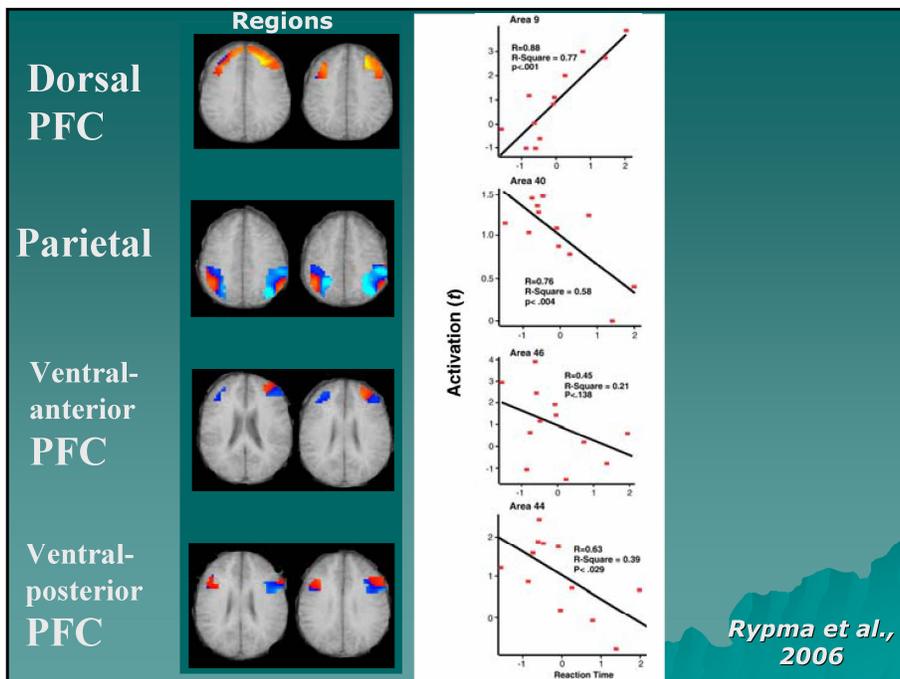
- *Psychometric research identified processing speed as basic cognitive ability*
- *Age-related variability in processing speed predicts variability in other cognitive tasks*

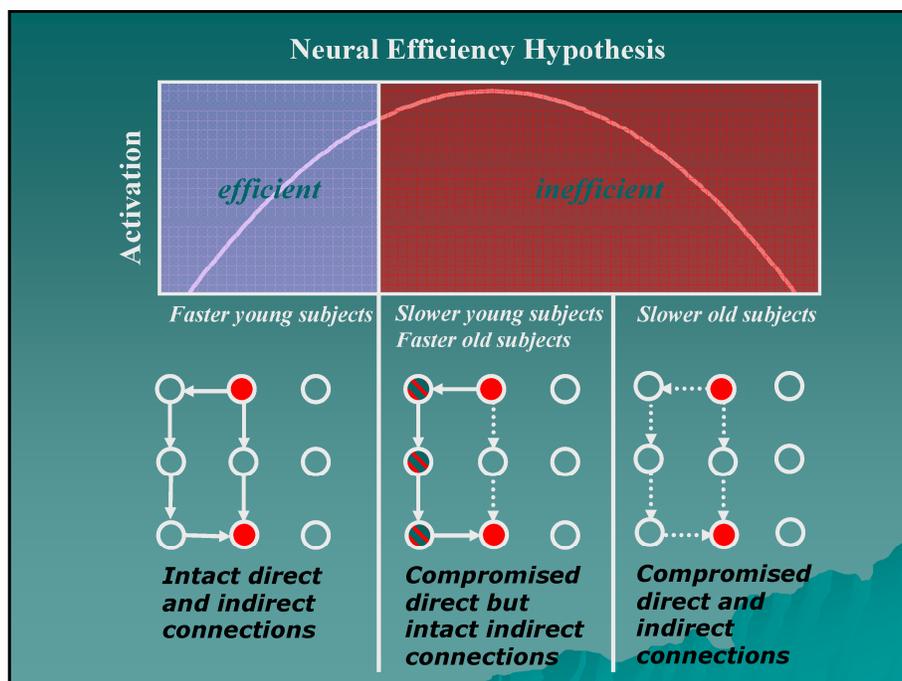
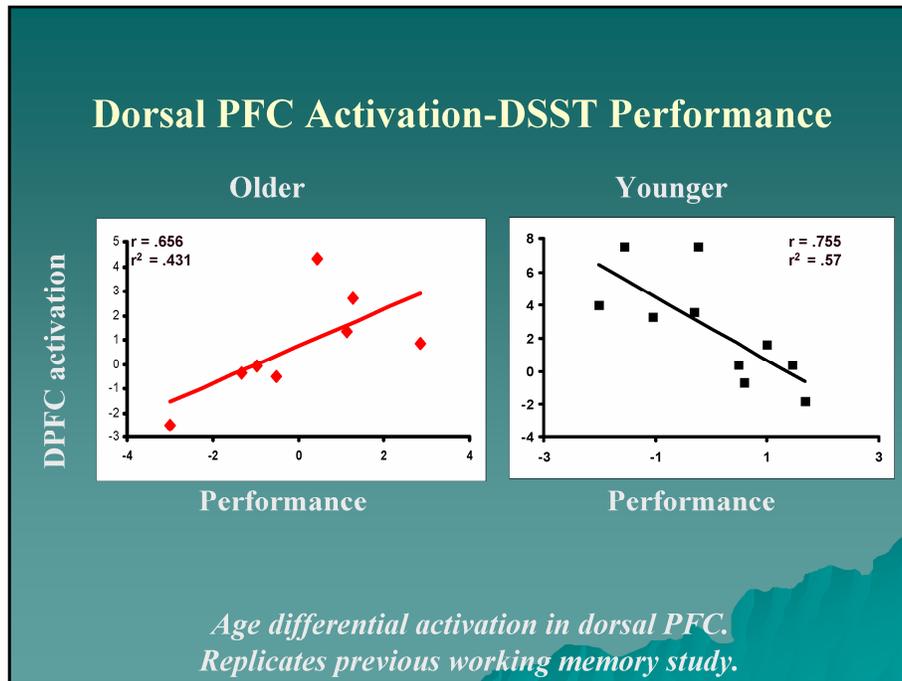
A Symbol-Digit Test for fMRI

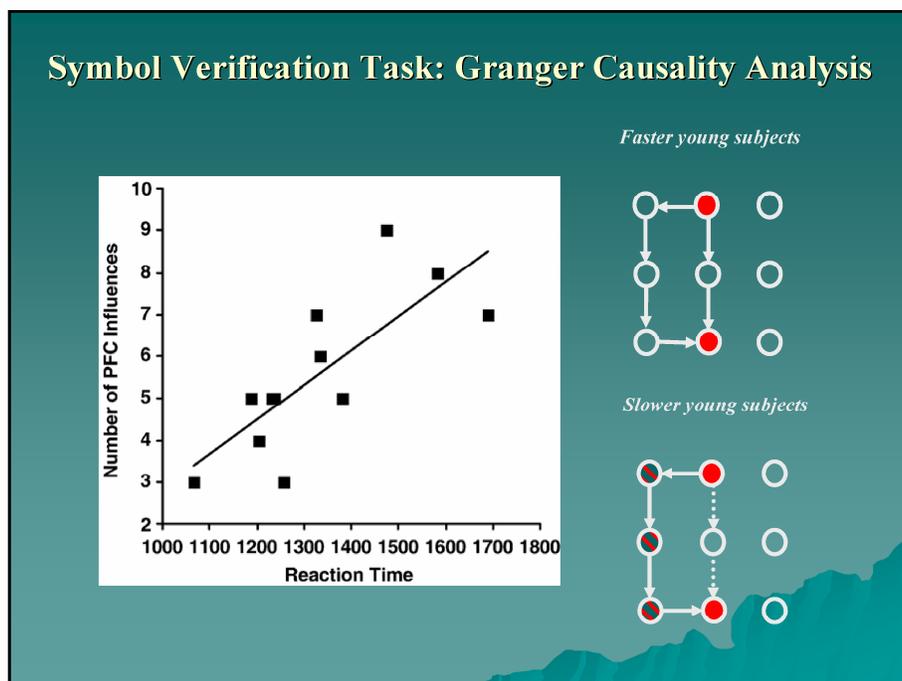
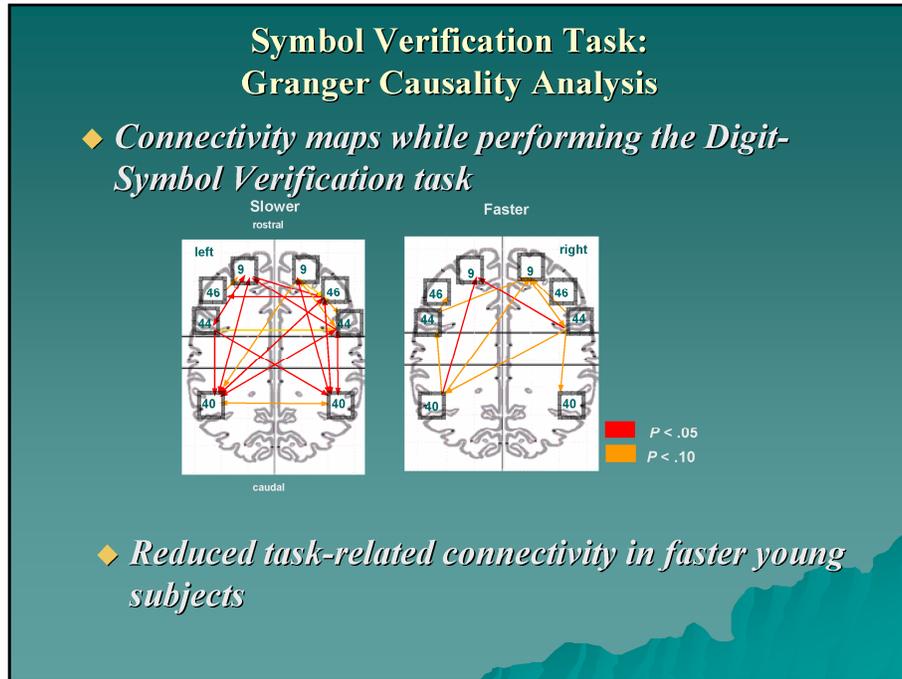
□	◦	┌	┐	└	>	+	□	◦
1	2	3	4	5	6	7	8	9



The "Symbol-Digit Verification Task"
Rypma et al., 2006

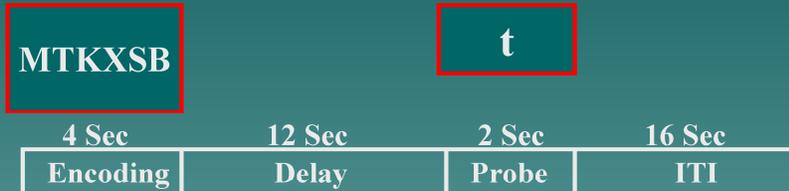




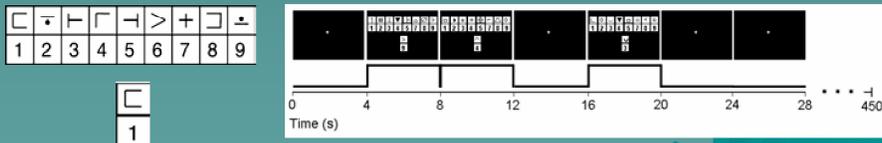


◆ *Question: Are Gulf-War Syndrome working memory changes related to neural efficiency?*

Working Memory Measure: Delayed Response Task



Processing Speed Measure: Digit-Symbol Verification Task



Hierarchical Regression

- ◆ Test Syndrome-Related Differences on WM and Processing Speed Tasks
 - Neural activity differences
 - Activity-Performance relationship differences
 - Task-related functional connectivity differences

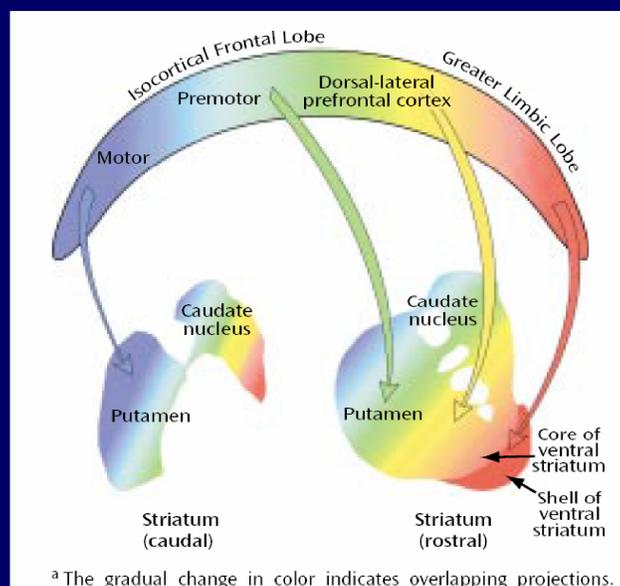
- ◆ Test Syndrome-Related Differences in Neural Activity Relationships Between Tasks



Presentation 6 – Wendy Ringe

Fronto-Striatal Systems in Depression & Gulf War Illness

- Depression is a prevalent complaint in GWI
- The extent to which it is primary or reactive is an ongoing topic of debate
- Basal ganglia dysfunction and altered central dopamine have been documented in GWI
- Striatal systems have been implicated in depression in other basal ganglia diseases
- **Recent advances suggest two distinct but interconnected prefrontal-subcortical systems**



Findings in Depression

Dorsolateral PFC

Dorsolateral PFC & dorsal cingulate

Involved in cognitive tasks like attention, problem-solving

Decreased in depression

Lateral orbital cortex

Active in normals during sadness

Increased in MDD -*r* with severity (Coping?)

Greater Limbic Lobe

Ventral anterior cingulate

Reactive to sadness in normals
Overactive in depression

Medial PFC

Active during emotions in both MDD and Normals

Amygdala

Overactive in MDD

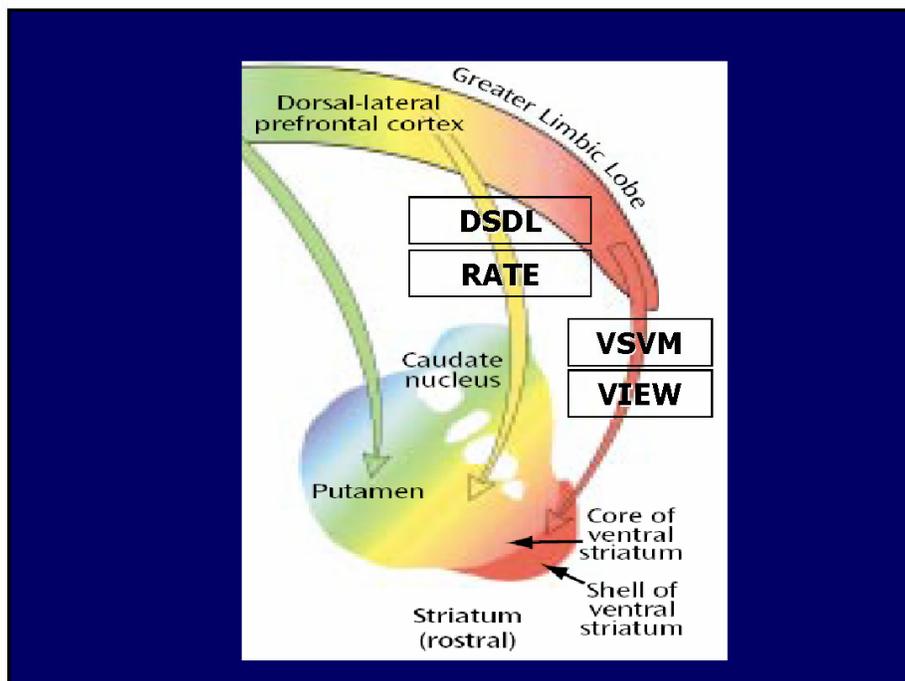
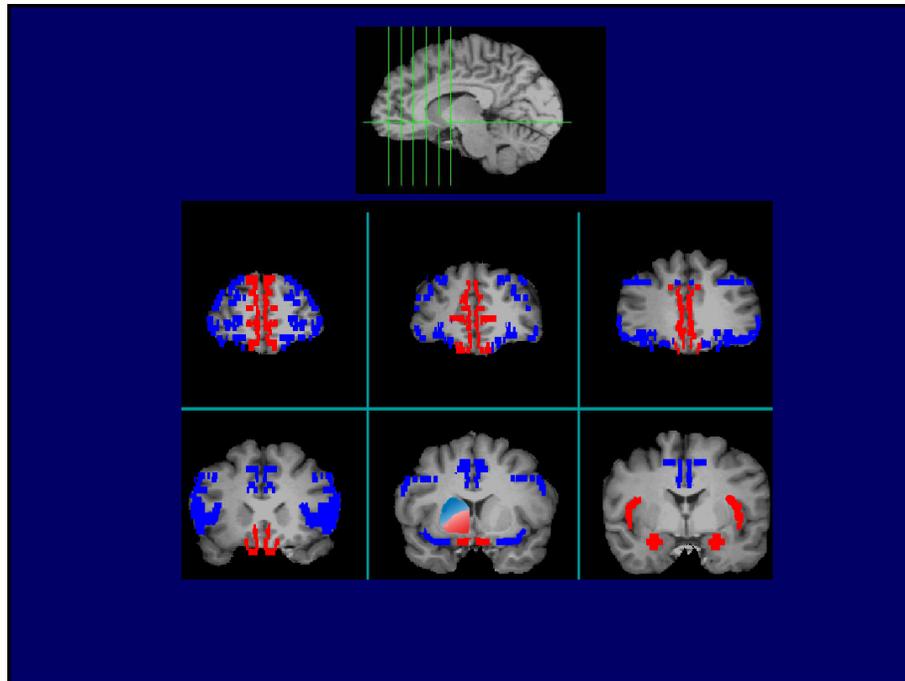
Frontostriatal Systems

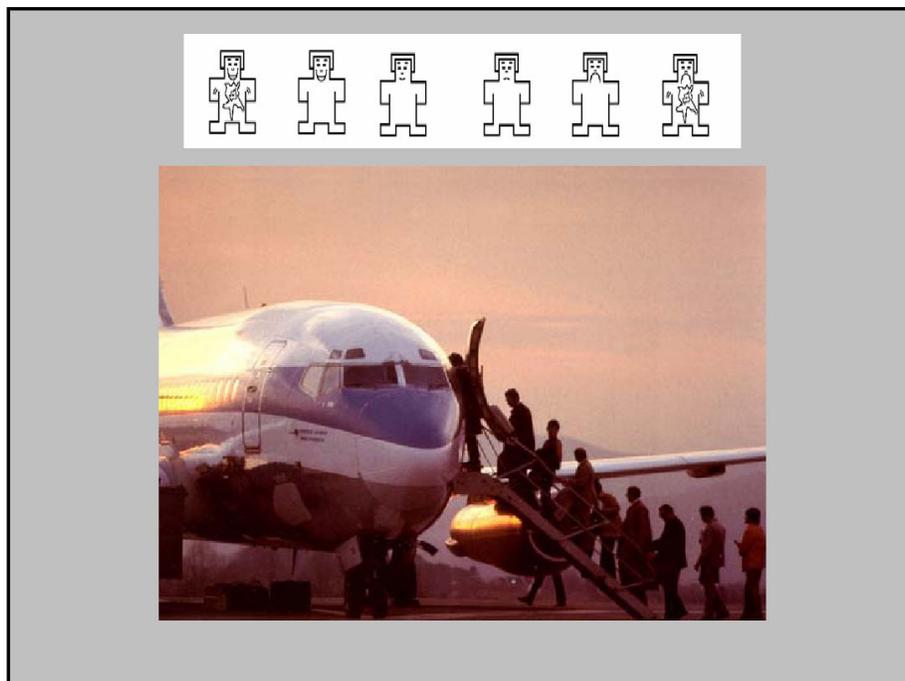
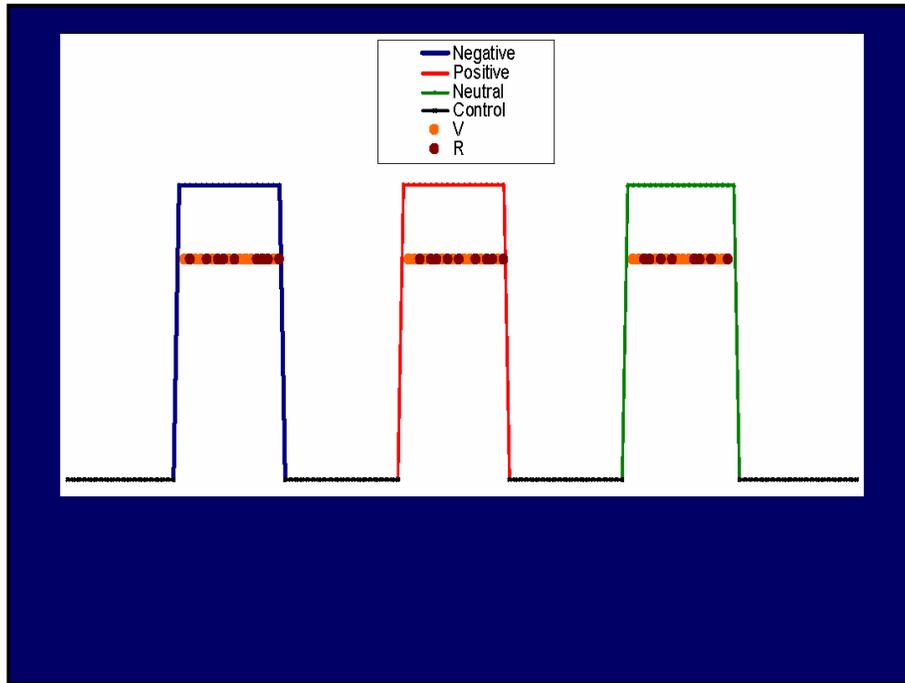
Dorsal Striatum – Dorsolateral PFC (DSDL)

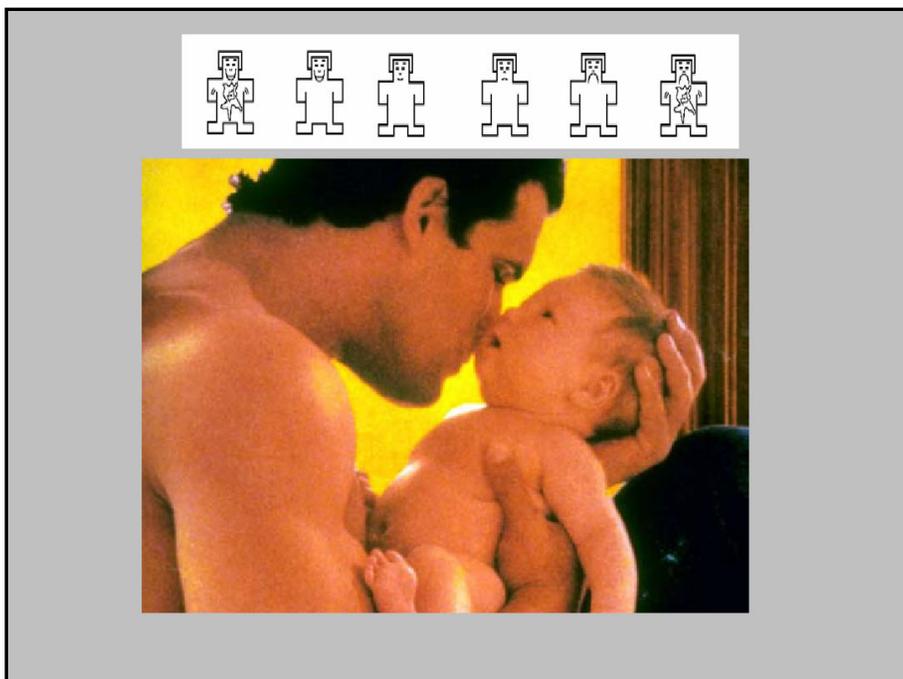
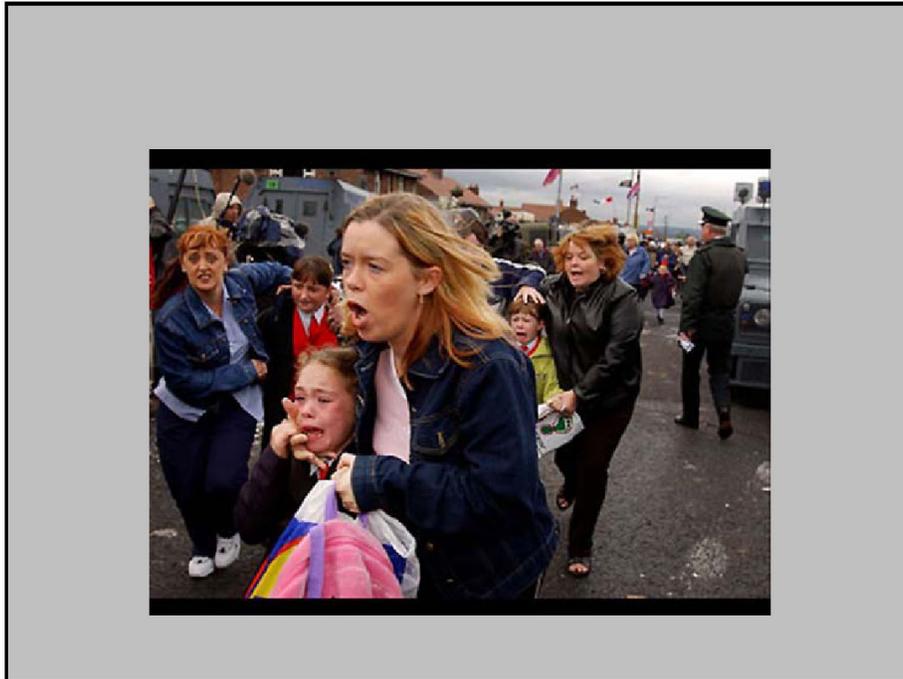
- Cognitive symptoms of depression
- Monitoring and directing responses to external stimuli (Coping)

Ventral Striatum – Ventromedial PFC (VSVM)

- Experience of emotion
- Mediates emotional approach-withdrawal reflex

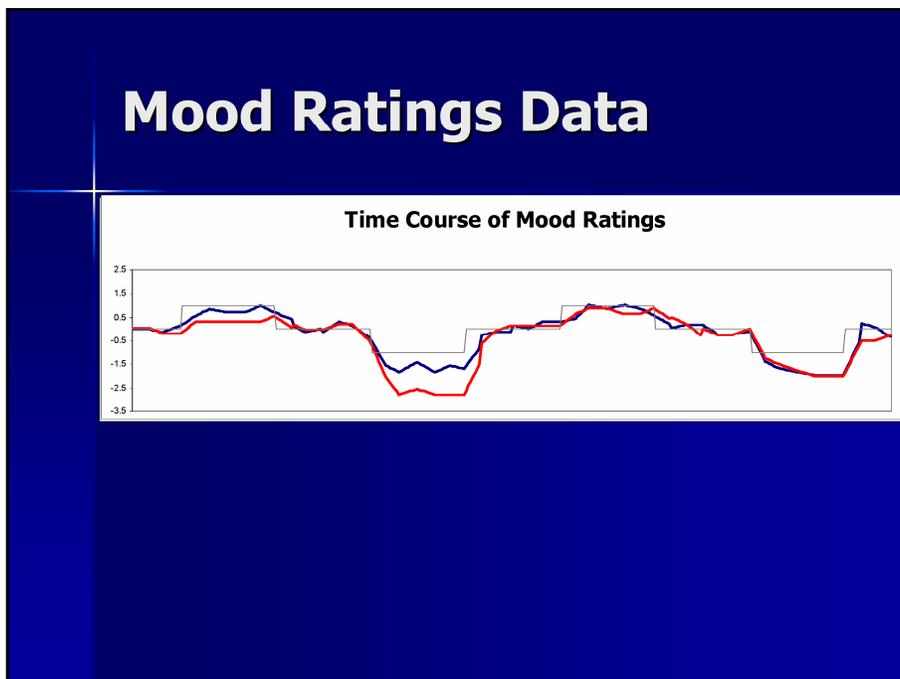




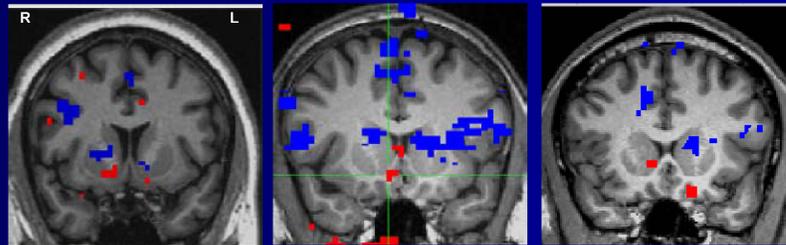


HOW ARE YOU FEELING
RIGHT NOW?

1 2 3 4 5 6 7 8
BEST -----WORST



FMRI Data



Opportunities

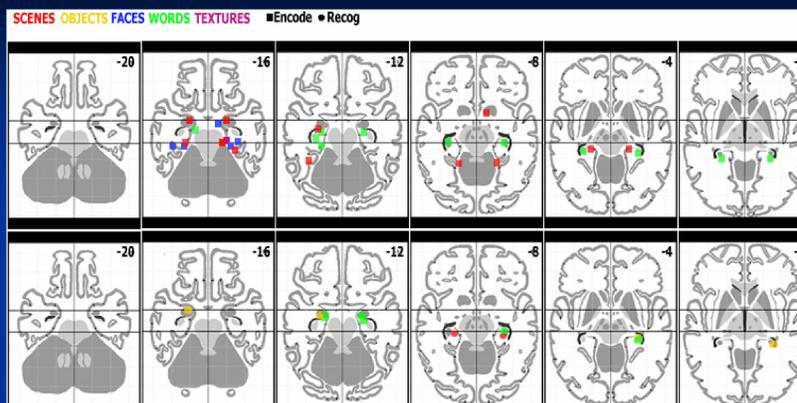
- Understand both disease and mood-specific effects in VSVM and DSDL Systems.
- Differentiate between depressed GWI and MDD.
- Other investigations to prospectively predict treatment response and thus optimize treatment approach.

Material-Specific Memory in the Medial Temporal Lobes

W. Ringe, K. Gopinath, S. Cheshkov,
S. Sarkar, R. Briggs, R. Haley

University of Texas Southwestern Medical Center, Dallas, TX

Heterogeneous Findings in Memory Studies



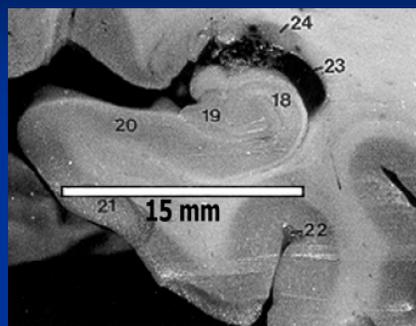
Cabeza et al., J. Cogn. Neurosci. 2004; Golby et al., Brain 2001; Greicius et al., Hippocampus 2003; Mandzia et al., Hum. Brain Mapp. 2004; Powell et al., Neuroimage 2005; Reber et al., Hippocampus 2002; Stark et al., J. Neurosci. 2000; Stark et al., Learn. Mem. 2001

Areas of activation foci plotted in this figure are approximate and are not meant to represent anatomically-precise findings of the studies cited.

Spatial Resolution

- Most fMRI memory studies lack spatial resolution to reliably differentiate material-specific activation in the various subregions of the MTL.
- Lateralization and parcellation potentially very important with respect to subtle memory deficits in Gulf War Syndrome

Hippocampus Anatomy



- 18 - Hippocampus
- 19 - Dentate gyrus of Hippocampus
- 20 - Subiculum
- 21 - Parahippocampal Gyrus
- 22 - Collateral Sulcus
- 23 - Temporal Horn of Lateral Ventricle
- 24 - Tail of Caudate

Right Mesial Temporal Lobe Structures

Image Adapted from:

The Human Brain: Surface, Blood Supply and Three-Dimensional Sectional Anatomy, 2nd edition. Duvernoy, H.M., 1991, Springer-Verlag/Wien, p. 247

High Resolution in MTL

- 1.72 mm x 1.72 mm x 2.3 mm (1.5T)
(Powell et al., NeuroImage 2005)
- 3.125 mm x 3.125 mm x 4.0 mm (3T)
(Grecius et al., Hippocampus 2003)
- 1.56 mm x 1.56 mm x 3.0 mm (3T)
(Zeineh et al., Science 2003)

This Work:

1.56 mm x 1.56 mm x 2.0 mm (3T)

Methods: fMRI task

- Event related design
- Encoding and recognition trials alternated with scrambled pictures
- Visually-presented words, objects, faces and nature scenes



High Resolution in MTL

- 1.72 mm x 1.72 mm x 2.3 mm (1.5T)
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1.56 mm x 1.56 mm x 2.0 mm (3T)

Methods: fMRI task

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- Visually-presented words, objects, faces and nature scenes



Methods: Data Acquisition

- Eight healthy subjects (5 F, 3M, mean age 30.3 yrs) participated
- 3T Siemens TIM MR Scanner with 12-channel receiver coil
- High resolution EPI: TR/TE/FA = 2000 ms/ 24.7 ms/ 90°;
FOV = 100 mm; 64 x 64 matrix (1.56 mm x 1.56 mm in-plane resolution), 33 2.0 mm contiguous coronal slices, covering the Medial Temporal Lobe

Data Acquisition (cont)



To avoid phase wrap in reduced FOV (100 mm) images, 38% phase oversampling (19% each hemisphere) is used

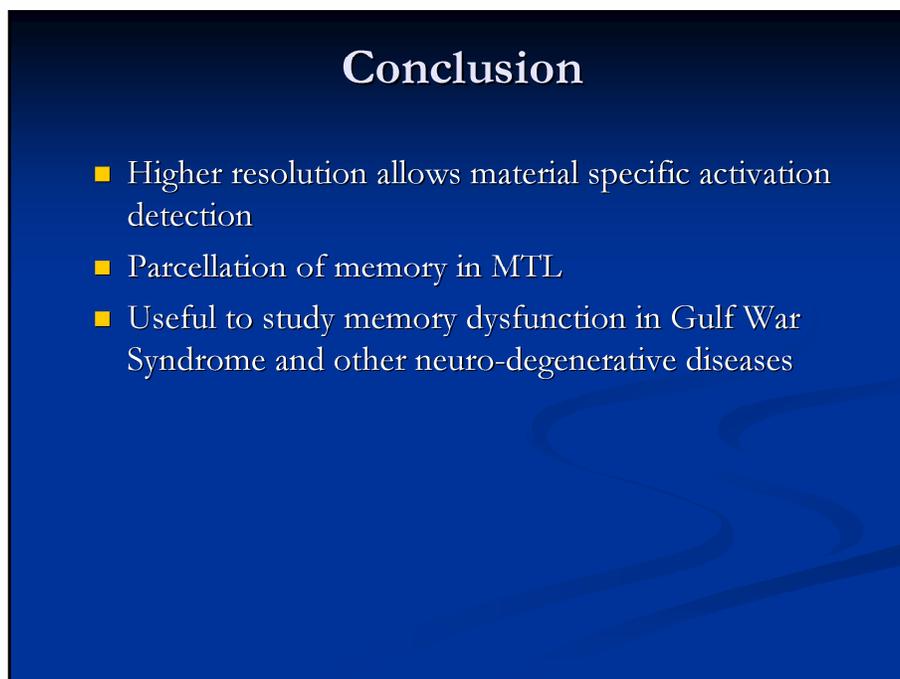
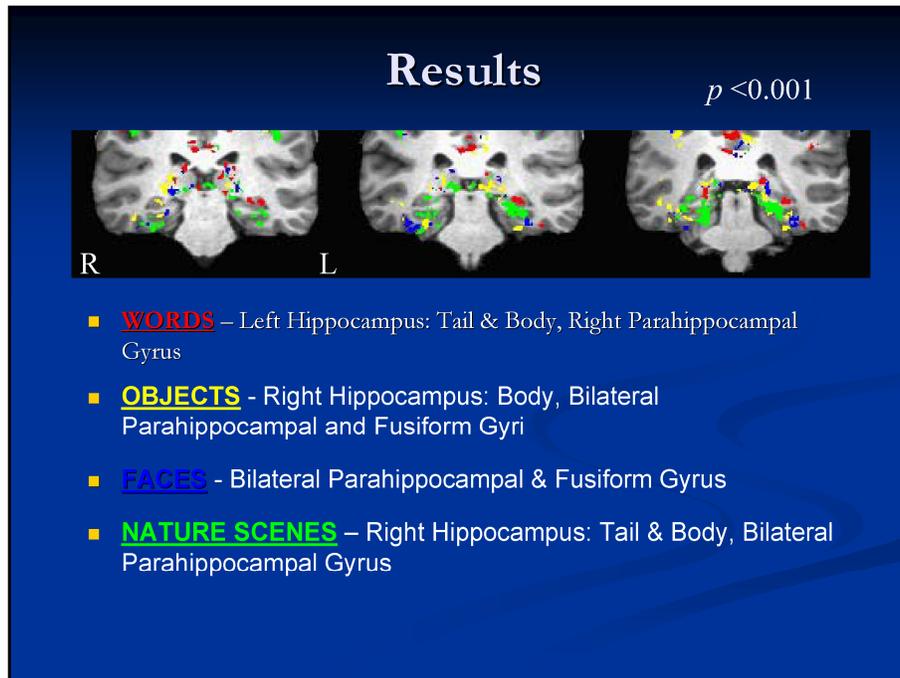


Data Acquisition (cont.)

- High resolution T1-weighted MPRAGE scan (matrix size=160x256x256 with resolution 1x1x1 mm³, TI/TR/TE=900/2250/2.97ms, Flip angle=9⁰, PF=7/8, iPAT factor=2 with 24 reference lines) acquired for anatomic reference
- 2D TOF MR Angiogram with same slice-prescriptions and FOV as EPI scans acquired for angiographic reference

Methods: Data Analyses

- fMRI voxel time-series modeled as convolution of 4 material-specific encoding stimulus vectors and constrained 2-parameter hemodynamic responses.
- Functional activation maps warped to Talairach space, resampled at a 1 mm³ resolution, and spatially smoothed with a Gaussian kernel (FWHM = 3 mm).
- Within-group ANOVA performed to assess significance
- t-maps of condition-level activations clustered ($|t_7| > 3.0$; cluster volume threshold 200 μ l; corrected $p < 0.001$).



Future Work

- Increase number of subjects
- MTL ROI analysis, Flat mapping
- Zoomed EPI (with outer volume suppression)
- Thinner slices for isotropic voxels
- Explore higher fields for SNR & resolution
- Improved functional-anatomic co-registration
(Gholipour et al., *proc. ICIP2007*)
- Optimize spatial smoothing using semivariogram
(Spence et al., JASA 2007)

Acknowledgments

Support from the Epidemiology Division, Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas and contract DAMD17-01-1-0741 from the U.S. Army Medical Research and Materiel Command.

The content of this presentation does not necessarily reflect the position or the policy of the U.S. government, and no official endorsement should be inferred.

Gulf War Syndrome

- Studies of the symptoms of ill-GWW have resulted in a diagnostic classification scheme broadly referred to as Gulf War Syndrome (GWS), with three syndrome variant:
 - 1) impaired cognition
 - 2) confusion-ataxia
 - 3) central pain

Haley, R.W., G.D. Luk, and F. Petty. *Use of structural equation modeling to test the construct validity of a case definition of Gulf War syndrome: invariance over developmental and validation samples, service branches and publicity.* *Psychiatry Res*, 2001, 102(2): p. 175-200.
Nisenbaum, R., et al., *Dichotomous factor analysis of symptoms reported by UK and US veterans of the 1991 Gulf War.* *Popul Health Metr*, 2004, 2(1): p. 8.

Gulf War Syndrome

- The cognitive deficits are associated with prior exposure to a combination of low-dose organophosphate nerve agents (sarin), pesticides, pyridostigmine, and DEET-containing insect repellent.

Haley RW, Kurt TL. Self-reported exposure to neurotoxic chemical combinations in the Gulf war: A cross-sectional epidemiologic study. *JAMA* 1997;277:231-37.

Exposure to Neurotoxins

- Repeated sub-clinical exposure to sarin gas to results in reduced acetylcholinesterase activity in the *hippocampus*, cortex, striatum, and olfactory bulb of rats.
- Suggesting a reduction in cholinergic receptors and as such, cholinergic activity in the affected regions.

Abdel-Rahman, A., A.K. Shetty, and M.B. Abou-Donia, *Disruption of the blood-brain barrier and neuronal cell death in cingulate cortex, dentate gyrus, thalamus, and hypothalamus in a rat model of Gulf-War syndrome.* Neurobiol Dis, 2002, 10(3): p. 306-26.

Exposure to Neurotoxins

- Stress, in combination with low doses of pyridostigmine bromide, DEET, and permethrin results in significant neuronal death in the *hippocampus*, thalamus, and cingulate cortex

Abdel-Rahman, A., et al., *Stress and combined exposure to low doses of pyridostigmine bromide, DEET, and permethrin produce neurochemical and neuropathological alterations in cerebral cortex, hippocampus, and cerebellum.* J Toxicol Environ Health A, 2004, 61(2): p. 163-92.

Heidecker, R.F., et al., *Response of P344 to S to inhibition of sublethal levels of sarin: exploring potential causes of Gulf War illness.* Toxicol Ind Health, 2001, 17(6-10): p. 294-7

Exposure to Neurotoxins

- MR spectroscopy and single photon emission computed tomography (SPECT) have identified *hippocampal* dysfunction in Gulf War veterans (GWW) reporting cognitive deficits
- Unclear whether the damage is
 - bilateral or largely restricted to the right hippocampus.
 - present in the hippocampal commissures connecting the left and right hippocampal formations.

Menon, M. et al. (2004). Hippocampal dysfunction in Gulf War Syndrome. A proton MR spectroscopy study. *Brain Research*, 1009, p. 189-194.

Gulf War Syndrome & Memory

- ill-GW vets commonly self-reported cognitive deficits in memory as well as in word finding, and concentration.
- Although memory deficits are among the most commonly reported symptoms associated with GWS, these self-report data have been met with considerable concern and occasional derision.
- GWW identified as having GWS commonly demonstrate performance on neuropsychological memory test batteries equivalent to that of controls.

Gulf War Syndrome & Memory

- However, difficulty in detecting objective memory deficits in ill-GWW could result from several causes.
 - 1) the use of neuropsychological testing instruments that fail to precisely target mnemonic functioning of the hippocampus
 - 2) compensatory strategies used by ill-GWW that may ameliorate effects of hippocampal damage in standard paper and pencil neuropsychological tests of memory.

Gulf War Syndrome & Memory

- Both hypotheses necessitate a targeted investigation comparing ill-GWW with appropriate controls with respect to
 - 1) behavioral performance in memory tasks known to involve the hippocampus
 - 2) hippocampal activity (inferred from BOLD response in fMRI) during performance of these tasks
 - 3) activity in other brain regions and larger brain circuits during the performance of these tasks (inferred from BOLD response in fMRI).

A key hippocampal function is memory *binding* (or conjunctive coding)

- Binding processes can be assessed in the *conjunction paradigm*.

The conjunction paradigm:
Faces

STUDY



TEST



The conjunction paradigm: Words

STUDY

JAILBIRD BLACKBOARD

TEST

BLACKBIRD

The conjunction paradigm: Face Names

STUDY



Robin



Mandy



Robin

TEST

A Typical Outcome (Jones, Bartlett & Wade (2006))

- Hit rate to old faces = .69
- False-alarm rate for conjunctions = .46
- False-alarm rate for new faces = .25

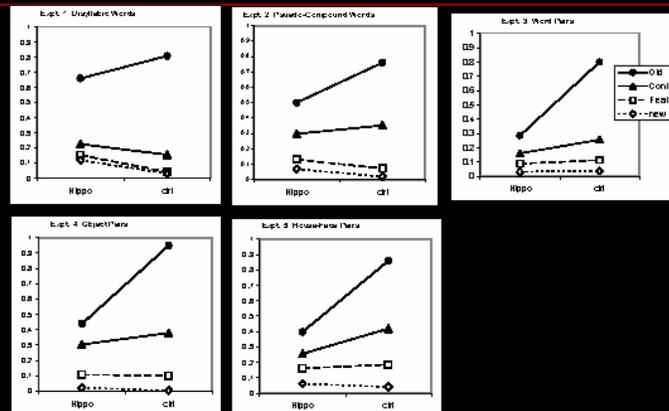
The hippocampus & conjunctions

- Several fMRI studies have found activation in hippocampal regions linked to encoding and retrieval in conjunction paradigms
- Hippocampal damage has been linked to impaired performance with conjunctions

Hippocampal damage reduces Old/Conj. Discrimination

- **Kroll et al. (1996)**
 - Left-sided damage \rightarrow Impairments with words
 - Left- or right-sided damage \Rightarrow Impairments with cartoon faces
- **Stark & Squire (2003)**
 - Bilateral damage \Rightarrow Impairments with five different stimulus types

Stark & Squire (2003)

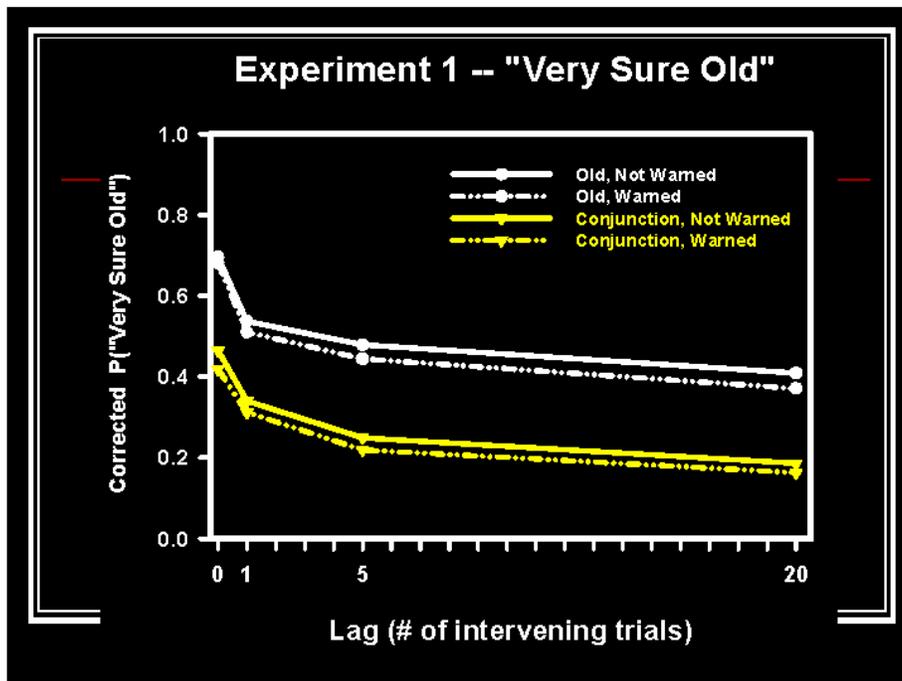
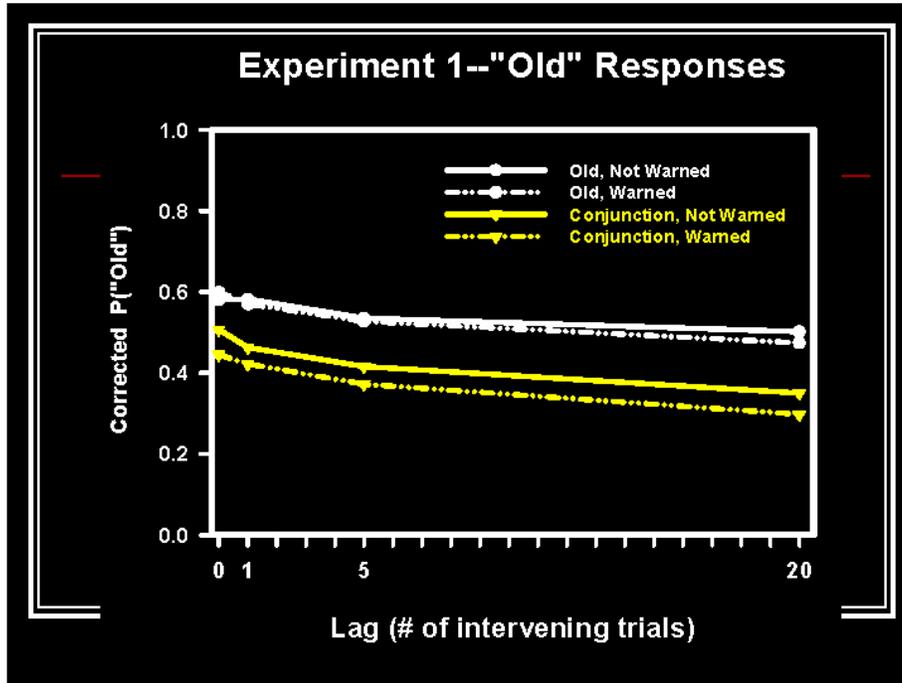


But the pattern varies

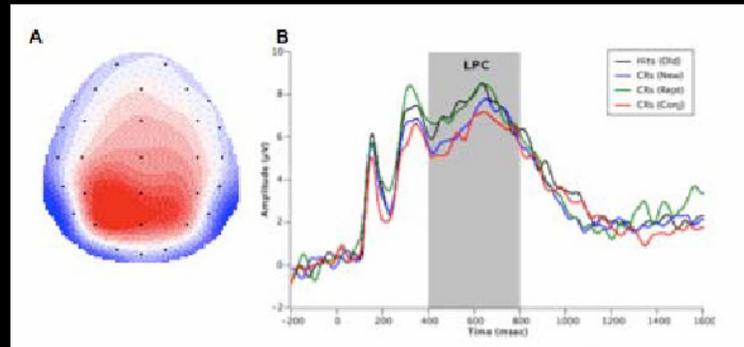
- Kroll et al. found increases in conjunction errors
- Stark & Squire found only declines in hits
 - And on this basis questioned the binding hypothesis
- A possible explanation: “Recollection-rejection” by controls in Kroll et al.

Facial conjunctions show minimal recollection-rejection:

- Jones & Wade (submitted)
- Shastri et al., in preparation)

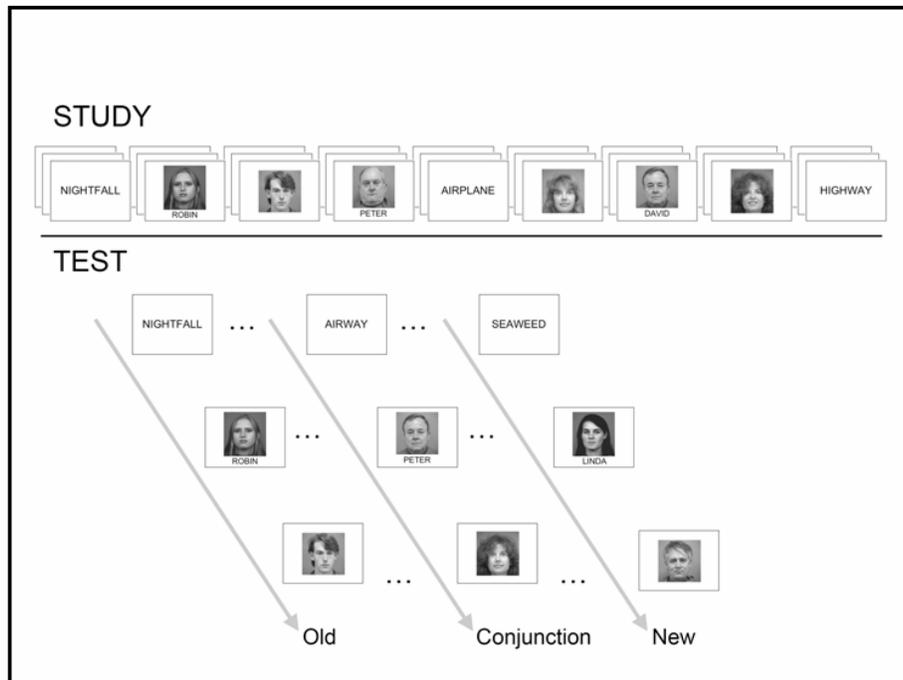


Shastri et al.: Conjunctions = new in the late positive component



Two aims for the project

- To determine the memorial profile of four groups of GWV (including GWV controls)
 - Using face- word-, and face-name conjunctions
- To assess right- and left-hippocampal dysfunction linked to performance impairments using fMRI
- To examine compensating strategies using fMRI



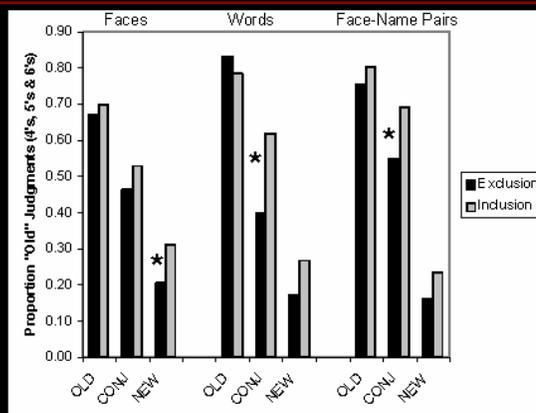
Behavioral Experiment 1 (n = 48)

- Compared conjunction-task performance with face, word and face-name stimuli:
 - To check performance levels
 - To assess recollection-rejection with all three item-types
 - Exclusion vs. inclusion instructions

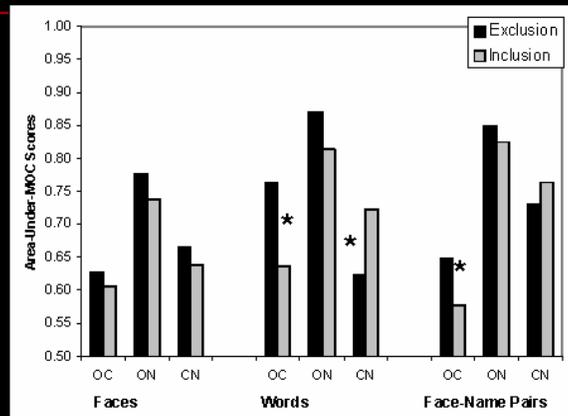
The logic:

- If a person is performing recollection-rejection s/he should **know** that conjunctions are conjunctions
- If not, s/he will only know that conjunctions have a certain level of familiarity
 - As when a friend looks different but you cannot say what has changed.

Exclusion & Inclusion Recognition Performance with Faces, Words, and Face-Name Pairs



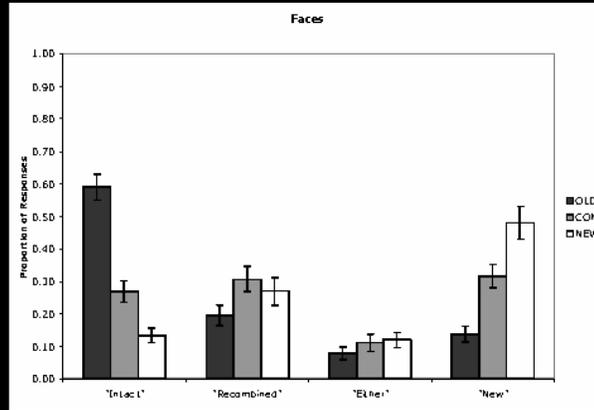
Discrimination Measures:



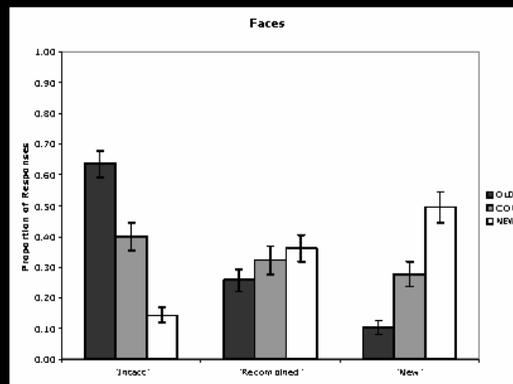
Behavioral Experiment 2 (n=24) and behavioral data from fMRI study 1

- Examined whether recollection-rejection might be enhanced in a paradigm suitable for the scanner
- The key change: Subjects made explicit "Intact" and "Rearranged" Judgments

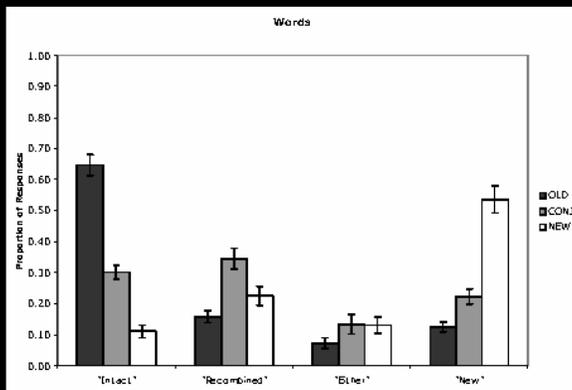
Face Recognition in Behavioral Experiment 1 (n=24)



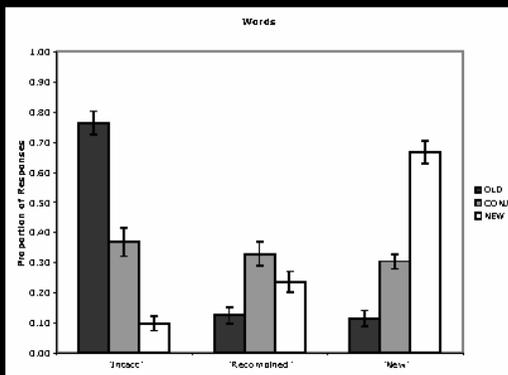
Face Recognition in fMRI Experiment 1 (n = 12)



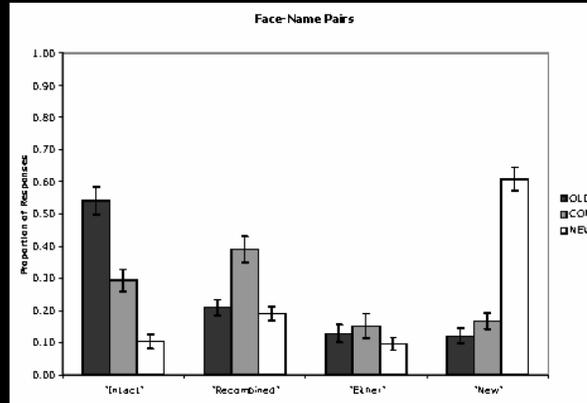
Word Recognition in Behavioral Experiment 1



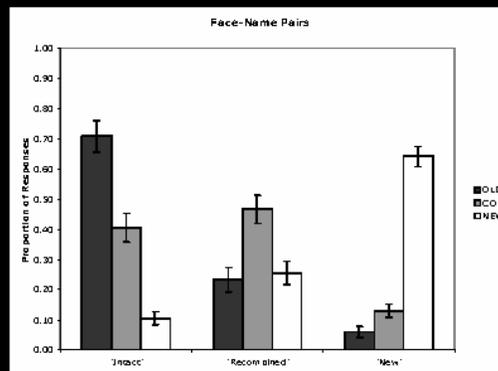
Word Recognition in fMRI Experiment 1



Face-Name Recognition in Behavioral Experiment 1



Face-Name Recognition in fMRI Experiment 1



Predictions for GWVs:

- GWS-III: No difference from GWS-controls
- GWS-I & GWS-II: Impaired accuracy of "old" judgments with faces and face-name pairs.
 - Impairment with words, if left-hippocampal damage is present
- Impaired accuracy of "intact" judgments with face-name pairs

One question for fMRI:

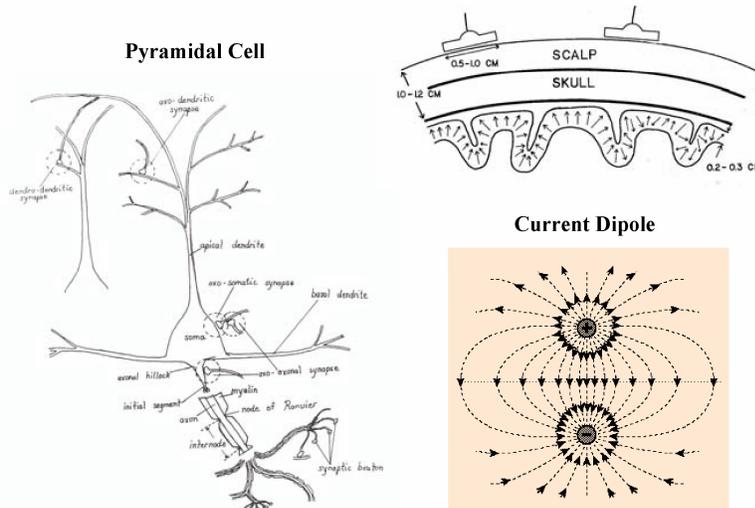
- Will hippocampal activation at study:
 - Predict discrimination conjunctions from old faces with "old" (and perhaps "intact" judgments)
 - Be reduced in GWS-I and GWS-II veterans
 - Explain performance differences between these veterans and controls

Presentation 8 – Thomas Ferree

EEG Program for Gulf War Research

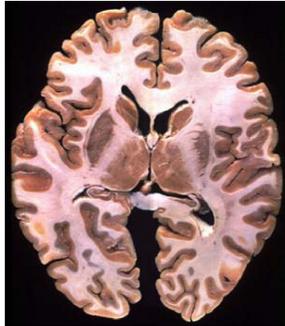
Thomas Ferree, PhD
*Department of Radiology
UT Southwestern Medical Center*

Cellular Sources of EEG



Cortical Sources of EEG

Cortical Sheet



Axonal Fibers



Added Value of EEG for Gulf War Research

General

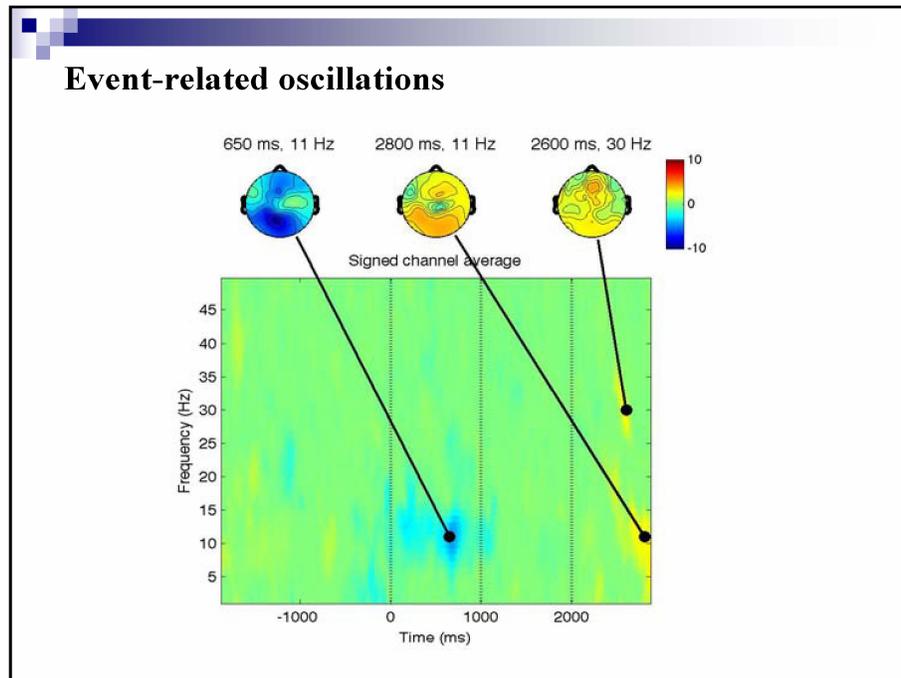
- Measure neural activity with millisecond timing
- Detect oscillations within and between brain areas
- Impairment within areas or communication between areas?

Word-Word Binding

- Associate oscillations with cognitive processes
- Distinguish processes through their temporal ordering

Continuous Performance

- Ability to analyze continuously through time
- Power spectrum correlates with performance



EEG Analysis Domains and Clinical Indices

Time Series Analysis

- Event-related transients (peak amplitude, latency)
- Event-related oscillations (amplitude, timing)

Spatial Analysis

- Electric head modeling
- Source localization (functional networks)

Integration with functional MRI

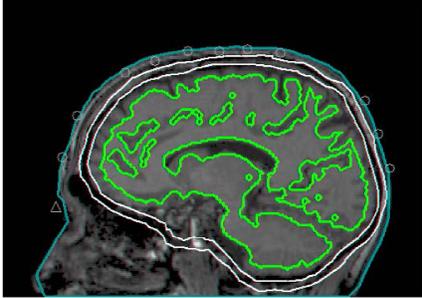
- Spatial co-registration
- Simultaneous recording

Functional connectivity

- Coherence (magnitude, phase, connectivity maps)
- Relationship to fMRI and DWI

Electric Head Modeling: Two Components

1. Geometry



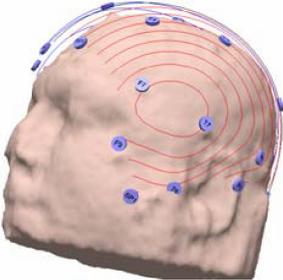
2. Conductivity

Tissue	Mean σ	Stdev σ
Brain	0.25	0.13
CSF	1.79	0.02
Skull	0.018	0.014
Scalp	0.44	0.2

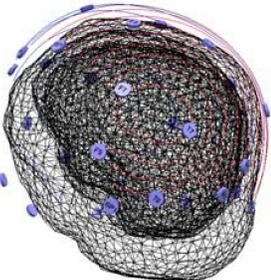
**Can measure conductivity non-invasively with EIT:
(Electric Impedance Tomography)**

Electric Source Localization

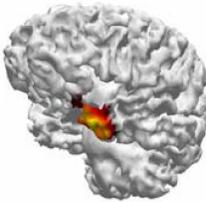
Scalp Voltage Data



Electric Head Model



Brain Source Current



Simultaneous EEG and Functional MRI

Motivations

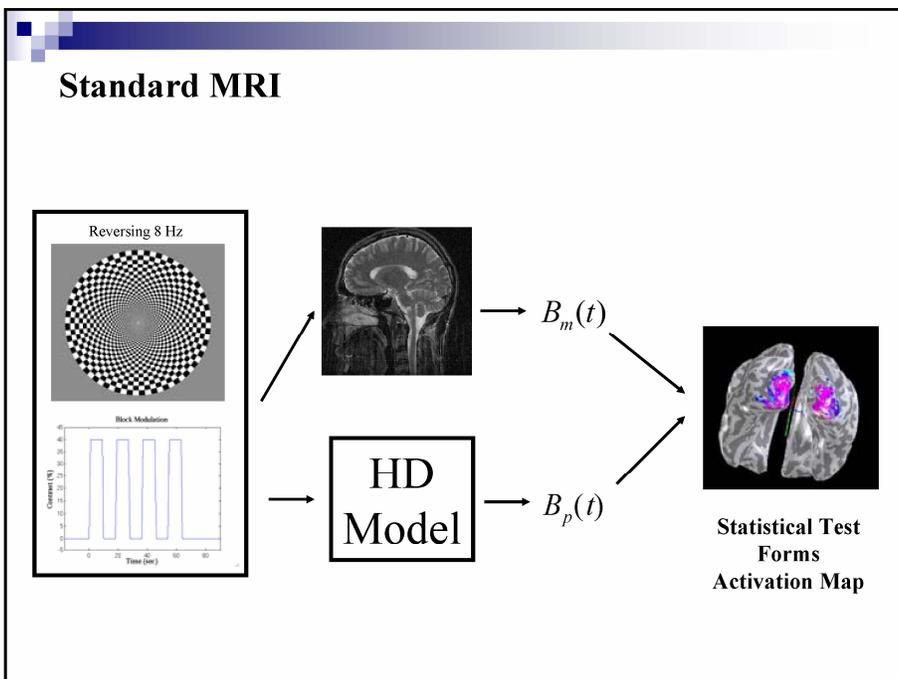
- Best of both worlds: spatial and temporal resolution
- Match recording environment and stimulation parameters
- Match subject state, e.g., alertness, etc.
- Avoid training effects
- Convenience

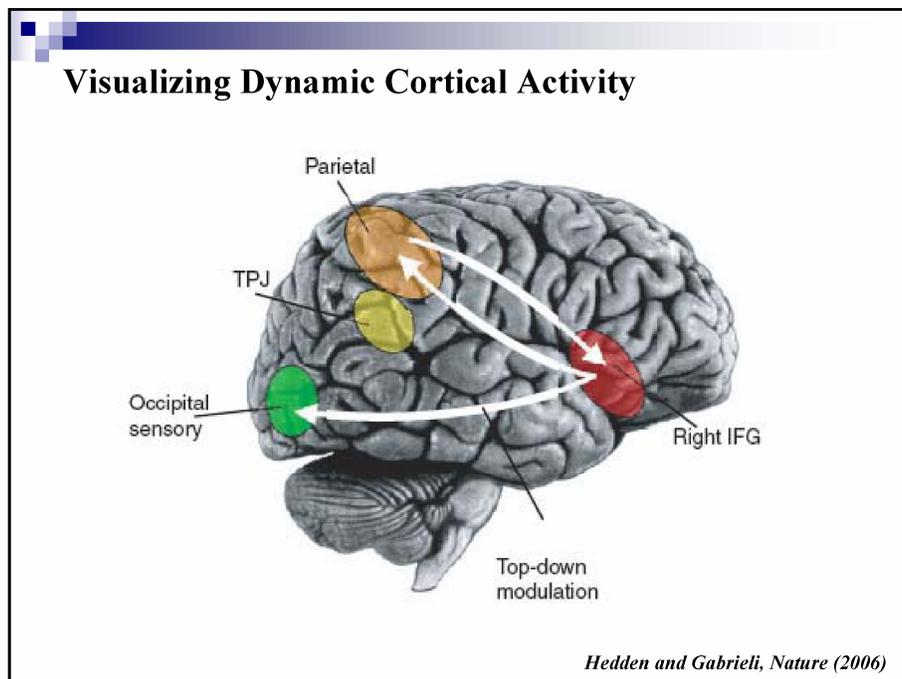
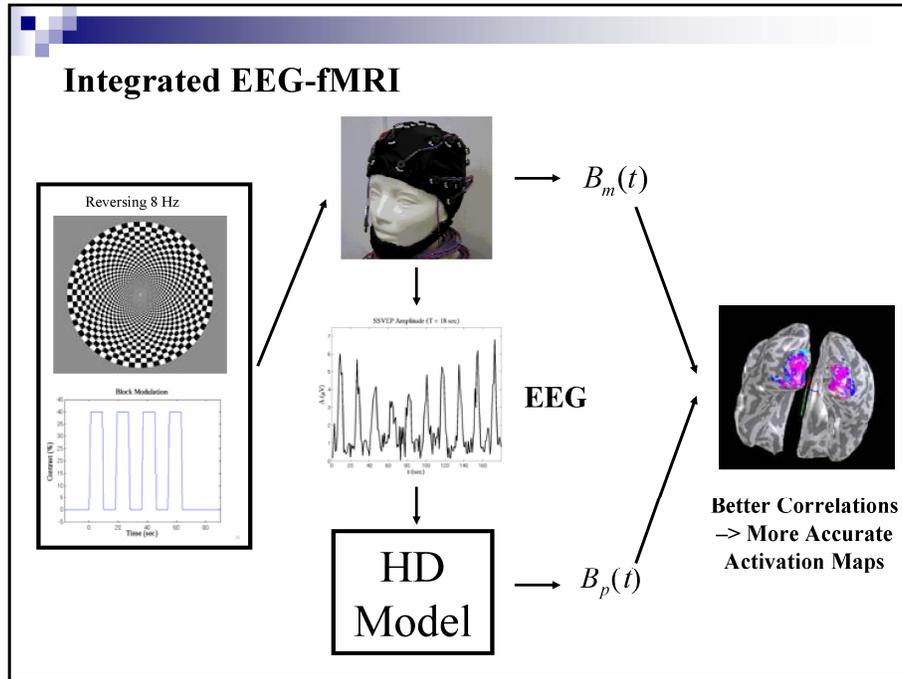
Challenges

- Artifacts induced by MR magnetic fields
- Optimize cognitive paradigms for EEG and fMRI

Larger Goals

- Clarify relationship between neural oscillations and fMRI maps
- Improved statistical tests for functional activation





EEG Program Development

Done

- IRB approval for EEG, EEG-fMRI
- Protocols for cap application, cleaning, etc.
- System integrity
- Data quality and artifact reduction
- EEG pilot studies in normal subjects
- Preliminary analyses of EEG data

To Do

- Integrate EEG/EIT into full pilot studies
- Extend IRB approval to EIT
- Space renovations, booth installation
- Equipment upgrades, purchases
- New hires, training

Main Collaborators

UT Southwestern

Richard Briggs
Priya Xavier
Audrey Chang
Aman Goyal
Kaundinya Gopinath
Mette Posamentier
Pat Carmack
Jeff Spence

UT Dallas

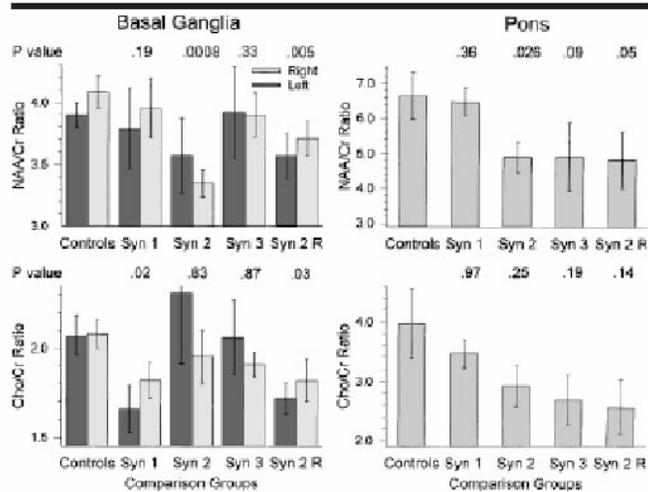
John Hart
Mandy Maguire
Gail Tillman
Cliff Calley
Matt Brier
Tim Green

SMU

Wayne Woodward
Henry Gray

...More To Come

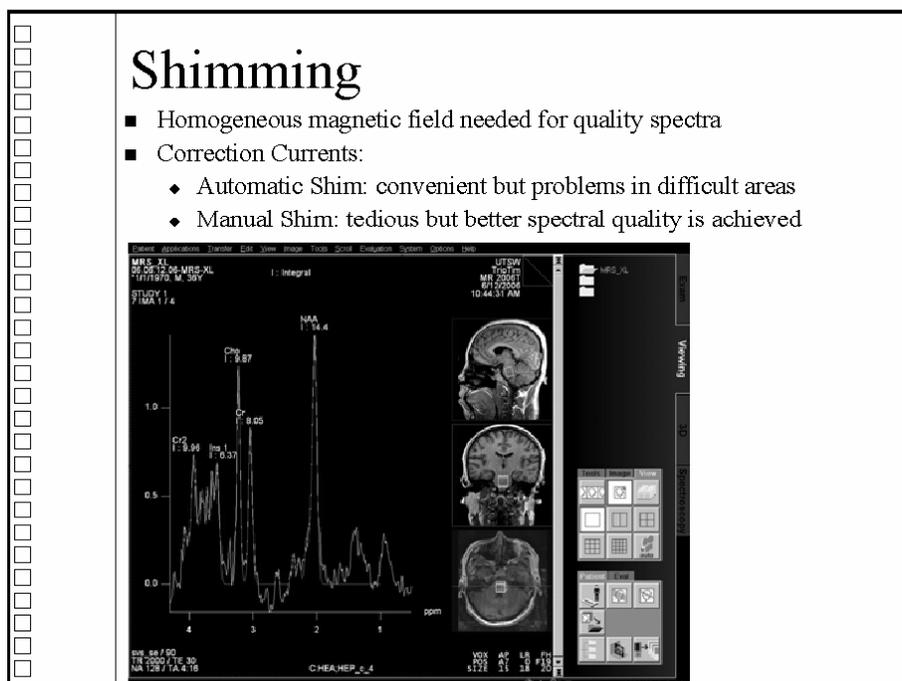
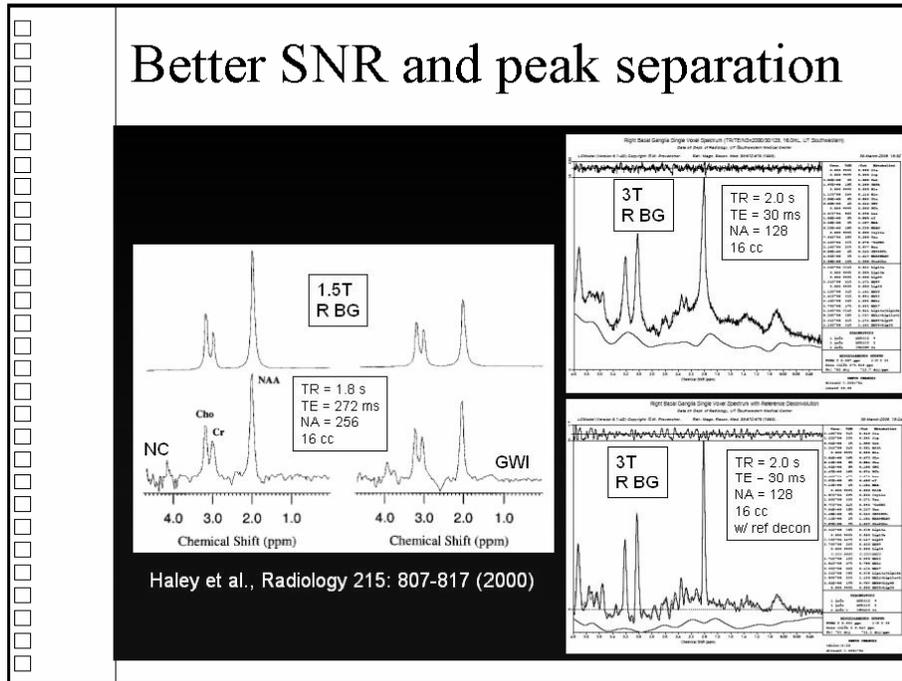
GW 1.5 T Findings (cont.)

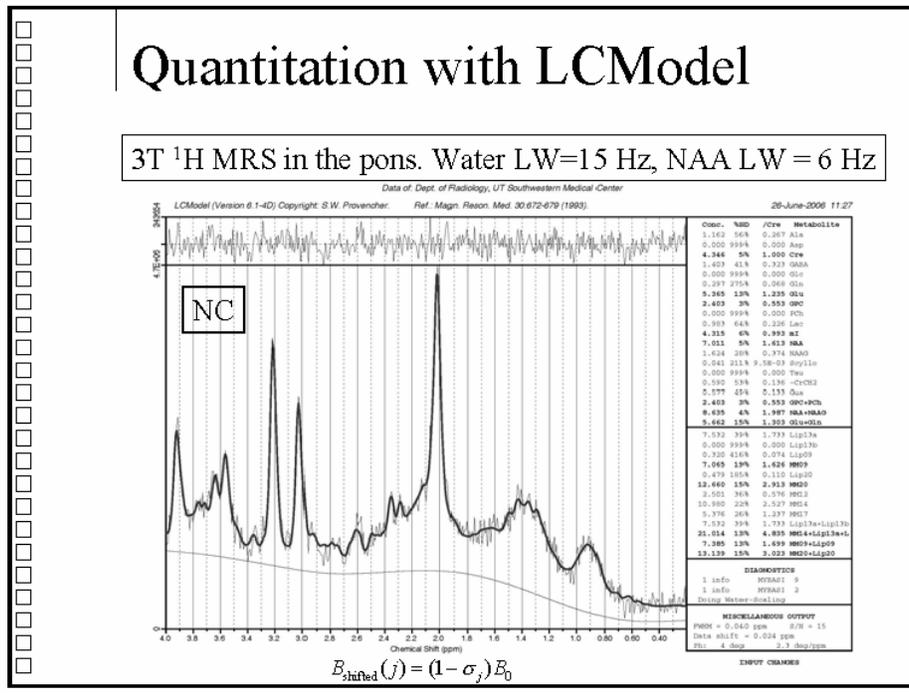


Haley et. al., Radiology, 2000; 215: 807-817

MRS of Brain Chemistry at 3 T

- Better SNR and spectral dispersion at 3T than 1.5T
- Single voxel MRS and Chemical Shift Imaging (CSI)
- Good shimming, (absolute) quantitation, and reproducibility
- Areas of interest: R&L Basal Ganglia, Pons, R&L Hippocampus
- Brain metabolites:
 - ◆ NAA, Cr, Cho (cell membrane)
 - ◆ mI (neuroglia marker), Glu (excitatory neurotransmitter)
 - ◆ Gln (metabolism)
- Metabolite relaxation times measurements





Reproducibility

- Voxel positioning
 - ◆ Manual positioning using high-res localizers
 - ◆ Siemens “AutoAlign” now available for Single Voxel MRS
- Different shims in different sessions (S. Cheshkov, A. Chang, S. Sarkar)

High quality reproducible shim

Spectral deconvolution methods

Subject motion

 - ◆ Kept to minimum
 - ◆ Protocol running time is important
- Natural variability

Relaxation Times T_1 and T_2

- Affect intensity of the signal
- Corrections to calculated metabolite concentrations:

$$f_{T_2} = \exp(-TE/T_2)$$

$$f_{T_1} = 1 - \exp(-TR/T_1)$$

- Use very short TE and very long TR?
- Metabolite relaxation times are of interest themselves, could be changing in pathology
- Difficult to measure in small areas

Relaxation Times (cont.)

Regional Differences in Metabolite T_2

NAA

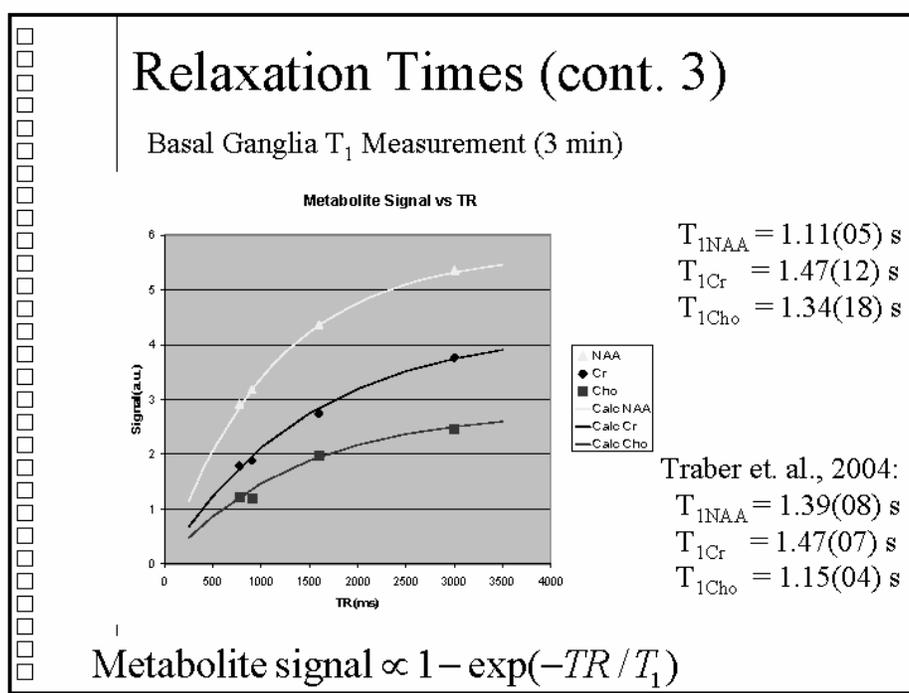
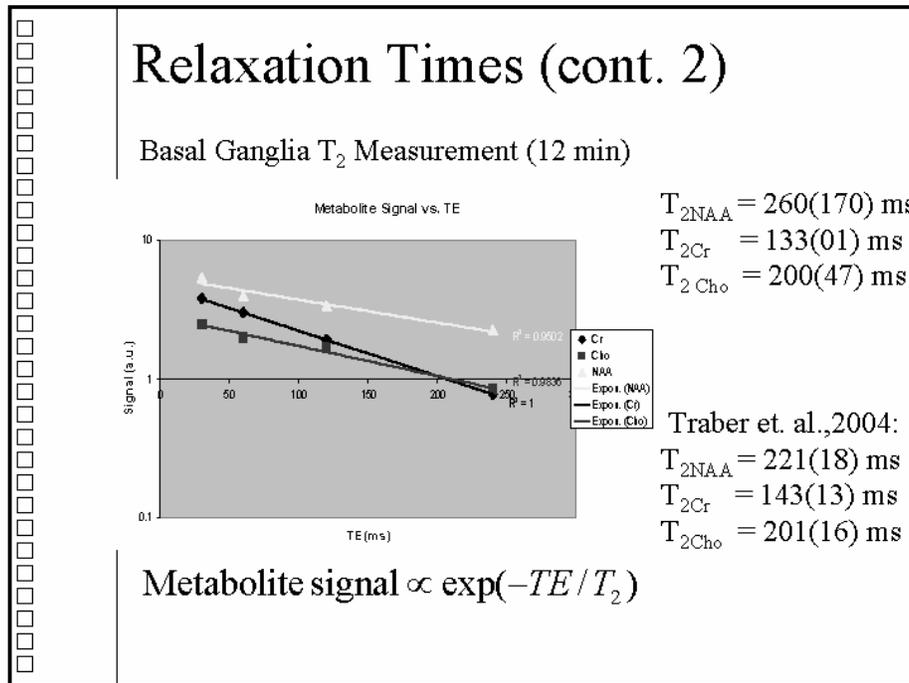
Region	N	Mean T2 [ms]
occ. WM	10	~300
frontal	7	~275
cingul	6	~255
mot. cort	10	~245
basal g.	8	~220

tCr-CH₃

Region	N	Mean T2 [ms]
occ. WM	10	~180
frontal	7	~170
cingul	6	~160
mot. cort	8	~160
basal g.	8	~145

Traber et. al., J. Magn. Reson. Imaging 2004;19:537-545

More at 3T in: Zaaraoui et al., MRM, 2007.



Future Work and State of the Art

- Further optimizing measurements of in vivo relaxation times T_1 and T_2 for absolute metabolite quantitation
- Brain compartments – in relation to quantitation
- Optimizing spectral deconvolution methods
- Implementing 2D and 3D CSI, e.g. EPSI for rapid CSI data collection and MIDAS for data analysis – research agreement with Siemens and University of Miami
- High-field (7T) MRS for improved SNR and spectral and spatial resolution – pilots beginning
- Multinuclear MR spectroscopy (^{31}P , ^{13}C) - to investigate pH, high-energy phosphate status, and detailed metabolic pathways

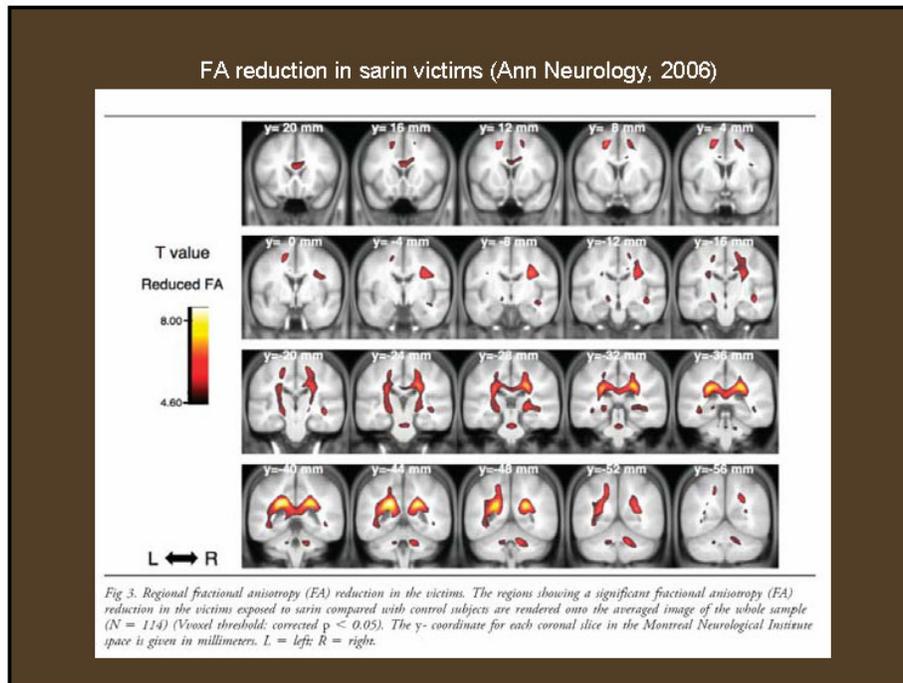
Presentation 10 - Roddy McColl

**DTI Sub-Core: Imaging
Protocol and Prelim Data**

Roddy McColl
July 18, 2007

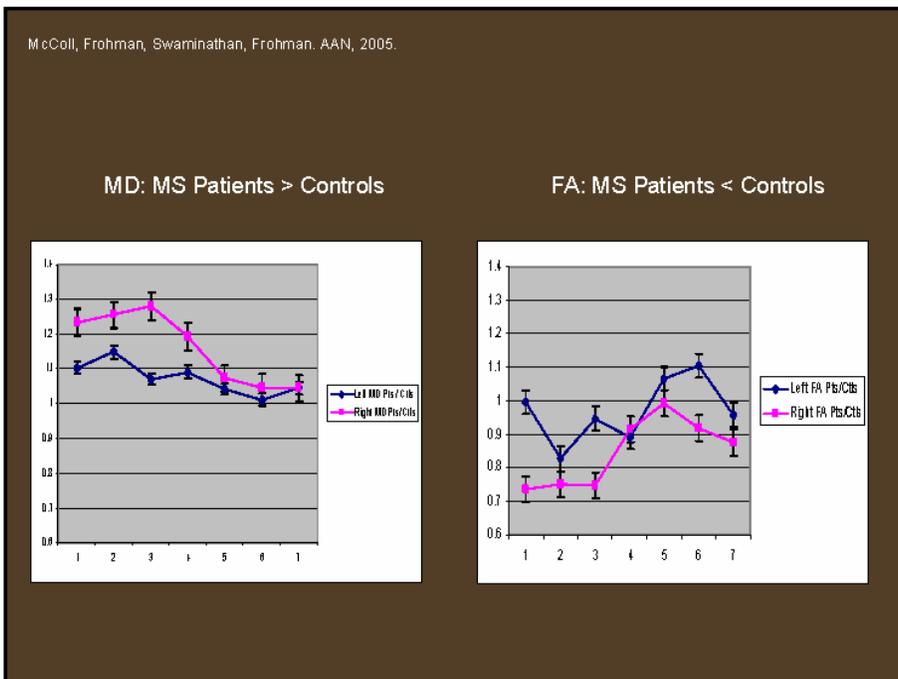
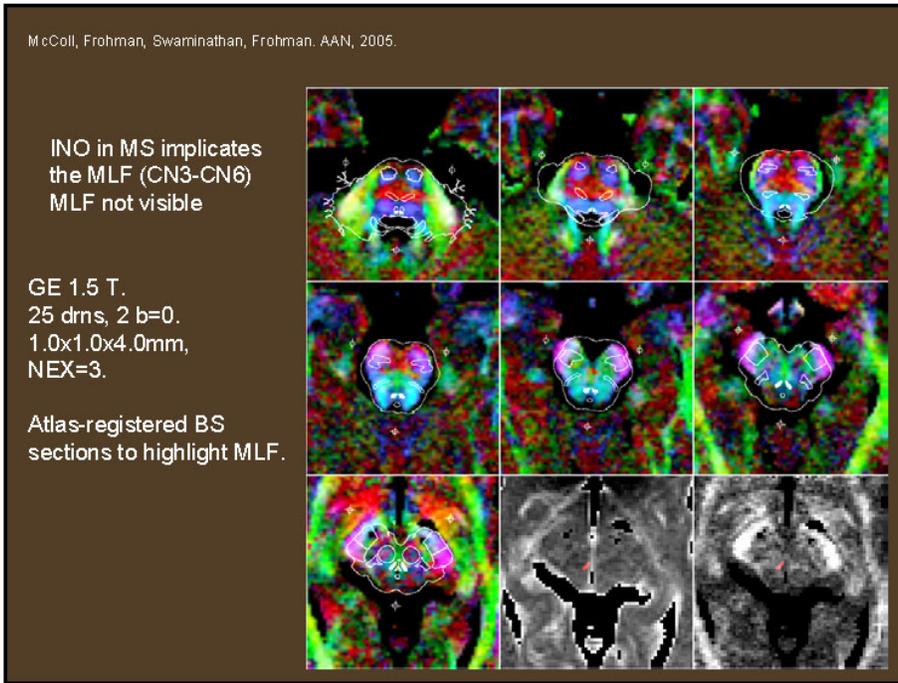
DTI: Motivation

- Possible involvement of white matter in one or more of the syndromes.
- Recent literature (sarin attacks) indicates FA changes in brainstem of victims.
- Both focal and diffuse WM changes possible given GWS symptoms.



Prelim Brainstem Studies (1.5T)

- Cohort: Multiple Sclerosis
- Brainstem DTI scanning (1mm in-plane, 4mm slice)



DTI: Imaging Goals

- Obtain sufficient data for global and local analyses with a 30 minute imaging session.
- Plan to include a global coverage scan with parameters suitable for tract analyses and other whole brain information.
- Plan to include a high in-plane resolution scan of the brainstem for in-depth interrogation of this region.
- Obtain enough data to support other models of diffusion than the 3x3 tensor.

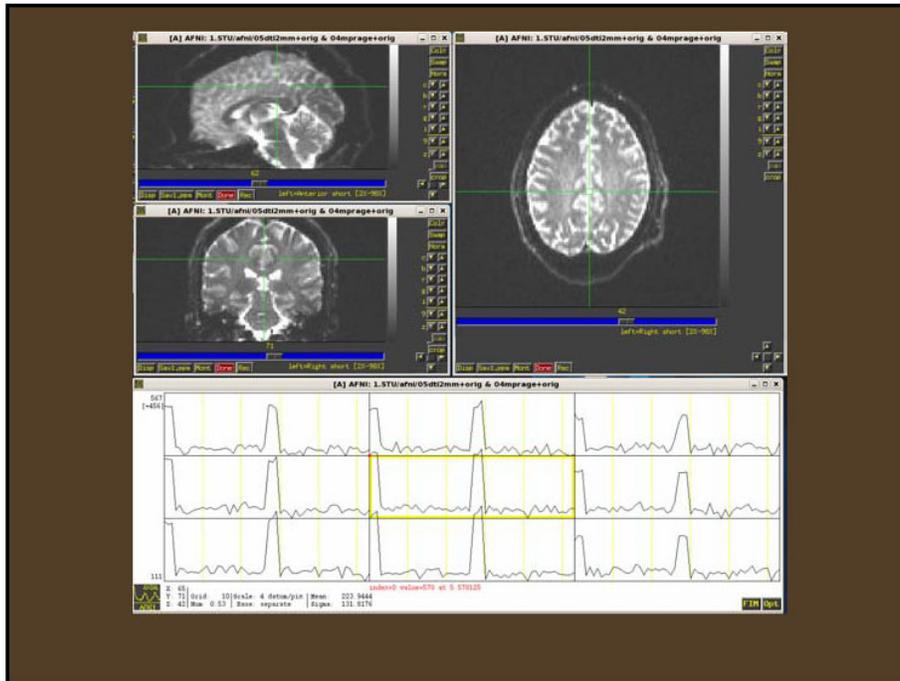
Imaging Protocol

- Obtain in 5 minutes a high-quality T1 volume scan e.g. MP-RAGE



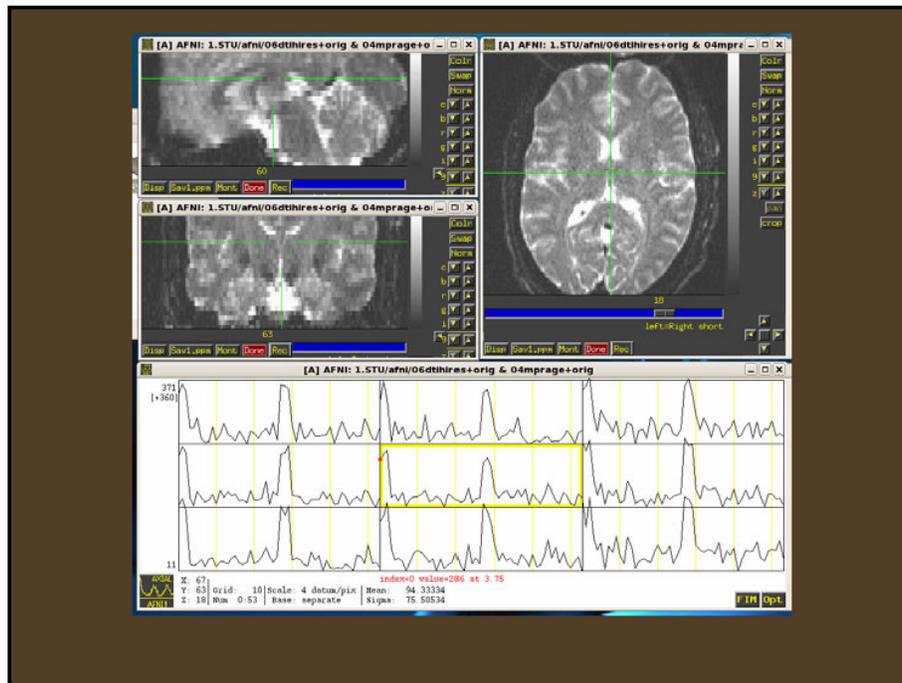
Imaging Protocol

- Obtain a 2x2x2 mm DTI scan with 24 directions at b=1000 and 3 b=0 sets (1:8 unweighted/weighted ratio)



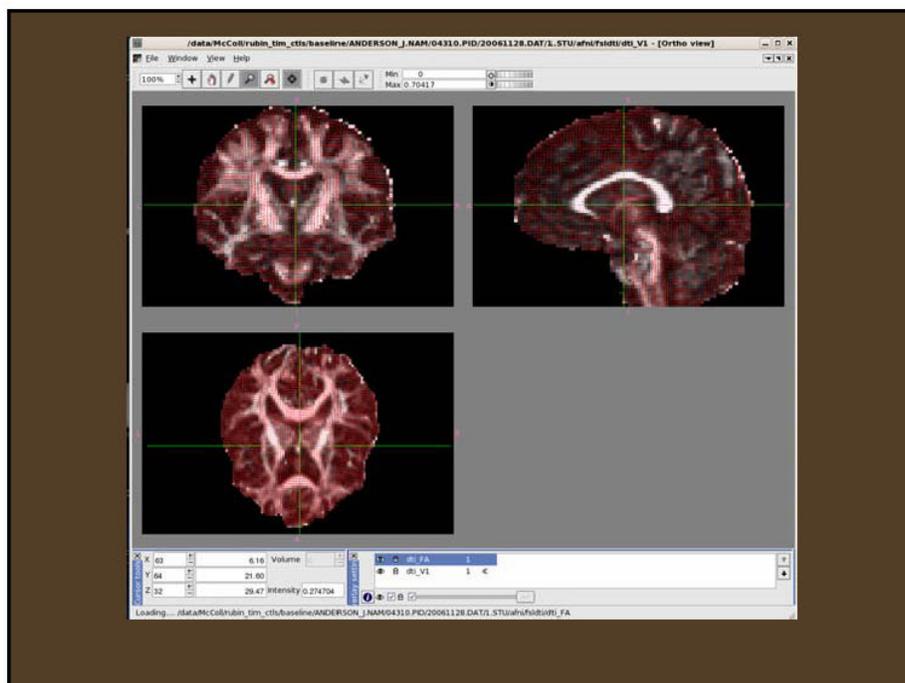
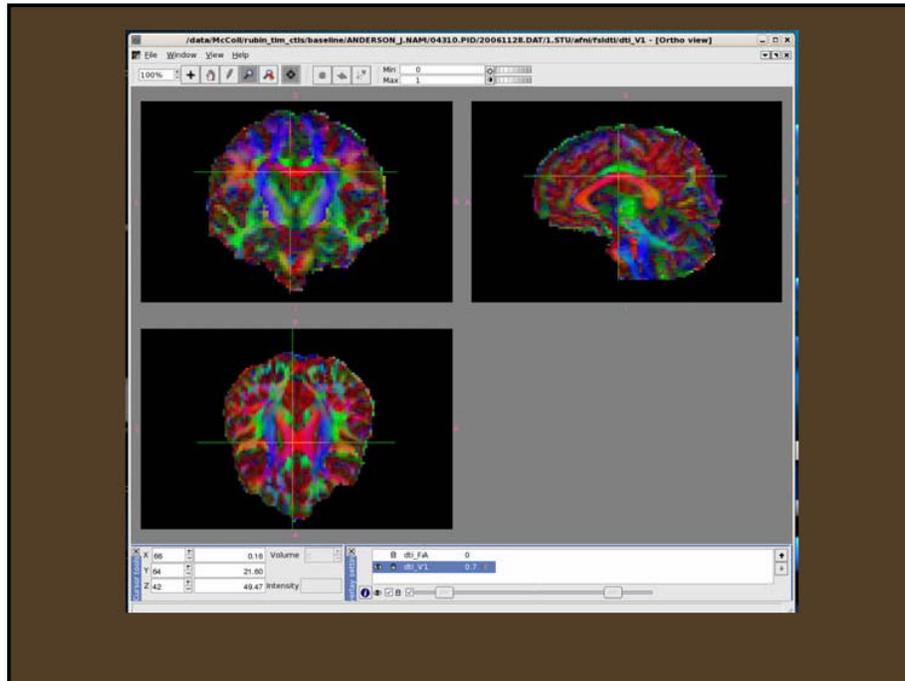
Imaging Protocol

- Obtain a high in-plane resolution DTI sequence of the brain stem (1 mm in-plane, 3mm slice) with 24 directions at $b=1000$ and 3 $b=0$ images. Due to lower SNR from smaller voxel, this is repeated twice.



Analysis Protocol

- We will use the FSL imaging toolkit developed by Oxford University Functional Imaging Laboratory.
- Toolkit include software for: eddy current correction/bulk motion, tensor fitting to the data, tractography, group analysis of white matter.



Pilot Study Notes

- Adult male, all series acquired within 30 minutes.
- Analyses time requirements: Are likely to evolve, currently approximately 1-2 hours of computation for eddy-current correct. Dti fit is rapid. Group analyses are more compute intensive (need to find “best” WM map, NP-complete problem).

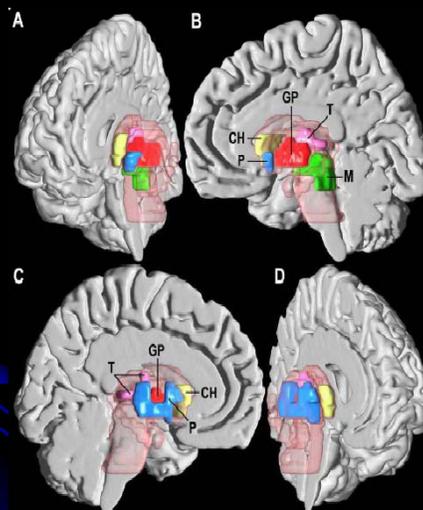
Presentation 11 – Richard Briggs

**Perfusion and Regional Cerebral Blood Flow
(rCBF) Using MRI Arterial Spin Labeling (ASL)**

Xiufeng Li
Hanzhang Lu (P.I.)
Richard Briggs
Kaundinya Gopinath
Subhendra Sarkar
Sergey Cheshkov

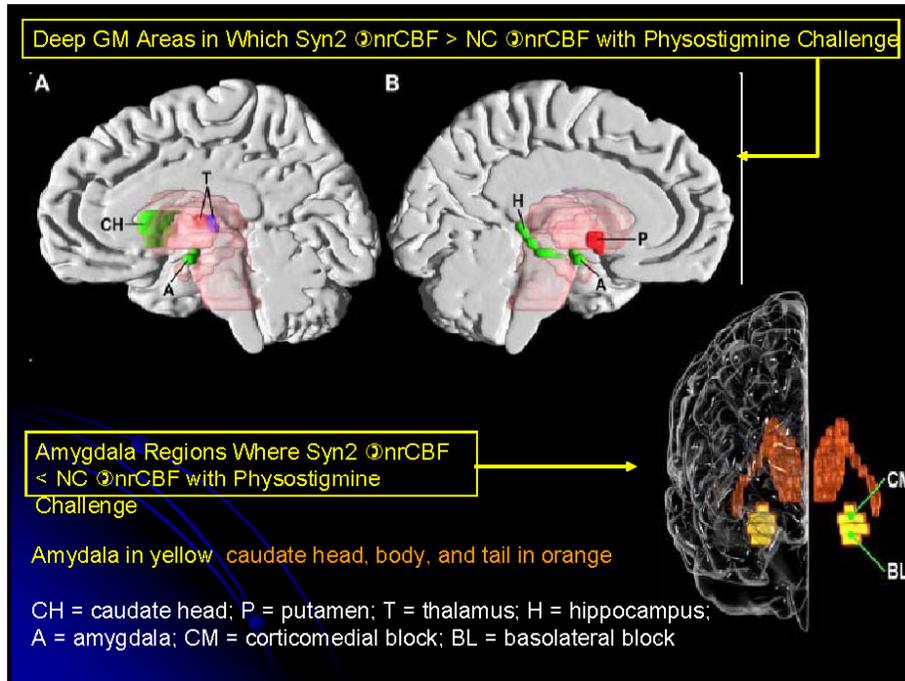
Neuroimaging Laboratory
Gulf War Illness and Chemical Agent Exposure Program
UT Southwestern Medical Center

Deep GM Areas in Which Baseline Syn2 nrCBF < NC nrCBF



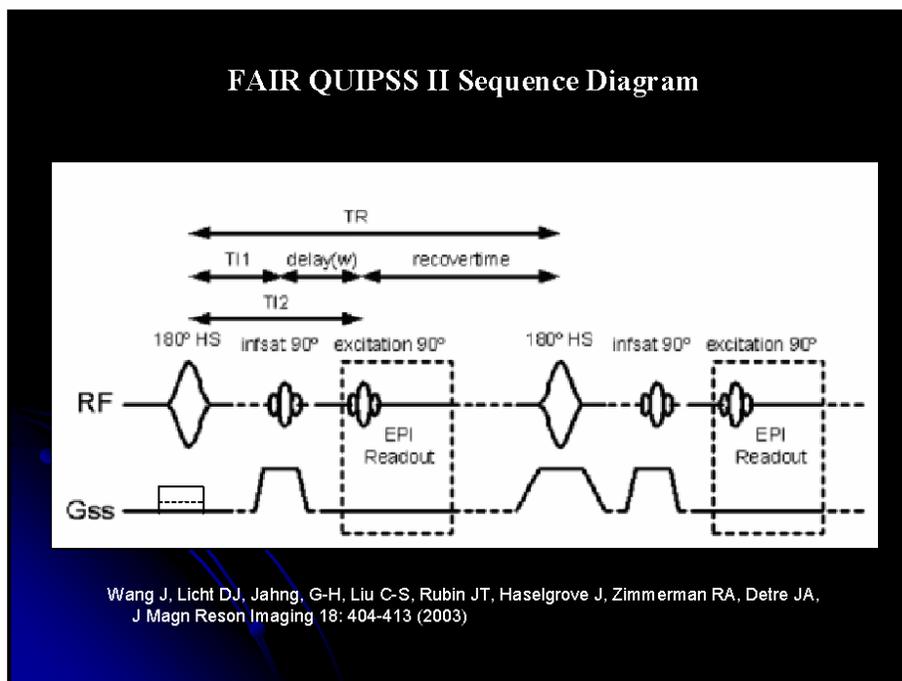
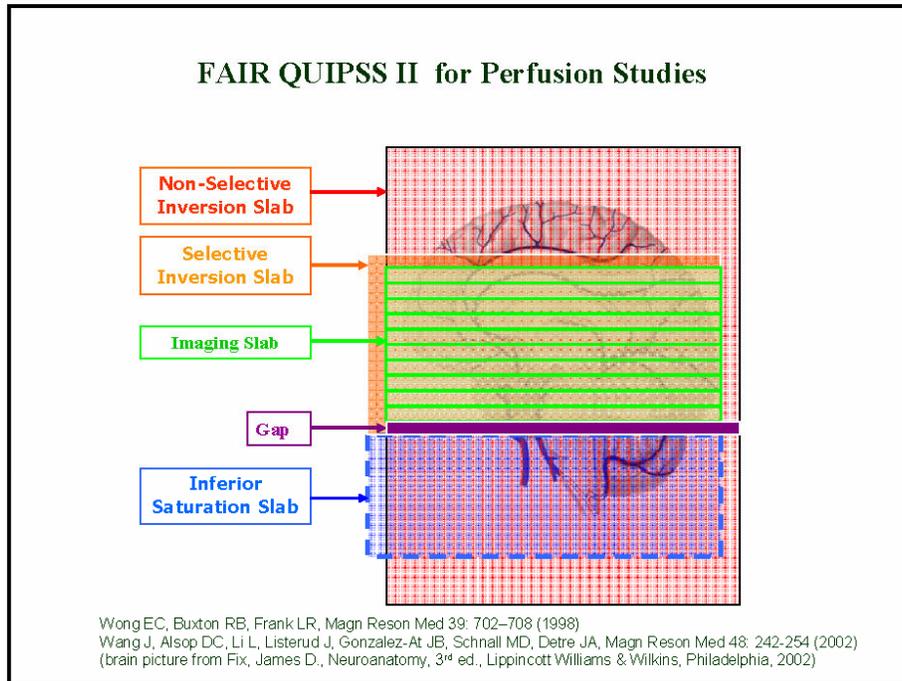
CH = caudate head
P = putamen
T = thalamus
GP = globus pallidus
M = midbrain

Haley RW, Spence JS, Carmack PS, Gunst RF, Schucany WR, Petty F, Devous MD Sr., Bonte FJ, Trivedi MH. Abnormal brain response to cholinergic challenge in chronic encephalopathy from the 1991 Gulf War. Unpublished results (manuscript in preparation).



Objectives of ASL Sub-Core

- To do a follow-up to the SPECT study in the original cohort of Gulf War veterans and controls, adding ASL for comparison and cross-validation
- To compare and cross-validate SPECT and ASL estimates of resting rCBF and responses to physostigmine challenge
- To develop and test improved methods for measuring both relative and absolute rCBF
- To apply these improved methods of quantitative mapping of brain blood flow and perfusion in GWI veterans from the RTI survey sample



ASL Protocol

Part I Preparation scans

1. Auto-align scout (0:46) aids reproducible slice positioning
2. Localizer (0:17) for slice position planning
3. MPRage (4:38) high-resolution, high-contrast anatomic reference
4. GRE (2:26) same slice orientation as ASL, allows better co-registration between ASL and MPRage images

Total Time = 8:07 min

Part II ASL perfusion scans

1. Large coverage whole-brain scans: (1) superior brain (2) inferior brain

Total time = 4:49 min x 2 (ROIs) = 9:38 min

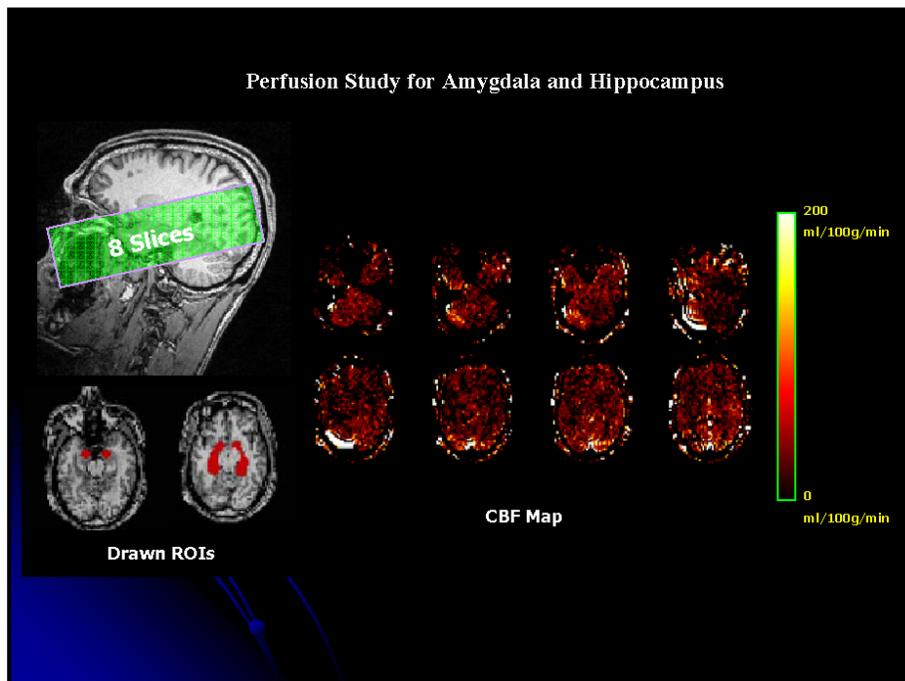
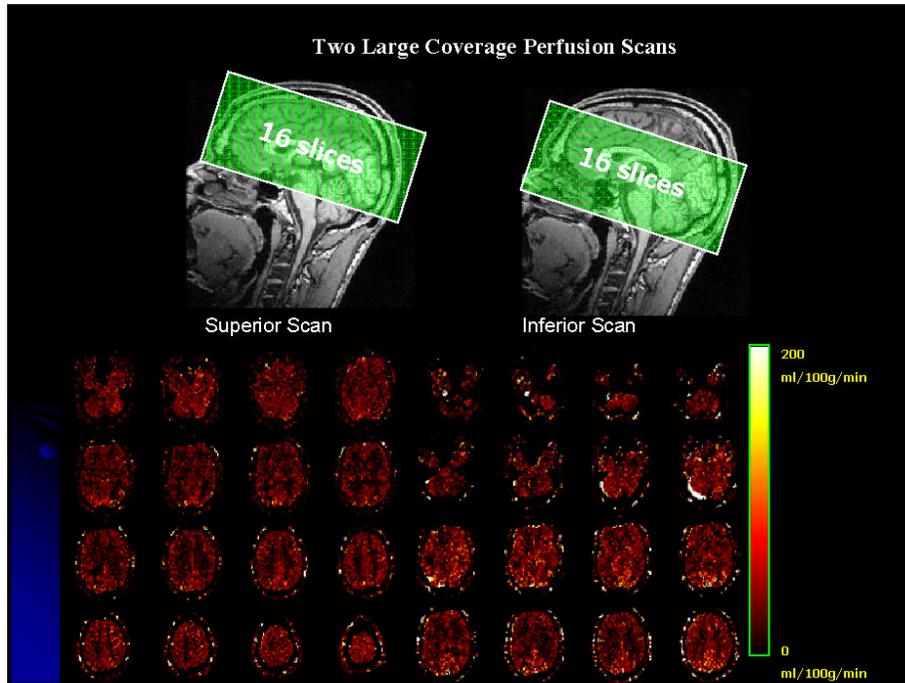
2. Smaller coverage scans: (1) deep brain (2) amygdala (3) pons and cerebellum

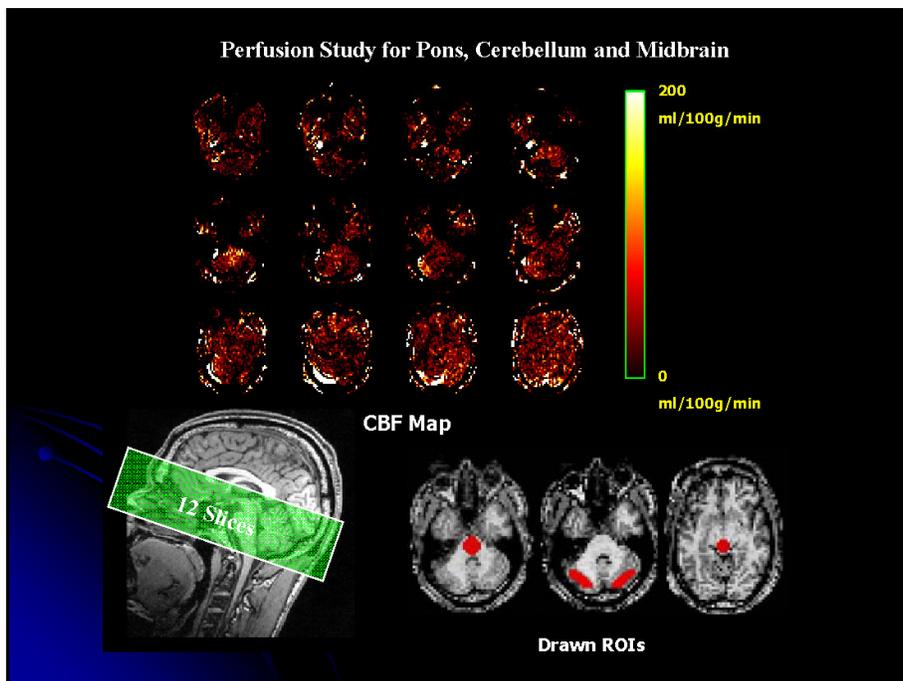
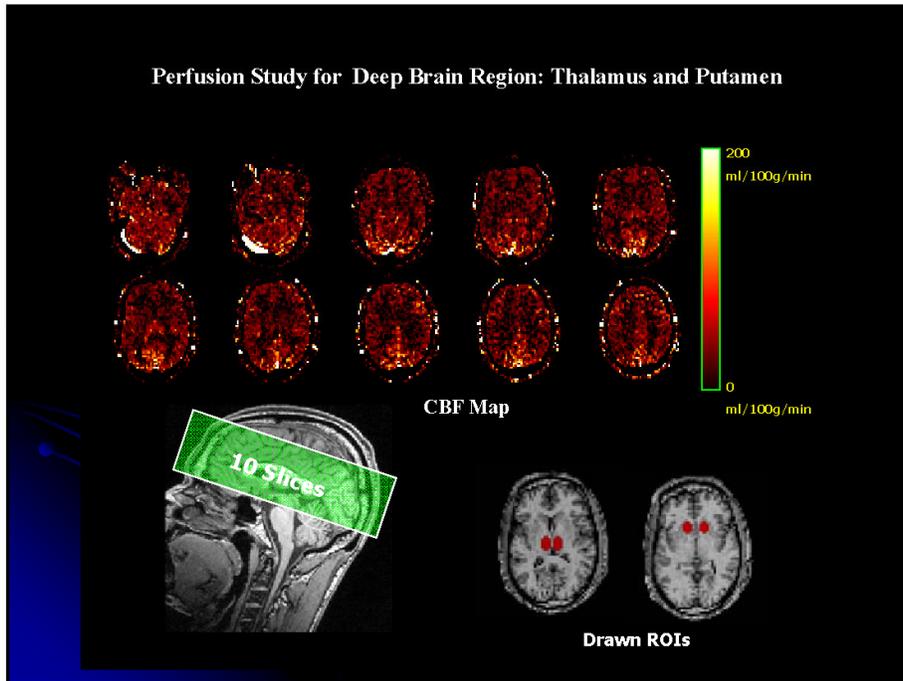
Total Time = 4:49 min X 3 (ROIs) = 14:27 min

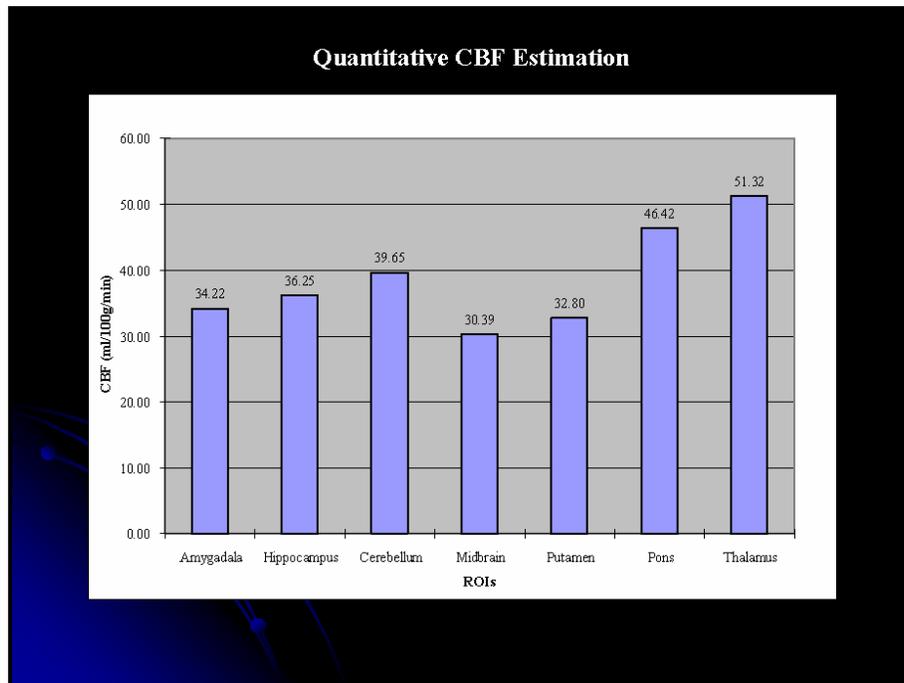
Total study time is about 32 minutes.

Data Analysis Strategy and Procedure

1. Check image quality for motion and other possible artifacts.
2. Pre-processed using SPM2: necessary motion correction, co-registration, segmentation, mean M0 calculation.
3. Analyze CBF data in original ASL image space; co-register high-resolution anatomic images to the CBF series.
4. Generate raw CBF maps by pair-wise subtraction of label and control images followed by parameter estimation using a single-compartment perfusion model.
5. Draw ROIs manually for each brain region on the co-registered anatomic images.







Discussion

1. EPI distortions cause slight (1-2 pixels) misregistration of perfusion and anatomic images in some regions (e.g., midbrain and amygdala).
2. The data processing is currently intensive and time consuming, about 10 hours per data set.
3. Effects on CBF of voxel size and number and position of slices need further examination.
4. Inter-subject variability of measured CBF is currently being studied.
5. Voxel-based CBF analysis is being considered.

Conclusions and Current Research

1. The protocol runs smoothly with a total time of 32 minutes.
2. The measured CBF for different ROIs from the three limited-coverage regional ASL scans appears to be robust and reliable.
3. ASL methods for higher spatial resolution and more accurate quantification of absolute rCBF are being developed.

Presentation 12 – Roberta White

MRI reveals evidence of structural
brain *differences* among veterans
deployed to the first Gulf War

Roberta F. White, PhD, ABPP/cn
RAC, 7/29/07, Dallas

Main study collaborators

- Kimberly Sullivan, PhD
- Frederick Powell, BA
- Ronald Killiany, PhD
- Maxine Kregel, PhD
- Lavinia Pinto, MS

Collaborators in this line of work:

Susan Proctor, DSc	Fred Powell, BS
Kimberly Sullivan, PhD	Judith Wellan, BA
Kristin Heaton, PhD	Kelly Labrecque, BA
Maxine Krengel, PhD	Don Gordon, MD
Timothy Heeren, PhD	Marlana Borgos, MA
Jessica Wolfe, PhD, MPH	Jennifer Davis, MA
Cynthia Stinson, DSc	Jeremi Moss, MD
David Ozonoff, MD, MPH	Lissa Davis, BA
Karen Lindem, PhD, PhD	Yelena Bogdanova, PhD
Megan Ciota, PhD	Livinia Pinto, BA
Sherral Devine, PhD	
Carole Palumbo, PhD	
Drue Barrett, PhD	
Frodi Debes, Cand Psych	Torbin Ishoy, MD
B. Gloerfelt-Tarp, Cand Psych	Bernadette Guldager, MD
Marete Appleyard	Poul Suadicani, Cand Odon
Finn Gyntelberg, MD	

Collaborators-3

- David Christiani, MD, MPH (EAC)
- Howard Hu, MD, ScD (EAC)
- Itamar Ronen, PhD
- Dae-Shik Kim, PhD
- Robert Kane, PhD
- Kevin Brailey, PhD
- Deborah Yurgelun-Todd, PhD

VA Merit Review Study of GW veterans 2004-2007

Hypotheses

- High symptom GW veterans will have lower white matter volumes than low symptom GW veterans
 - Pilot data
 - Site of action of neurotoxicants
- Structural findings from MRI will relate to functional findings from neuropsychological tests

Study participants

- Devens Time 3 cohort members
- DoD treatment study cohort members
- (Pain clinic patients with high symptoms)

Ft Devens subjects

- Fort Devens cohort: Time 1 survey
 - 2949 US Army GW veterans who were interviewed at Ft Devens when they returned from the Gulf (Spring 1991)
 - Psychological and health symptom questionnaires
- Fort Devens Cohort--Time 3 study
 - 220 Devens cohort members examined in Boston
 - Sampled to include individuals with low symptom complaints (<5/20), high symptom complaints (5 or more); over-sampled for women

Treatment seeking population

- Treatment seekers; GW-era veterans
 - 207 GW deployed; 53 non-GW deployed
 - VA clinical patients
 - Studied twice

Symptom division

- High symptom ($\geq 5/20$ symptoms when first evaluated)
- Low symptom ($< 5/20$ symptoms when first evaluated)

Outcome measures

- Structural MR
- Neuropsychological test results
 - California Verbal Learning Test
 - Grooved Pegboard

Preliminary results

(American Academy of Neurology poster,
May 2007)

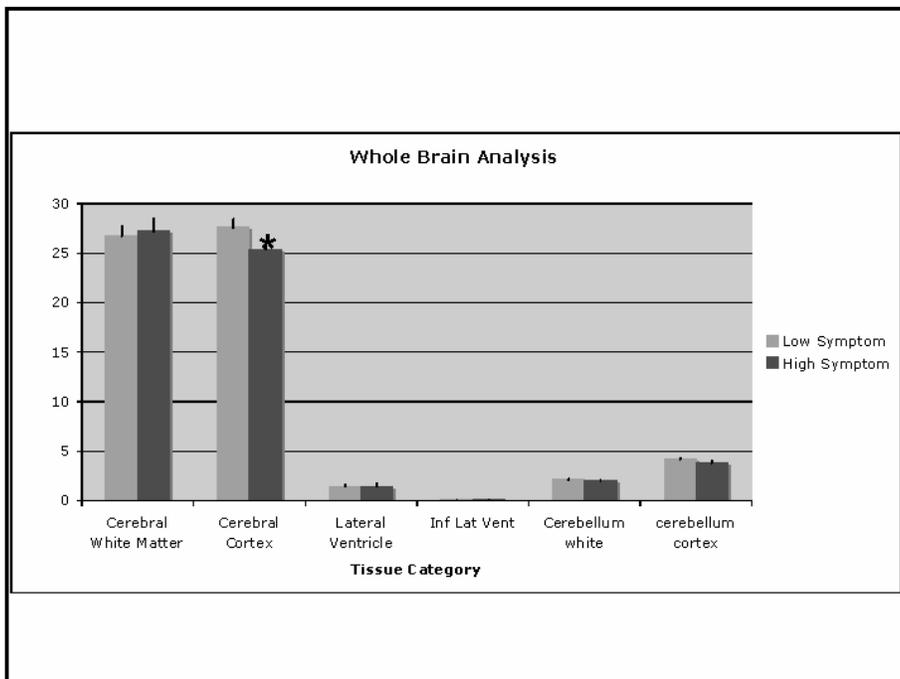
Participant groups

- 18 high-symptom veterans
- 18 low-symptom veterans
- 78% male, mean age=47, mean education=14 years

Neuroimaging

- MPRAGE sequence, FOV of 256 with a matrix of 256, 170 slices 1.2mm thick, TR of 3000mms
- MPRAGE images post-processed with FreeSurfer
- Each brain processed through automated Talarach based analysis with skull removed, checked for errors of grey and white matter borders, segmented and statistically corrected for intracranial cavity volume

Preliminary results



Results-1

- High symptom veterans showed lower total cortical brain volume (5% difference)
- Cingulate measures smaller in high symptom veterans (6% difference)

California Verbal Learning Test

D.C. Delis, J.H. Kramer, E. Kaplan, & B.A. Ober (1994)

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 ___

Results-2

- High symptom veterans performed 15% worse on the distractor task (List B) from the CVLT; this was related to overall cortical brain volume
- High symptom veterans also performed worse on the CVLT short delayed recall and this was associated with smaller rostral cingulate gyrus measures

Conclusions

- These data are *preliminary*
- They suggest structural *differences* in brains of high and low symptom veterans
- We know nothing about causation vs. vulnerability factors at this point

Next steps

- All 59 subjects (data collected)
- FreeSurfer analyses
- Structure-function explorations
- White matter measures
- Connectivity measures
- Relate findings to exposure measures
- Relate findings to both past and current symptom rates
- Relate to CMI

Presentation 13 – Bill Meggs

**Environmental Medicine
&
Gulf War Illnesses:
Does the map fit the territory?**

Research Advisory Committee on Gulf War Illnesses
July 2007

William Joel Meggs, MD, PhD, FACMT, FACEP
Current Practice: Academic Medical Toxicologist
Does not practice environmental medicine

Case Report

- 32 year old woman
- Presents to medical school allergy clinic
- Referred by her internist
- Opinion requested: use of IV nutrients (especially IV magnesium) to treat asthma
- Huge stack of medical records

Past Medical History

- **Severe asthma**
 - Multiple hospitalizations
 - Multiple medications
 - Frequent courses of IV and parenteral corticosteroids
- **Severe bipolar disorder**
 - Multiple psychiatric hospitalizations
 - Treatment with lithium, anti-psychotics, anti-depressants

Family History

- Summarized by patient as “Bad genes.”
- “I will never have children.”

Treatment at Environmental Health Center -- Dallas

- Rotation diet with elimination of many common foods
- Organically grown foods
- Bottled spring water
- Housed in environmental control unit
 - Building materials selected to minimize outgassing
 - Activated charcoal filtered air and bath water

Adjuncts to Food & Chemical Avoidance

- Provocative-neutralization skin testing and antigen injection therapy
- Low flow oxygen using ceramic mask
- Sauna detoxification
- IV nutrients

State of health at clinic visit

- Bipolar disorder in remission
- Asthma in remission
- On no medications
- No hospitalizations or acute visits since treatment at EHCD
- Suffers from food intolerances and chemical sensitivities

Severe limitations on every day life

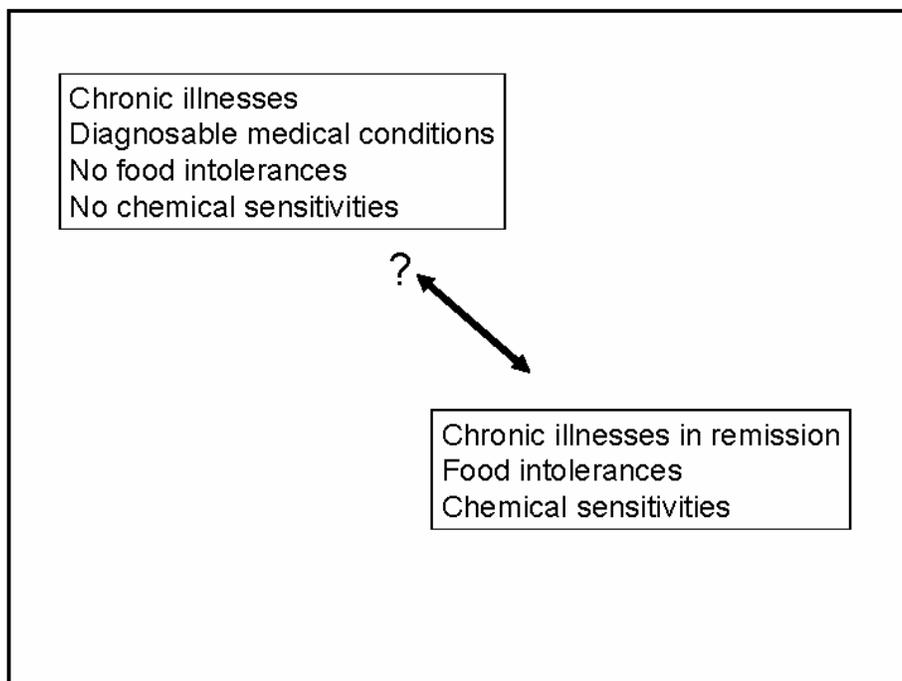
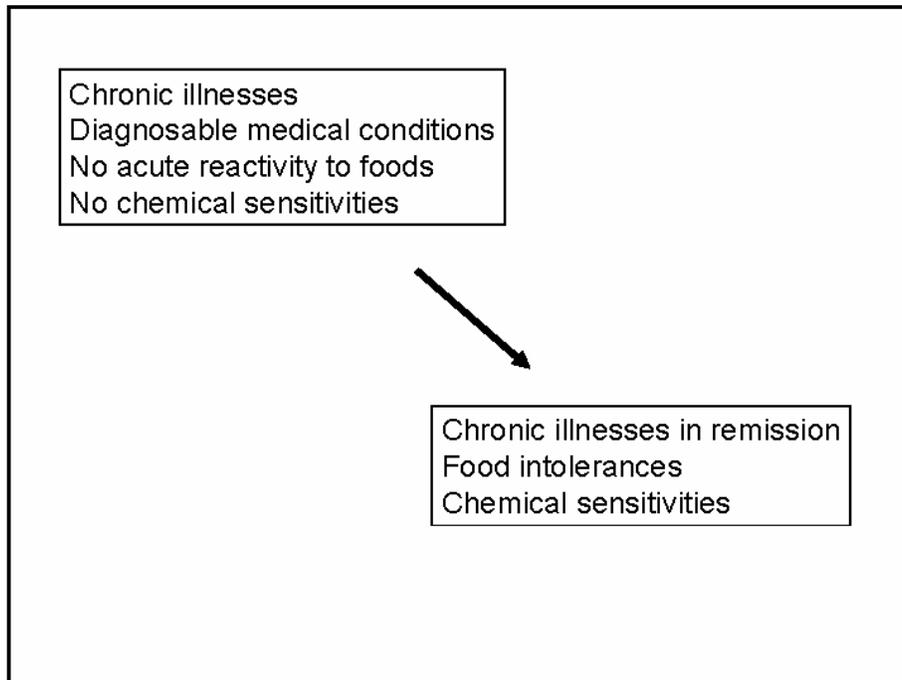
- Social isolation
 - Unable to visit family & friends
 - Unable to attend church
- Unemployed
 - Social security disability
- Spends a great deal of time on health
 - What to eat
 - what to wear
 - where to go, how to travel.

Chemical Avoidance

- Products of combustion
 - Tobacco smoke, diesel and gasoline vehicle exhaust, furnace fumes, gas cook stoves and appliances
- Perfumes and fragrances
- Drinking water contaminants
- Commercial foods, used organic foods only
- Products for Cleaning
- Pesticides
- Paints and other solvents
 - Outgassing of VOCs from fabrics, carpets, etc.

Food Avoidance

- **Rotation diet**
 - One food per meal
 - Pure foods, no mixtures
 - Only eats a food once each 5 to 7 days
- **Monitors reactivity to each food**
 - Eliminates any non-tolerated food from rotation
- **Organic foods**
- **Bottled spring water**



Historical Roots of Environmental Medicine

- Allergists
- American mid-west
- 1930's and 1940's

Early Beginnings

- Food intolerance
- *Masked* food allergy
 - Tolerance of food if ingested daily
 - Period of abstinence followed by re-exposure results in acute reaction
- **Cyclical vs. Fixed food allergy**
 - REF: *Food Allergy* by Rinkel HJ, Randolph TG, Zeller M. CC Thomas, Springfield IL, 1951. [out of print].

Diagnostic Approach

- Period of avoidance
- Re-exposure
- Monitor for symptoms
- Non-reaginic [not IgE mediated]

Case Report: Dr. HJ Rinkel

- Son of egg farmer
- Impecunious medical student with family
- Father sent gross of eggs each week
- Profuse rhinorrhea
 - Multiple physician visits without help
- Egg was suspected
- Egg avoidance for five days– rhinorrhea resolved
- Ate birthday cake containing egg and had severe reaction

Systemic Manifestations of 'Food Allergy'

- Fatigue
- Headache
- Brain-fag
 - Difficulty with cognition, memory, concentration
- depression, psychosis
- Myalgias
- Arthralgias, arthritis
- Cardiovascular manifestations
 - Fluid retention
 - Tachycardia

Methodology

- Setting: private practice
- Detailed history
- Trial & error
- Abstinence followed by re-exposure
- Carefully record signs & symptoms of illness
- Generalizations from individual cases

Fasting

- Introduced by Dr. Donald Mitchell, Montreal dermatologist & environmental physician
- Hospital practice
- Fast on spring water with sodium and potassium bicarbonate [2:1] until symptoms clear
- Re-expose to foods one by one

Rotation Diet

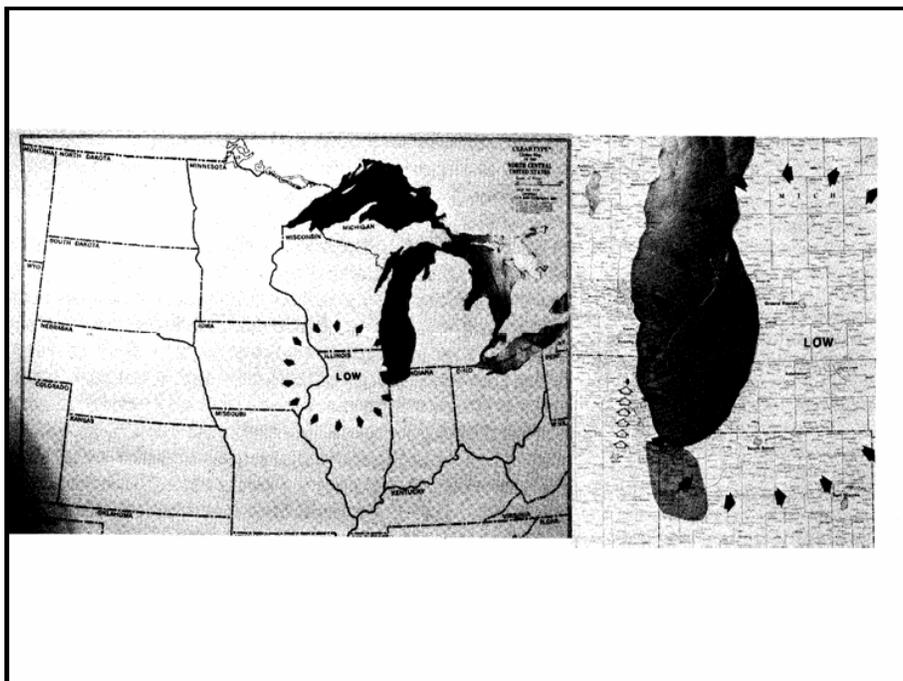
- One food per meal
- Repeat each food every 5 to 7 days
- Monitor for reactions
- Use organically grown, untreated, pure foods
- Eliminate any foods with untoward reactions

Pesticide Sensitivity

- Patient tested and found allergy to peaches
- Patient reported peaches from abandoned orchard gave no reaction
- Patient found to be intolerant of grocery store peaches but tolerant of peaches from abandoned orchard
- Sulfites, fungicides, insecticides

Sensitivity to 'Air Pollution'

- Allergy to the South Wind
- Industrial area
- Symptoms flare in some individuals when the winds are from the south



Gas Appliances

- Burn unvented natural gas in cook stoves, water heaters
- Patients turn off their gas for 5 to 7 days, use a hot plate, toaster oven, electric frying pan, etc., then turn it back on.
- “Shock Reactions” can occur, considered diagnostic
- Homes with gas cook stoves have levels of sulfur dioxide and oxides of nitrogen above levels allowed in factories

Chemical Sensitivity

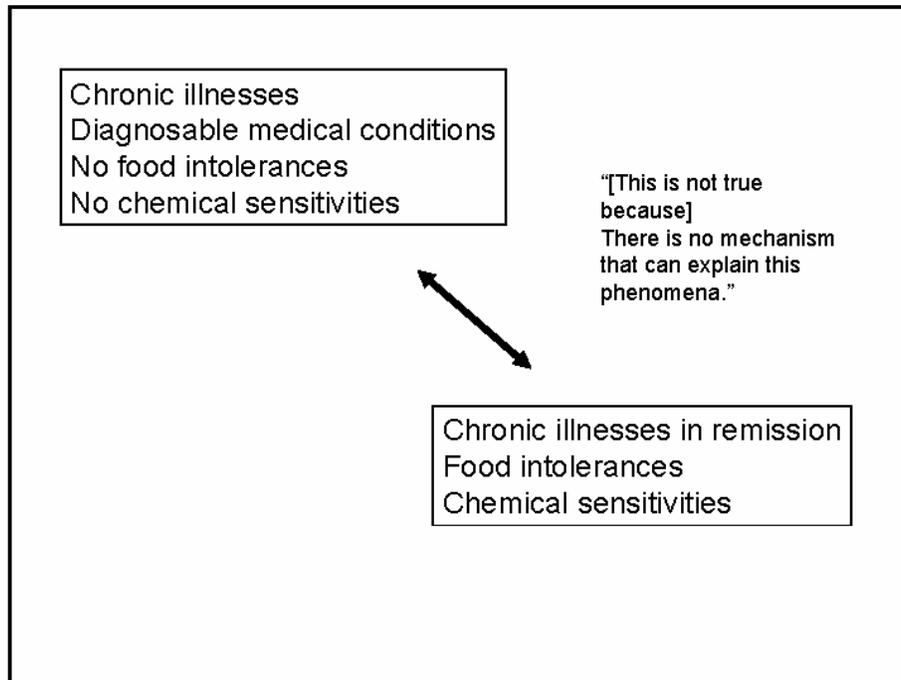
- Individual susceptibility
- Products of combustion
 - Tobacco smoke, vehicle exhaust, furnace fumes, gas appliances
- Perfumes and fragrances
- Products for Cleaning
- Pesticides
- Paints and other solvents
 - Outgassing of VOCs

Exposures said to drive ...

- **Spreading**
 - Sensitivity to increasing numbers of substances
- **Progression**
 - To include more and more symptoms, more and more organ systems

Induction

- Onset of chemical sensitivity often associated with a single high dose exposure.



Generalized Adapatation Syndrome

- Discovered by Hans Selye, MD
- Injecting impure extracts of ovary and placenta into rats [? new hormone]
- Resulting definitive syndrome
 - Adrenal enlargement
 - Atrophy of lymphatic structures: thymus, spleen, lymph nodes
 - Hemorrhagic ulcers of stomach and duodenum

Puzzling Observation

- No matter what extracts he injected into the rats, he got the same syndrome
 - Liver, kidney, spleen
- He injected rats with formalin and got the same syndrome
- Non-specific toxic reactivity

Selye H. A syndrome produced by diverse noxious agents. 1936. *J Neuropsychiatry Clin Neurosci.* 1998 Spring; 10(2):230-1.
Selye H. *The Stress of Life.* McGraw-Hill. New York 1956

3 stages

- Alarm reaction
- Stage of resistance
- Stage of exhaustion

Generalized Reaction to Stress

- Non-specific
- Diverse noxious agents
- Psychological stress cross reacts with physical stress

Generalized Adaptation Syndrome

Stage I. Preadaptation (Nonadapted)	Shock Reaction (Acute reactivity to chemicals)
Stage II. Addicted (Adapted) IIa. Adapted IIb Maladapted	Tolerance Chronic Illness
Stage III. Postadapted (Nonadapted)	Exhaustion

Chemical Stress Syndrome.

Stage 0. Normalcy	Tolerance of chemical exposures, wellness without symptoms
Stage 1. -algia	Sensory Hyper-reactivity. Subjective symptoms associated with chemical exposures. (arthralgias, myalgias, etc.)
Stage 2. -itis	Inflammatory reactions to chemicals (arthritis, myositis, etc.)
Stage 3. -osis	Fibrosis. Necrosis. Tissue destruction (arthritic deformities, muscle atrophy and necrosis, etc.)

Organ system involvement in chemical sensitivity

Respiratory	Asthma, Rhinitis, Sinusitis, Pneumonitis
Musculoskeletal	Myositis, Arthritis, Collagen Vascular diseases
Gastrointestinal	Irritable Bowel Syndrome, Inflammatory Bowel Disease
Dermatological	Dermatitis, Rosacea, Cutaneous Vasculitis

Organ system involvement in chemical sensitivity

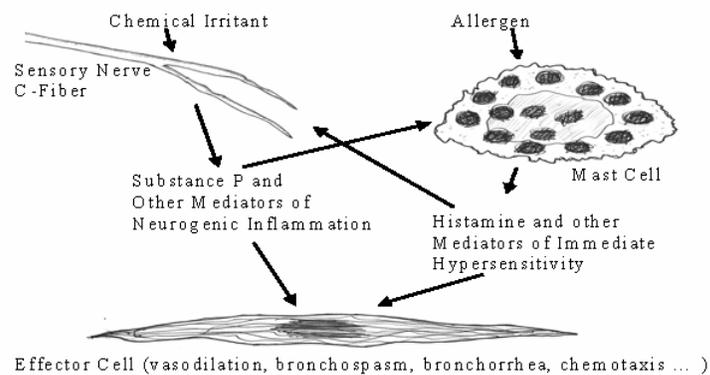
Cardiovascular	Hypertension, Arrhythmias, Vasculitis, Recurrent Anaphylaxis
Neurological	Migraine, Fatigue, Cognitive dysfunction, Seizures, Coma
Psychiatric	Bipolar disorder, Depression, Psychosis

Mechanism of Chemical Sensitivity

- Best studied in the airway
- Airway remodeling
- Pathology of airway is changed in a way that makes one more sensitivity to irritants

Crossover Network

- Nerve fibers have histamine receptors
- (some) Mast cells have substance P receptors



Irritant Rhinosinusitis

- Acquired disorder with onset related to irritant exposures.
- Persistent airway inflammation.
- Exacerbations by irritant exposures that were previously tolerated.
- Burning rather than itching sensation with irritant exposures

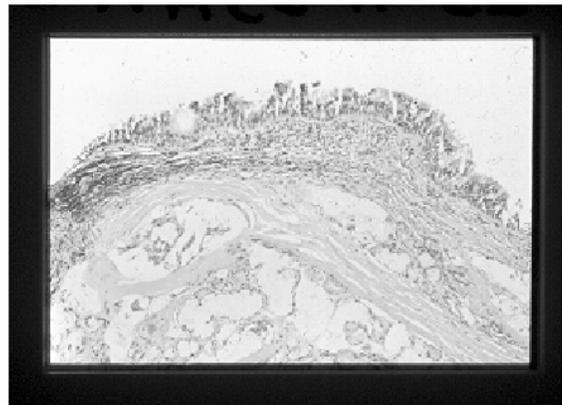
Irritant Rhinosinusitis: Physical Findings

- Edema and hypertrophy of the airways
- Abnormal mucous
 - Thick, white to yellow, crusty exudates
- Nodular hyperplasia
- Hemorrhage
- Injection
 - Posterior pharynx, uvula, soft pallet
- Discoloration
 - Pale yellow to white patches of mucosa with prominent blood vessels



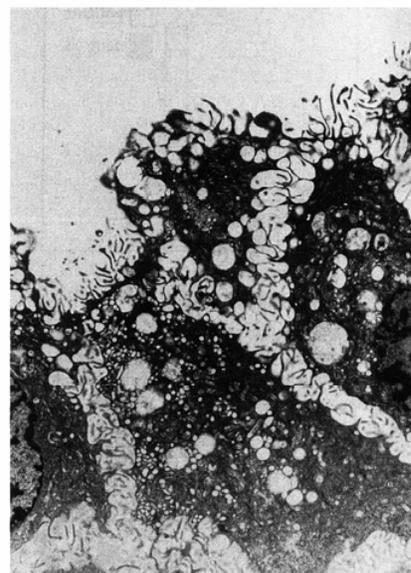
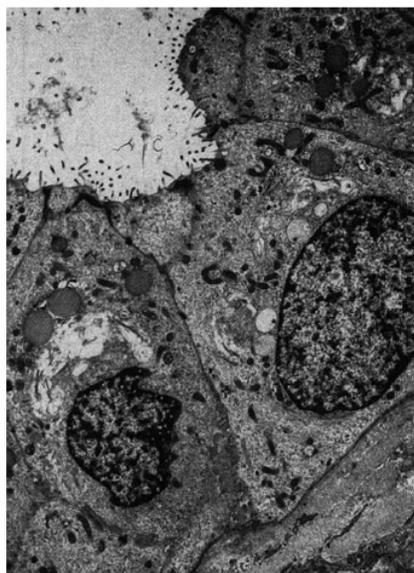
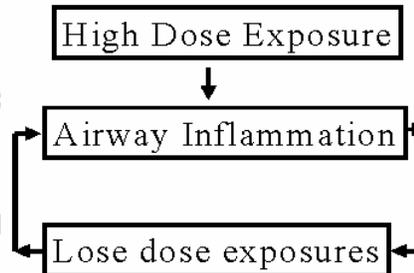
Irritant Rhinosinusitis: Pathological Features

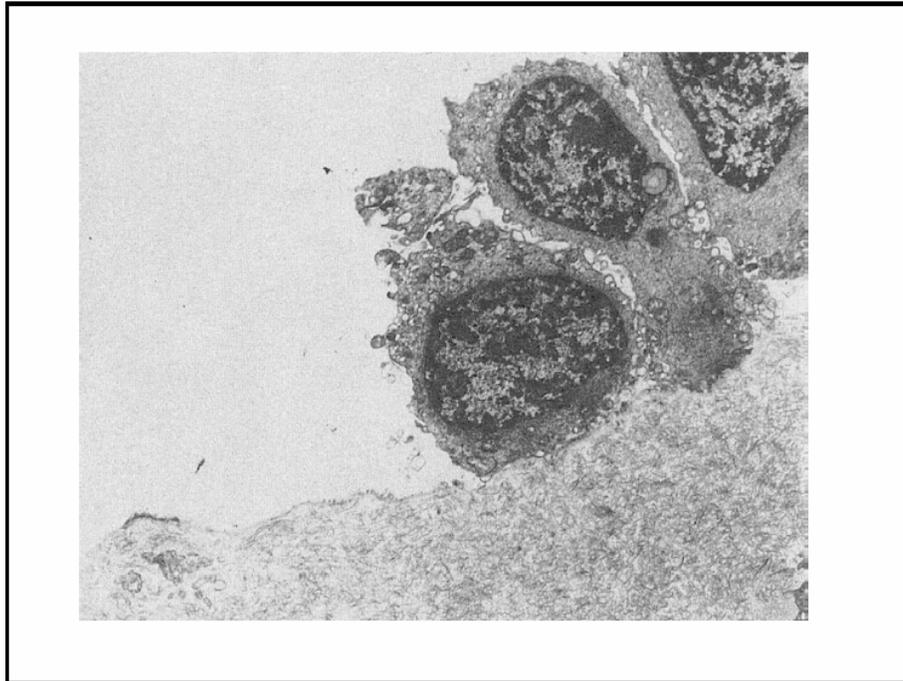
- Chronic inflammation with lymphocytic infiltrates
- Glandular hyperplasia
- Basement membrane thickening
- Nerve fiber proliferation
- Desquamation of the respiratory epithelium
- Defects in tight junctions



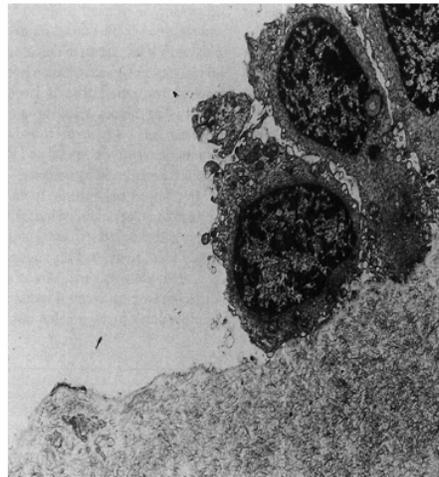
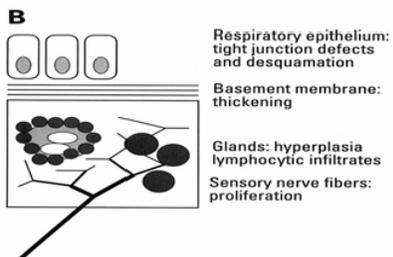
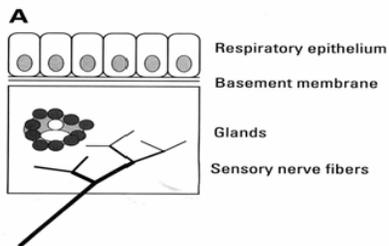
Induction Mechanism

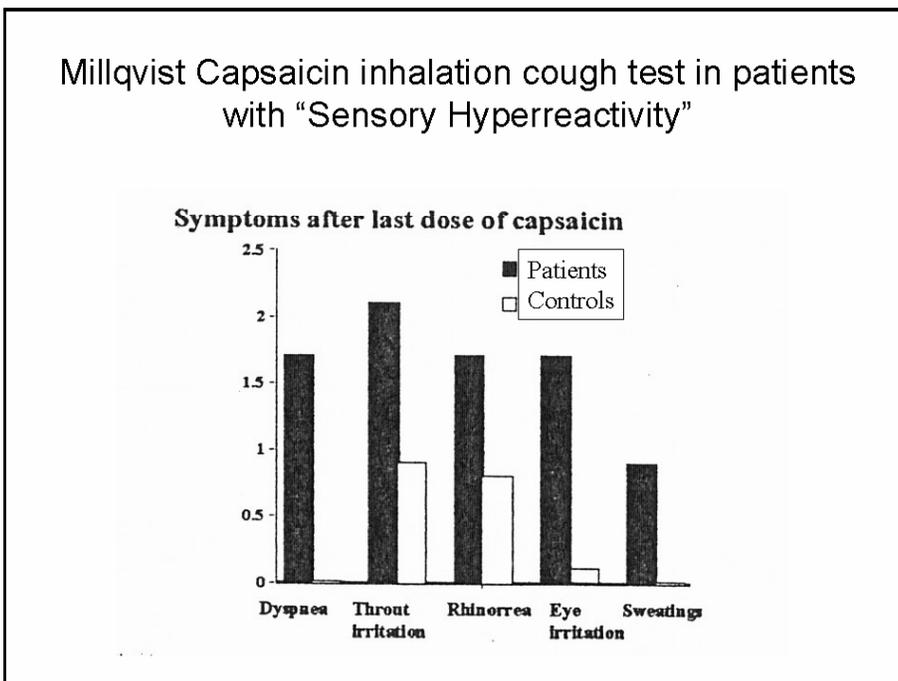
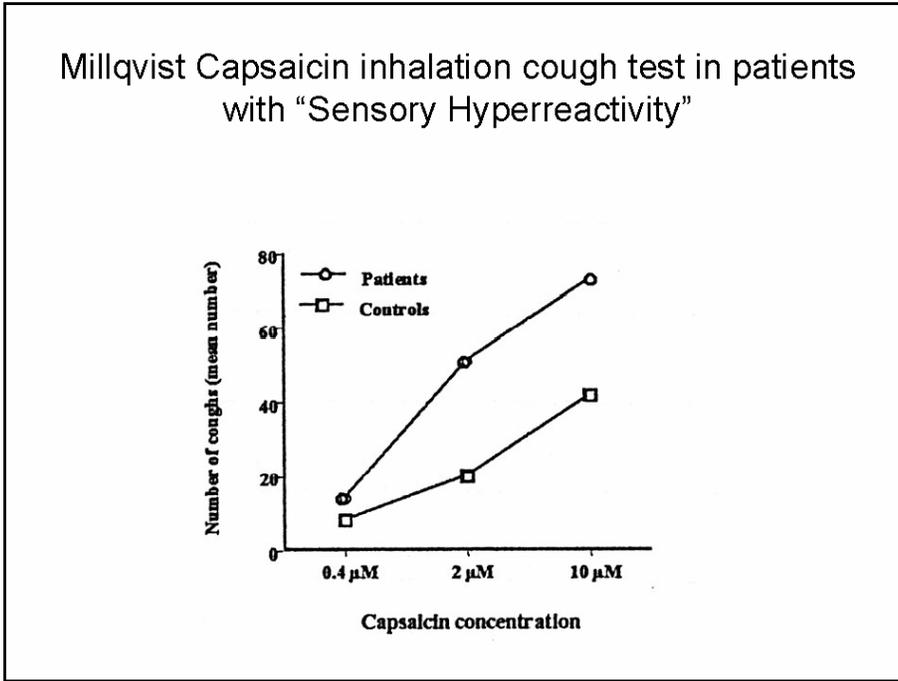
- Positive feed back loop
- Induction exposure produces neurogenic inflammation
- Inflammation produces remodeling
- Remodeled airway more sensitivity to irritants

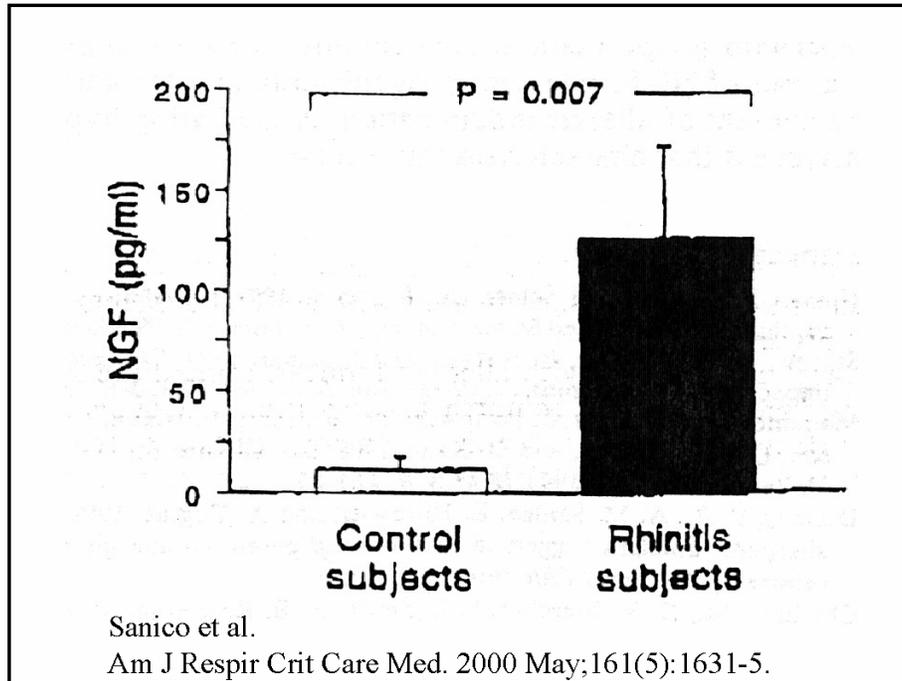




End Organ Sensitization







Millqvist E et al.

- Changes in levels of nerve growth factor in nasal secretions after capsaicin inhalation in patients with airway symptoms from scents and chemicals.
- Environ Health Perspect. 2005 Jul;113(7):849-5

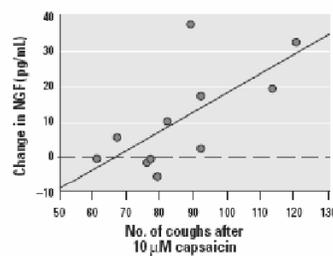


Figure 2. Correlation between change in NGF after provocation with three concentrations of capsaicin and number of coughs after inhalation of the highest dose of capsaicin (10 µM). $r = 0.7$.

Methods

- 13 patients with Sensory Hyper-reactivity and 14 control subjects
- provoked with capsaicin inhalation at three different doses
- Nerve Growth Factor measured in Nasal Lavage Fluid before and after provocation
- cough and capsaicin-induced symptoms recorded

Results

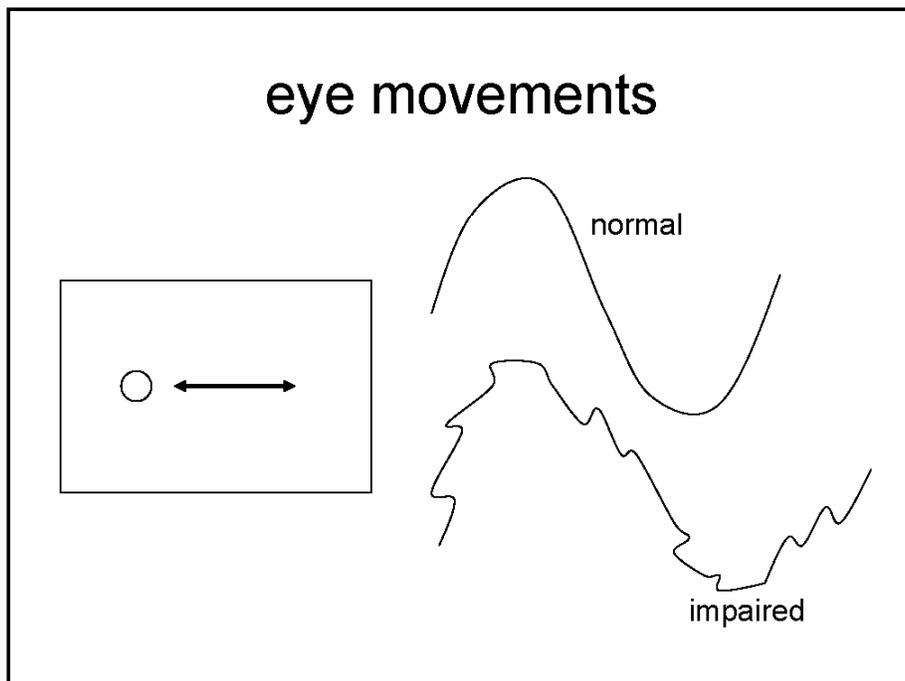
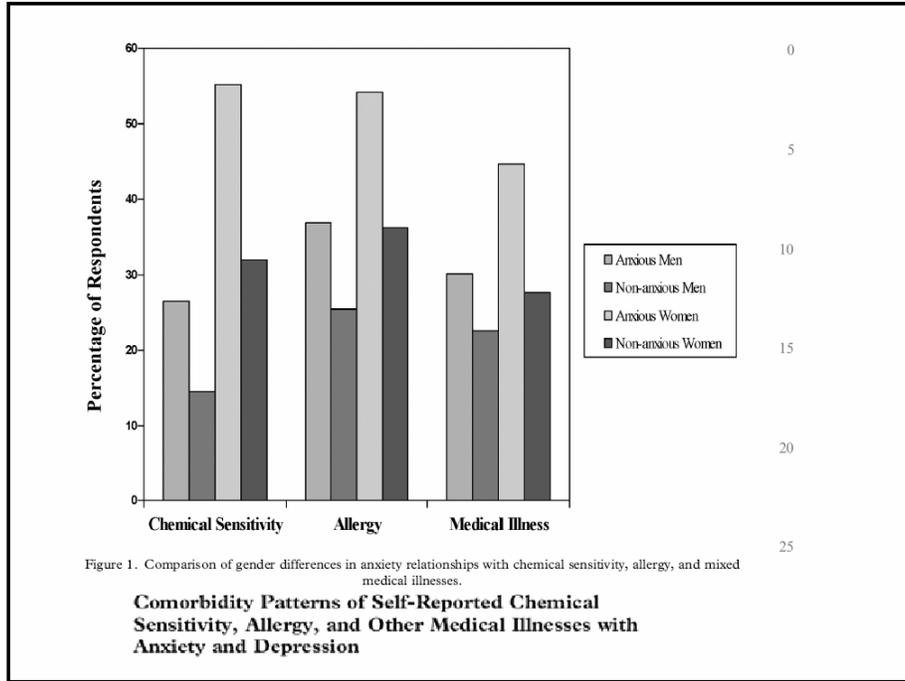
- All subjects demonstrated a dose-dependent cough response to capsaicin inhalation
- more pronounced in patients than in controls.
- Basal levels of NGF were significantly lower in the patient group than in the control subjects ($p < 0.01$).
- After capsaicin provocation, the patients showed a significant increase in NGF ($p < 0.01$)
 - related to capsaicin cough sensitivity

Conclusion

- In patients with airway symptoms induced by scents and chemicals, sensory hyperreactivity is real and measurable, demonstrating a pathophysiology in the airways of these patients compared to healthy subjects.

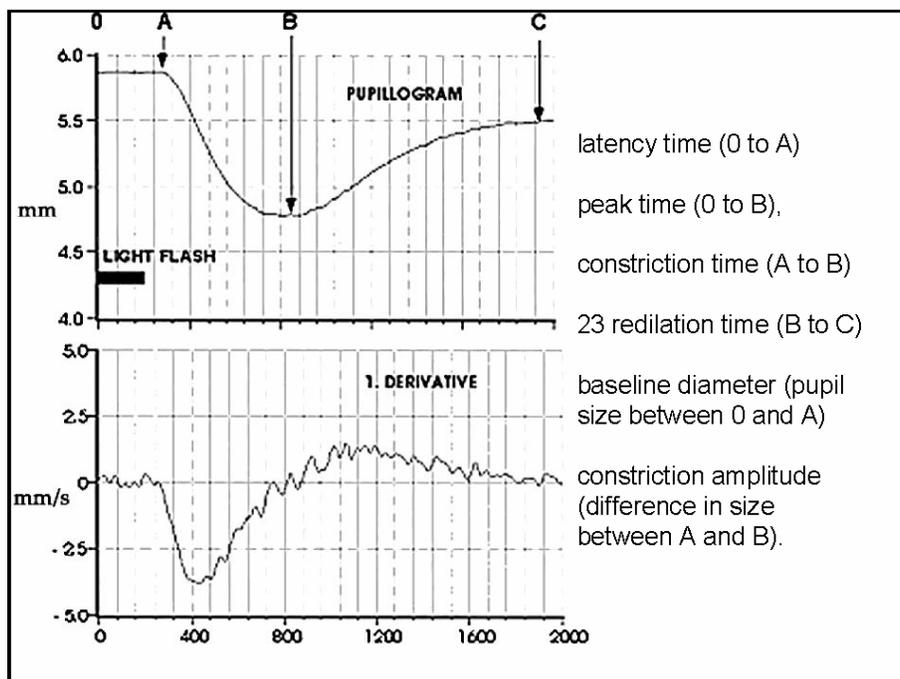
“Subtle” Neurotoxicity

- Bedside neurological examination is often normal.
- CNS imagining often normal.
- Abnormal results of tests such as heart rate variability & pupillography correlate with other neurological deficits.



Professor S. Ishikawa

- [Former Chair] Department of Ophthalmology, [Former Dean] School of Medicine, Kitasato University, Tokyo, Japan.
- 20+ year study of *subtle* neuro-ophthalmological abnormalities in poisoned individuals [organophosphate pesticides]
- Pupillography – autonomic dysfunction
- Defects in extra-ocular movements



Classic Study

- 1st study to assess effects of OPs on autonomic nervous system
- Pupillography
- Controlled study
- 20 patients, 18 controls
- Autonomic dysfunction is 18/20 patients (90%)

Shirakawa S. Ishikawa S. Miyata M. Rea WJ. Johnson AR. [A pupillographical study on the presence of organochlorine pesticides in autonomic nerve disturbance]. [Japanese] Nippon Ganka Gakkai Zasshi - Acta Societatis Ophthalmologicae Japonicae. 94(4):418-23, 1990 Apr.

Defects in Pupil Response

- pupil area (p less than .006), velocity of both constriction and dilatation (p less than .001), and dilatation time (p less than .02)
- Sympathetic nerve inhibition i.e. sympatholytic pattern in 10/18 (55%)
- toxicity of the pesticide on the autonomic nerve appear as an inhibitory effect on pupil light reflex.

Shirakawa S. Ishikawa S. Miyata M. Rea WJ. Johnson AR. [A pupillographical study on the presence of organochlorine pesticides in autonomic nerve disturbance]. [Japanese] Nippon Ganka Gakkai Zasshi - Acta Societatis Ophthalmologicae Japonicae. 94(4):418-23, 1990 Apr.

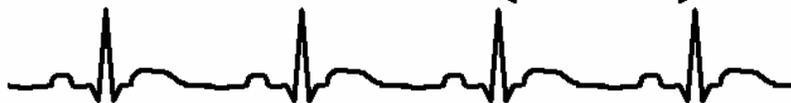
Occupational organophosphate insecticide Exposure

- Abnormal pupillography in workers with occupational exposure to organophosphate insecticides
- Recommend use of pupillography in detecting poisoning in workers

Filippov VL. Shumakova KM. Tsimbal FA. [Use of pupillometry in the diagnosis of neurologic disorders caused by organophosphorus compound poisoning]. [Russian] *Meditsina Truda i Promyshlennaia Ekologiya*. (6):11-6, 1997.

Heart Rate Variability

- Measure of integrity of autonomic nervous system
- autonomic nervous system related to cardiovascular disease, cardiac sudden death [30% of population]
- Commercial devices
- Evaluation of RR interval

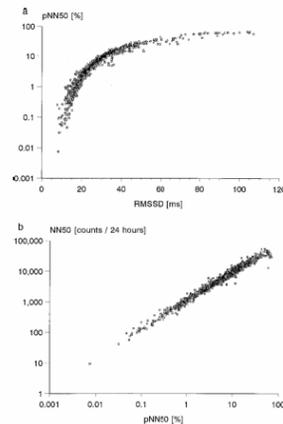


Simple Time Domain Variables

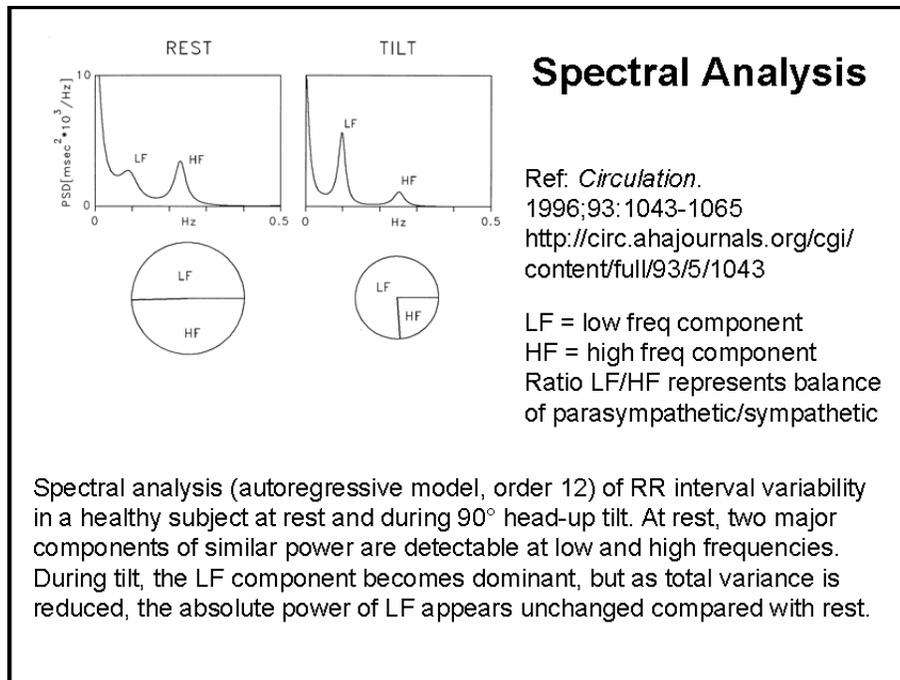
- mean RR interval
- mean heart rate
- difference between the longest and shortest RR interval
- difference between night and day heart rate
- variations in instantaneous heart rate
 - respiration, tilt, Valsalva, phenylephrine, etc.

complex statistical time domain measures

- RR [NN] interval measurements
 - Standard deviation of RR interval = variance
 - Varies with recording period
- Differences in RR intervals



RMSSD = square root of the mean squared differences of successive NN intervals
NN50 = number of interval differences of successive NN intervals > 50 ms
pNN50 = proportion derived by NN50 / total number of NN intervals

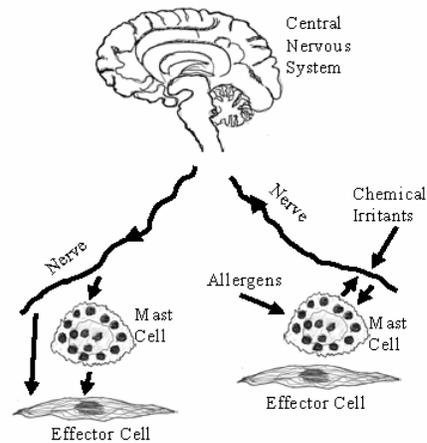


Syndromes with Neurotoxicity and Autonomic Dysfunction

- Gulf War Syndrome
- World Trade Center Syndrome
- Solvent neurotoxicity
- Organophosphate toxicity [OPIDN]
- Chronic fatigue syndrome
- Sick building syndrome & so-called 'MCS'

Neurogenic Switching

- The site of inflammation can be switched from the site of stimulation
- Occurs in both allergic and irritant airway inflammation
- May play a role in many disease processes



Gulf War Syndrome

What is Gulf War Illness?

- Significant % of the ~700,000 Gulf War Veterans affected
- Not a symptom based syndrome
- Chronic, multi-system disease
 - Neurological
 - ALS
 - Constitutional
 - Respiratory
 - Gastrointestinal
 - Dermatological
- Correlates with chemical exposures in epidemiological studies
- Prevalence varies with geographic assignments

Chemical Exposures in the Gulf War:

- Nerve gas: Khamasia and other demolitions
- Kuwaiti oil fires
- Organophosphate pesticides
- DEET and pyrethroids
- Diesel fuel, kerosene
- Pyridostigmine bromide
- Anthrax and other vaccines
- Depleted uranium

Treatment

Table 2. Perceived efficacy of 101 treatments tried by 917 persons with MCS.

	Number tried	Very harmful (%)	Somewhat harmful (%)	No noticeable effect (%)	Somewhat helpful (%)	Very helpful (%)	Harm ratio*
Environmental medicine and oasis techniques							
Chemical avoidance	875	0.5	0.3	4.7	38.0	56.5	116.6
Chemical-free living space	820	0.1	0.5	4.5	39.6	56.2	155.2
F-N for chemicals with preservative	159	22.0	18.1	25.4	27.1	7.3	0.8
F-N for chemicals without preservative	218	11.9	12.8	28.3	31.4	15.5	1.9
F-N without glycerin or preservative	178	12.5	8.3	25.0	30.2	24.0	2.6
Sauna at clinic	151	7.1	7.7	20.5	30.3	34.2	4.4
Sauna at home	245	7.1	11.4	19.6	38.8	23.1	3.4
Rotation diet	560	1.6	4.1	22.1	44.0	28.2	12.7
Air filter (to prevent exposure)	786	1.8	4.2	11.8	47.5	34.6	13.7
Charcoal mask	598	4.5	8.3	9.8	55.1	22.3	6.0
Aluminum foil to seal off-gassing	253	5.6	5.3	14.7	35.7	38.7	6.8
Personal oxygen to cope with exposures	326	2.9	4.4	14.2	39.8	38.6	10.6
Individual nutritional supplements							
Intravenous magnesium	176	4.2	6.8	25.5	40.8	22.9	5.8
Buffered vitamin C powder	516	4.0	8.8	29.4	37.3	20.5	4.5
Other vitamin C	663	2.9	6.7	28.0	35.3	16.4	5.5
Vitamin E supplements	708	2.1	5.1	53.1	29.3	10.3	5.4
Coenzyme Q10	517	2.5	5.8	51.4	28.9	11.5	4.9
Magnesium supplements	644	2.3	3.8	41.4	34.4	16.0	8.8
Calcium supplements	663	2.8	5.2	58.8	25.0	10.6	4.8
Chromium supplements	399	3.8	4.5	57.8	22.2	11.8	4.1
Other mineral supplements	666	2.0	5.7	42.4	35.0	13.9	6.4
Grapefruit seed extract	325	7.7	11.6	43.3	27.6	9.8	1.9
Echinacea	515	5.6	11.8	48.8	29.0	11.0	2.0
Gallberry	298	5.8	13.5	48.4	21.5	10.9	1.7
Siberian ginseng	283	5.9	15.0	48.3	25.2	4.5	1.5
MIB, thistle seed	458	3.2	8.5	41.8	39.8	15.1	5.0
Garlic	555	5.2	10.2	48.5	25.9	12.2	2.5
Acidophilus	661	0.9	3.2	41.0	32.8	19.2	12.7
DHEA	352	8.2	15.1	46.4	20.7	9.5	1.3
Theroid supplements	406	3.8	8.4	39.8	28.1	19.9	3.9
Herbal therapies							
Herbal therapy with homeopathic doctor	401	4.9	9.1	32.6	33.8	16.5	3.8
Over the counter homeopathy	426	4.8	8.8	38.6	40.1	17.6	4.8
Bach flower remedies	226	2.5	6.6	50.2	29.6	11.1	4.5
Acupuncture	422	3.9	6.3	38.0	32.5	21.3	5.3
Herbal medicines	650	4.2	7.6	24.5	41.8	22.0	5.5
Macrobiotic diet	162	13.5	15.1	24.0	33.3	14.1	1.7
Jiujing	315	4.4	8.8	47.0	31.2	13.6	3.4
Acupuncture	127	19.0	20.5	19.1	33.5	9.9	1.0
Chelation	131	11.0	13.2	27.2	31.8	16.8	2.0
Neural therapy	56	10.7	10.7	28.0	35.0	14.7	2.4
Detoxification							
Remove mercury dental fillings	425	3.1	6.1	47.1	27.3	16.5	4.8
Hulse Reghev Clark's parasite program	67	18.7	9.3	36.4	27.1	8.4	1.3
Coffee enemas	146	5.4	14.3	32.0	32.7	15.6	2.5
Colonoscopy	222	4.8	8.4	28.2	38.3	20.3	4.4
Liver flushes	148	9.6	9.6	25.5	35.7	19.7	2.9
Balloon/catheter flushes	95	3.8	9.5	33.3	38.2	17.1	4.0
UltraClear	232	8.7	27.0	30.3	11.2	22.8	1.0
Hydrogen peroxide therapy	123	17.4	13.2	40.3	15.3	13.9	1.0
Eastern origin techniques							
Meditation	423	0.7	2.1	43.3	41.2	12.6	10.2
Yoga asana (postures)	260	3.0	5.9	41.8	37.4	11.9	5.5
Tai chi	154	3.2	9.0	54.5	21.8	11.5	2.7
Qi gong	108	3.3	8.5	40.7	38.6	13.0	5.1

Continued, next page

Table 2. Continued.

	Number used	Very harmful (%)	Somewhat harmful (%)	No noticeable effect (%)	Somewhat helpful (%)	Very helpful (%)	Helps/harms ratio*
Body therapies							
Traditional chiropractic	488	2.2	8.1	47.4	31.8	12.5	5.3
Chiropractic with applied kinesiology	278	2.2	3.9	41.7	35.6	15.0	7.5
Network chiropractic	63	11.6	15.1	36.0	23.3	14.0	1.4
Chiropractic with contact reflex analysis	57	18.8	5.7	32.9	28.6	14.3	1.8
Best chiropractic	29	7.1	14.3	38.1	23.8	16.7	1.9
Applied kinesiology without chiropractic	191	7.1	5.8	32.0	34.0	21.3	4.4
Alexander technique	38	4.9	4.9	60.3	19.5	2.4	2.3
Trager	31	7.1	14.3	50.0	23.8	4.8	1.3
Reiki	170	2.7	4.8	44.6	34.4	13.4	8.4
Acupressure	388	1.0	3.5	29.3	46.0	21.2	14.9
Massage	591	0.8	7.9	32.5	39.4	19.4	6.8
Teach for health	75	2.5	1.3	41.8	35.4	18.0	14.3
Polarity balancing	117	3.3	4.9	45.9	29.5	16.4	5.8
Reflexology	294	2.4	2.4	38.5	43.4	13.2	11.6
Rolling	60	7.8	14.1	35.9	26.5	15.6	1.9
Osteopathic adjustment	171	5.0	5.5	44.2	30.4	14.0	4.3
Craniosacral work	270	4.0	2.8	38.6	38.6	20.1	8.6
Total body modification	42	8.6	8.9	29.3	38.2	18.0	3.8
Newer therapies							
Myofascial release	57	10.8	15.4	53.8	10.8	9.2	0.8
Diaphragm therapy	182	5.8	5.1	20.3	44.1	24.8	8.4
Eye movement desensitization and reprocessing	64	15.8	7.9	51.3	17.1	7.9	1.1
Neurolinguistic programming	37	8.8	2.9	64.7	17.6	5.9	2.0
Prescription items							
Normal	153	16	17.8	26.2	31.3	8.8	1.2
Nystatin	402	7.8	14.5	32.2	31.8	12.5	7.0
Diflucan	249	9.9	14.5	28.9	31.4	15.3	1.9
Prozac	183	27.6	21.5	25.8	9.7	5.4	0.3
Zoloft	148	45.5	22.7	23.4	5.8	2.8	0.1
Elavil	149	33.9	23.8	27.3	9.7	5.5	0.3
Other antidepressants	308	32.4	17.8	27.2	17.6	5.1	0.5
Naproxen	100	19.0	15.7	24.5	24.5	10.7	1.1
Other anti-inflammatories	75	37.6	12.9	24.7	18.5	8.2	0.5
Antibiotic therapy for Mycoplasma fermentans	38	17.4	13.0	21.7	21.7	28.1	1.8
Acyclovir (Zovirax)	88	18.8	13.8	40.7	18.5	7.4	0.8
Transfer factor	64	13.2	13.2	26.5	30.9	16.2	1.8
Valium	125	23.1	21.5	34.3	17.2	3.7	0.5
Xanax	134	25.0	29.8	27.8	18.4	8.9	0.6
Glutathione in nasal spray	54	18.2	17.8	35.3	25.0	5.9	0.9
Glutathione in nebulizer	33	18.0	10.0	22.0	26.0	24.0	1.8
Other							
Changed residence	933	2.9	4.5	8.0	42.3	44.3	11.7
Enzyme-potentialized desensitization	81	18.1	10.3	1.8	20.8	32.4	1.8
Nasal/lipid desensitization	297	3.8	3.8	38.6	31.0	22.9	7.1
Magnets	255	11.1	9.0	40.4	20.4	11.1	1.6
Prayer	609	0.7	0.7	34.4	35.6	28.6	48.3
Faith-healer	127	3.1	1.8	51.8	25.8	18.0	9.3
Exercise	783	4.3	10.4	23.7	40.3	21.3	4.2
Hypnosis	111	7.1	6.3	60.3	16.7	9.5	1.9
Psychotherapy to cure MCS	200	6.6	8.0	65.1	15.5	4.7	1.4
Psychotherapy to cope with MCS	382	3.8	7.0	24.1	47.7	17.3	8.0
Support group	520	1.5	2.2	15.5	42.3	33.6	8.7

*Ratio of number reporting help to persons reporting harm.

Chemical Avoidance

Very harmful	0.5%
Somewhat harmful	0.3%
No effect	4.7%
Somewhat helpful	38%
Very helpful	56.5%

Gibson PR et al. Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity. Environ Health Perspect. 2003 Sep;111(12):1498-504.

Rotation Diet

Very harmful	1.6
Somewhat harmful	4.1%
No effect	22.1%
Somewhat helpful	44%
Very helpful	28.2%

Environmental Control Unit

- Developed in 1950's, USA
- A hospital unit to isolate patients, de-adapt them from their environment, and reintroduce agents one-by-one
- Attention to air, water, food
- All Hospital based Environmental Control Units in this country have been shut down
 - Germany, Japan

Environmental Control Unit Protocol

- Highly Individualized
- Day One
 - Admitted to unit
 - History and physical examination with extensive environmental, dietary, and occupational history.
 - Routine laboratory testing was performed.
 - No inhalants on the unit

Environmental Control Unit Protocol

- Stage 1: Approximately 5 to 7 days
- Fasting stage
 - Patients fasted on distilled spring water
 - Monitored for withdrawal symptoms: headache, nausea, vomiting, myalgias, arthralgias, etc.
 - Alkaline salts: 2:1 NaHCO₂:KHCO₂
 - Monitored for electrolyte abnormalities, dehydration: Rehydrate with IV, glass bottles
 - Fast terminated when withdrawal symptoms end

Environmental Control Unit Protocol

- Stage 2: Approximately 10 to 20 days
- Food testing to establish a safe diet
- 'Suspected Safe' Foods eaten on rotation
- Each meal consisted of single organically grown pure food
- Monitor for adverse reactions

Environmental Control Unit Protocol

- Stage 3: Approximately 7 days
- Food testing to test highly suspect foods, pesticides, additives
- Patients continue their safe diet on 5 to 7 day rotation
- Highly suspect foods and contaminated foods introduced as single feedings, one by one

Environmental Control Unit Protocol

- Stage 4: Approximately 7 days
- Chemical testing
- Highly individualized
- Challenge testing to natural gas, vehicle exhaust, items from home

Environmental Control Unit Protocol

- Stage 5: Discharge
- Patients have been taught to evaluate reactions and avoid those things that make them sick
- Patients instructed to continue rotation diet of safe foods
- Patients instructed to modify home and work environment, automobile, etc.

Residence Inn Dallas Central Expressway
10333 North Central Expressway
Dallas, Texas 75231 USA
Phone: 1-214-750-8220
Fax: 1-214-750-8244
Sales: 1-214-622-1010
Sales fax: 1-214-750-8244



Sauna

	At clinic	At home
Very harmful	7.1	7.1
Somewhat harmful	7.7	11.4
No effect	20.6	19.6
Somewhat helpful	30.3	38.8
Very helpful	34.2	23.1

pharmaceuticals

	Prozac	Zoloft	Elavil	Valium	Xanax
Very harmful	37.8	45.5	33.9	32.4	19.6
Somewhat harmful	21.5	22.7	23.6	17.9	15.7
No effect	25.9	23.4	27.3	27.2	24.5
Somewhat helpful	9.7	5.8	9.7	17.6	24.5
Very helpful	5.4	2.6	5.5	5.1	15.7

Provocative-neutralization

- Skin testing with allergens and chemicals
- Serial dilutions
- Monitor response
 - Wheal & flare
 - symptoms
- Neutralization dose is one dose before the dose that produces wheal & flare [skin reactivity] or dose that ablates symptoms

Provocative-Neutralization

	With preservatives	Without preservatives	Without glycerine or preservatives
Very harmful	22	11.9	12.5
Somewhat harmful	18.1	12.8	8.3
No effect	25.4	29.3	25
Somewhat helpful	27.1	31.4	30.2
Very helpful	7.3	15.5	24

Provocative-Neutralization: Baylor ENT Study

- 37 patients, 5 foods
- Comparison of IPFT SK and IPFT PR with oral food tests
- Double-blinded, 3 tests 7 days apart
- validity coefficients, 0.78 & 0.61, $p < 0.01$
- Reliability coefficients, 0.68 and 0.40, $p < 0.05$

King WP et al. Provocation-neutralization: a two-part study. Part I. The intracutaneous provocative food test: a multi-center comparison study. *Otolaryngol Head Neck Surg.* 1988 Sep;99(3):263-71

Provocative-Neutralization: Nova Scotia Study

- 13 foods, 9 chemicals, and 4 placebos
- 132 people, double-blind, randomized study
- Reaction by ***symptoms*** to foods, chemicals, and normal saline solution showed a random pattern, although wheal reactions showed a distinct pattern.

Fox RA et al. Intradermal testing for food and chemical sensitivities: a double-blind controlled study. J Allergy Clin Immunol. 1999 May;103(5 Pt 1):907-11.

Nutrients

- Rational: co-factors for detoxification, nutrient elimination
- Well accepted adjuncts for certain acute poisonings
 - Folate for methanol poisoning
- Extensively used in alternative and Complementary Medicine practice

Nutrients

- Given both IV and PO
- Relatively safe
- Testable by double-blinded, placebo controlled challenge

Insecticides & chemical sensitivities

- Agricultural workers with acute organophosphate insecticide poisoning
- Intolerance of previously tolerated agricultural and other chemicals.

Tabershaw IR, Cooper WC. Sequelae of acute organic phosphate poisoning. J Occup Med. 1966 Jan;8(1):5-20.

Insecticides & chemical sensitivities

- 125 people
- Well-documented exposure to cholinesterase inhibitor or remodeling
- Developed chemical sensitivities
- Sx severity > in insecticide group
- Employment: 81% to 12.5%

Miller CS, Mitzel HC. Chemical sensitivity attributed to pesticide exposure versus remodeling. Arch Environ Health. 1995 Mar-Apr;50(2):119-29.

Plasma Levels of substance P, VIP, NGF

- Controlled study
- Three groups
 - MCS
 - Atopic eczema/dermatitis
 - Normal control group
- Measurements at baseline and after chemical challenge
 - Oil based paint

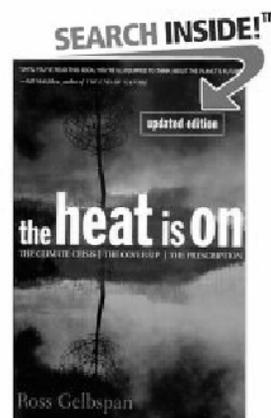
REF: Kimata H. Effect of exposure to VOCs on plasma levels of neuropeptides, NGF & histamine in patients with self-reported chemical sensitivity. Int J Hyg Environ Health 2004;207:159-163.

Results

- Baseline plasma levels of SP, VIP, NGF, but not histamine were elevated in MCS group but not other groups.
- VOC exposure increased plasma SP, VIP, NGF in MCS pts but not other two groups.
- Exposure to VOCs increased skin wheal response to histamine in MCS but not other two groups.

Suppression of Environmental Medicine in the USA

- Small group of physicians
- Close ties to commercial interests
- Anecdotal, no scientific evidence
 - Absence of evidence is not evidence of absence
 - There is evidence
- Argumentum *ad hominem*
 - attack the person, not the argument.



Suppression of Environmental Medicine in the USA

- Position statements: pts are crazy & doctors are quacks
 - AMA, AAAAI, California Medical Society
- Industry funded conferences
 - After National Research Council Conference recommended federal funding of ECU
- Lobbied insurance companies to deny payment
- Physicians lost their licenses
- Network TV shows roasting physicians & patients

Recommendations from US Federal Advisory Groups

- NAS sub-committee on Immunotoxicology, Washington, DC, 1991
- NRC Workshop on Multiple Chemical Sensitivity, Irvine, 1991
- Expert Panel on Multiple Chemical Sensitivity, ATSDR, 1993
- Exp Approaches to Chemical Sensitivity, EOSI & NIEHS, Rutgers, 1995
- CDC Gulf War Syndrome Meeting, Atlanta, 1999
- ? Research Advisory Committee on Gulf War Illnesses

**Environmental Medicine
&
Gulf War Illnesses:
Does the map fit the territory?**

**Environmental Medicine
&
Gulf War Illnesses:
Does the map fit the territory?**

yes

Gulf War Illnesses & Chemical Sensitivities: Similarities

- Onset with exposure to *diverse noxious agents*
- Similar or same Multi-organ system complaints
 - Neurocognitive, Fatigue, etc
- Poor response to pharmaceutical therapies
- Persistence
- Association with organophosphate exposures
- Autonomic dysfunction

Research Suggestions

- **Controlled study of plasma levels of Substance P, nerve growth factor, VIP**
- **Clinical trial of substance P antagonists**
 - Aprepitant, Emend®
- **Environmental control unit**
 - ? Collaboration with EHC-D
- **Upper airway evaluations**
 - Characteristic findings, nasal washings for NGF, ...

Presentation 14 – Beatrice Golomb

**Update on Research in
Persian Gulf War Veterans
Illnesses**

July 2007

Beatrice Alexandra Golomb, MD, PhD

TOPICS

- I. Epidemiology**
- II. Human Markers**
- III. Exposure Effects: Animals**
- IV. Human Gene or Gene-Environment**
 - ALS**
 - CFS (Dr. Kerr)**
 - MCS**
- V. Human Treatments**

Epidemiology

- **Physical Sx Persist in GWV**
- **Mental Sx Persist but may Somewhat Abate in GWV**
- **GWV have increased pain**

Symptoms Persist in GWV

Finding: Little change sx # or severity on 5yr f/u.

Ss: 390 randomly selected from previously surveyed members of US DVA Gulf War registry who completed time-1 & time-2 survey
At time 1 divided into low vs hi sx clusters (mean 14 & 35sx).

Design: Mailed symptom survey questionnaires with 48 sx identical to time 1. Assess if "persistent or recurring" sx in the last 6 mo; and whether "mild," "moderate" or "severe"

Time 1: year 1995, 2011 GWV, 60% response

Time 2: year 2000: 60% of orig cohort "randomly" mailed 1-pg questionnaire, 2 wks B4 scheduled phone interview.

71% of these completed.

Ozakinci 2006 *Environ Health Perspect* 114:1553 Persistence of symptoms in veterans of the First Gulf War: 5-year follow-up.

Symptoms Persist in GWV

Outcomes: severity; change in # sx; cluster membership

Analysis: Effect of time on outcomes by Repeated measures Mancova

Adjusted for: age, sex, rank, race, marital, educ, branch service, duty (active vs NatGuard/Reserve), smoker.

Also: cluster membership Highly symptomatic (40%) vs mod (60%) at time 1, except if this is outcome.

Ozakinci 2006 *Environ Health Perspect* 114:1553 Persistence of symptoms in veterans of the First Gulf War: 5-year follow-up.

Symptoms Persist in GWV

Result: Little change in sx number or severity with time over 5 yrs.

Sx number similar: 22.1 (12.9) → 22.7 (12.9), NS (p = 0.14)

Sx severity similar: 0.83 (0.62) → 0.84 (0.62), NS

Mildly symptomatic time 1: showed ↑ +2.3 sx after adjust ANCOVA

Highly symptomatic time 1: showed a ↓ -2.0, p < 0.001

[BUT: "regression to the mean" for vbls w measurement variability: Regression dilution bias]

Black race & older age associated with increase in sx

Similar findings for sx severity.

Interpretation: "The symptom outbreak following the 1991 Gulf War has not abated over time in registry veterans, suggesting substantial need for better understanding and care for these veterans"

Pain is increased in GWV

Finding: "A higher proportion of veterans of the PGW reported sx of pain than military comparison groups"

Design: Weighted "meta-analysis" of published studies assessing pain in GWV vs comparison veteran group.

20 studies that include prevalence of some type of pain in GWV and comparison group of nonGulf veterans

	OR	95% CI
Abd:	3.2	2.3-4.5
Muscle	3.1	2.2-4.3
Joint	2.8	2.3-3.4
Chest pain	2.5	2.2-2.9
Back pain	1.6	1.2-2.0

Thomas 2006 BMC Musculoskeletal Disorders 7:74. Pain in veterans of the Gulf War of 1991: a systematic review

Mental Health Probs in GWV

Finding: Increased mental health problems in GWV starting at deployment and present at reduced rate 10 yrs later.

Design: Assess prevalence of mental disorders in GWV vs non, beginning in deployment period, and continued prevalence 10 years later, *based on retrospective report.*

Ss: 1016 deployed veterans vs 1128 nondeployed veterans, from National Health Survey of Gulf War Veterans and their Families in 1995, a stratified random sample from 15,000 each were examined.

Evaluation period: 1998-2001

Called "Gulf Era Onset" if reported onset btn Jan 1 1991 and Jul 30 1993 (not by whether they were in the Gulf then)

Toomey, Kang, Karlinsky, Baker, Vasterling, Alpern, Reda, Henderson, Murphy, Eisen Br J Psychiatry 190: 385

Mental Health is Reduced in GWV

Outcomes:

Mental disorders diagnosed by structured clinical interviews, with onset time by self-report (not blinded to GW participation state)

- Clinician Administered PTSD Scale
- BDI Beck Depression Inventory
- BAI Beck Anxiety Inventory
- SF-36 for QOL, Mental Component Summary only
- Quality of Life Inventory: satisfaction with 16 domains of QOL.

Toomey, Kang, Karlinsky, Baker, Vasterling, Alpern, Reda, Henderson, Murphy, Eisen Br J Psychiatry 190: 385

Mental Health is Reduced in GWV

Outcomes:

53% participation rate of those solicited to participate. Participants more likely older, white, women, reservists and National Guard, officer, and army vs other.

Deployed group 2yr younger, more AA, less educated, less likely married, less likely officers.

0.9 or higher interrater reliability on most sx; 0.77 for current PTSD

Analysis: Linear or logistic regression weighted for stratification (probability of sampling)

Adjustments: age, gender, ethnicity, education (dichotomized at 12yrs), duty type (active v reserve/guard), branch (army/marine v Navy/air force), rank (officer v not)

Toomey, Kang, Karlinsky, Baker, Vasterling, Alpern, Reda, Henderson, Murphy, Eisen Br J Psychiatry 190: 385

Mental Health in GWV: Current

	GWV	Nondeployed	p (adjusted)
SF-36 MCS mean	49	53	<0.0001
PTSD checklist score	28	23	<0.0001
BeckDI mean score	7.8	4.7	<0.0001
Mod/severe %	10.6	4.9	<0.0001 by group
BeckAI mean score	4.8	2.8	<0.0001
QOL inventory			
%V.low	15	8	0.002 by group
%“below average”	25	16	

By group p-values were based on all groups: min,mild,mod,severe; or vlow, low, average, high

Implications: The prevalence of GEO anxiety, depression, PTSD “abates with time” – but is still increased.

Toomey,Kang, Karlinsky, Baker, Vasterling, Alpern, Reda, Henderson, Murphy, Eisen Br J Psychiatry 190: 385

Mental Health: Era Onset

<u>Era Onset Mental Health</u>	% GW: not	Adjusted OR	95% CI
Any mental disorder	18:9	2.1	1.4-3.1
Any mood disorder	8:4	1.9	1.1-3.3
Major Depression	7:4	1.8	1.0-3.2
Anxiety disorders	9:2	4.4	2.5-7.9
PTSD	6:1	5.8	2.6-13
Panic d/o	1.2:0.1	10.5	2.0-56
Specific phobias	1.9:0.8	2.8	1.1-7.5
Pain disorder	0.9:0.01	91.7	10.5-798.2
Brief psychotic rxn	0.2:0.9	0.23	0.06-0.91

Toomey,Kang, Karlinsky, Baker, Vasterling, Alpern, Reda, Henderson, Murphy, Eisen Br J Psychiatry 190: 385

Mental Health: Improvement over time?

War-era onset (WEO) depression 10 yrs later:

3.2%:0.8% OR 3.3 p< 0.01

Remission less likely in deployed: p = 0.048

No difference in initial severity of depression

Among depressed: ↑ co-morbid war-era onset psych d/o 46%:26%

If depression: co-morbid anxiety d/o incl PTSD: p = 0.07

PTSD- WEO 10yr later 3x ↑ (not signif: 1.8%:0.6% p = 0.12)
 nonPTSD- WEO anxiety differs 2.8:1.2%, aOR=2, p = 0.01

Toomey,Kang, Karlinsky, Baker, Vasterling, Alpern, Reda, Henderson, Murphy, Eisen Br J
 Psychiatry 190: 385

Mental Health Problems w/ WEO abate

Medication Use 4 War-Era Onset (WEO) "mental health"

Taking Meds4This @ Time of Assessment

	%GWV	%Nondeployed	p
WEO anxiety d/o still active: N=78	12	22	NS
WEO anxiety d/o that remitted N=57	5	37	0.02
WEO anxiety d/o: Current med use	8	27	

Possibilities: Different disease; different tolerance to treatment; differential care; chance

WEO depression still active N=44 (36:8)	17	33	0.43
WEO depression that remitted N=89	13	5	0.25
WEO depression: Current med use	15	11	NS

In this sample: more deployed had preGW (pre Jan 1 1991) onset nonPTSD anxiety d/o13:9% p = 0.02

Toomey,Kang, Karlinsky, Baker, Vasterling, Alpern, Reda, Henderson, Murphy, Eisen Br J Psychiatry 190: 385
 Vasterling, Alpern, Reda, Henderson, Murphy, Eisen Br J Psychiatry 190: 385

Mental Health is Reduced in GWV

Satisfaction with QOL reduced in GWV vs. nondeployed

<u>QOL DOMAIN</u>	<u>p-value</u>
health	0.0001
learning	0.001
play	0.01
self-esteem	0.02
love	0.03
goals and values	0.04
children	0.049

Toomey, Kang, Karlinsky, Baker, Vasterling, Alpern, Reda, Henderson, Murphy, Eisen Br J Psychiatry
190: 385

Human Markers

Changes in Cortisol /ACTH

Ss: 31 GWV: 20 current PTSD, 11 never PTSD, no psych d/o
16 healthy nondeployed, no gulf theater

Marker: AUC Plasma ACTH & cortisol, q 30min for 24h

Result:

GWV w/o PTSD or psych d/o, vs health OR GWV+PTSD had

- No difference in cortisol
- Signif lower 24h plasma ACTH
- Signif higher cortisol: ACTH

Comment: Self reported acute effects of pesticides and PB during deployment were assoc with lower ACTH controlling for BMI and PTSD

Changes in Cortisol / ACTH

Baseline comparability table:

- Sim demographics
- Diff sx expression

Area under the curve:

	Nondeployed			
	Healthy	PTSD+	PTSD-	P
Cortisol (C):	158	154	154	NS
ACTH (A)	638	619	419 ↓	<0.05
Ratio C/A:	0.30	0.28	0.45 ↑	<0.0005

Ug/dl-hr cortisol; pg/ml-hr ACTH

Golier 2007 *Biol Psychiatry* early e-pub

Changes in Cortisol / ACTH

Previously reported increased cortisol and ACTH suppression to dexamethasone in GWV assoc with chronic musculoskel sx

– enhanced responsivity to cortisol feedback effect may be partly responsible.

Golier 2007 *Biol Psychiatry* early e-pub

Markers in CFS: RBC oxidative stress

Finding: Increased RBC oxidative stress, morphol changes

Background: RBC metabolism and shape relate to deformability/morphology; altered morphology seen in CFS; and morphology correlates with RBC oxidative damage.

Goal: confirm these correlations.

Ss: 31 CFS; 41 “age and gender matched” “healthy controls”
10/33 male and 18/41 male; age 41+/-28 CFS, 40+/-25 control.

Outcomes:

- RBC levels of reduced glutathione (GSH); malondialdehyde (MDA); methemoglobin (metHb)
- 2,3-diphosphoglyceric acid (2,3 DPG): an RBC mb regulator, ↓ deformabil, ↓ O₂ affinity
- Scanning EM of RBC

Richards 2007 *Arch Med Res* 38: 94

Markers in CFS: RBC oxidative stress

Results:

Signif ↑ oxidative damage (prooxidant>antioxidant protection)

↑ 2,3 DPB $p < 0.05$: ↓ RBC deformability, ↓ O₂ affinity (release more

↑ MetHb, $p < 0.005$. Oxid damage Hb, ↓ RBC deformability, ↑ rigidity

↑ MDA, $p < 0.01$: Marker of lipid peroxidation

Significant RBC morphological abnormality

↑ Stomatocytes in blood vs nl ($p < 0.005$)

Interpretation:

RBC changes could be a marker of oxidative stress that may be a common cause for symptoms

RBC changes could also causally affect energetics if they affect oxygen transport to tissue – but may ↓ or ↑

Richards 2007 Arch Med Res 38: 94

Markers in FM: Oxidative Stress

Ss:

- 30 fem w/ Primary FM by ACR criteria (Am Coll Rheumatol)
- 16 “age-matched” healthy controls

Markers: TBARS/MDA, SOD, adenosine deaminase (ADA), xanthine oxidase, nitrite as index of NO production

Clinical assessments: TMS (aggregates 21 pain pressure thresholds), HAM-D, HAM-A, FM-impact questionnaire (FIQ)

Finding:

- FM have Higher TBARS (lipid peroxidation marker), Lower nitrite
- No correlation to clinical measures
- TMS scale corr. negatively with xanthine oxidase, an antioxidant

Ozgoemen 2006 Rheumatol Int 26: 598

Markers in FM: Oxidative Stress

Test		FM	Ctrl	P
TBARS	μM/L	1.4 ± 0.7	1.0 ± 0.5	<0.05
Nitrite	μM/L	51.9 ± 24.5	69.5 ± 10.9	<0.05
ADA	U/L	219 ± 73	181 ± 67	NS
SOD	U/ml	6.2 ± 2.1	6.4 ± 2.4	NS
XO	U/L	2.4 ± 0.9	2.6 ± 1.0	NS

Ozgoemen 2006 Rheumatol Int 26: 598

ANIMAL STUDIES OF EXPOSURES

- Aluminum adjuvants cause health problems
- Jet fuel promotes noise-induced hearing loss – associated with oxidative stress
- Uranium causes oxidative stress in brain
- Chlorpyrifos affects microtubules (which transport mitochondria to different parts of the cell)

Anthrax vaccine adjuvants

Goal: To examine whether adjuvant compounds might contribute to neuronal deficits associated with GWI, an animal model for examining the potential neurological impact of aluminum hydroxide, squalene, or aluminum hydroxide combined with squalene was developed.

Ss: Young, male colony CD-1 mice

Exposure: injected with “the adjuvants” at doses equivalent to those given to US military service personnel.

Outcomes: battery of motor and cognitive-behavioral tests over a 6-mo period postinjections.

Postmortem: Following sacrifice, central nervous system tissues were examined using immunohistochemistry for evidence of inflammation and cell death.

Anthrax vaccine adjuvants

Behavioral Results:

Aluminum: Motor deficits in form of progressive ↓ strength by the wire-mesh hang test (final deficit at 24 wk; about 50%).

Combined aluminum-squalene: Cognitive deficits (signif) in water-maze learning (4.3 error/trial) vs controls (0.2 error/ trial) @ 20 wk.

Postmortem Results:

Aluminum: Apoptotic neurons with signif ↑ activated caspase-3 labeling in lumbar spinal cord (255%) & primary motor cortex (192%) vs controls.

Signif motor neuron loss (35%)

↑ # of astrocytes (350%) in the lumbar spinal cord.

“The findings suggest a possible role for the aluminum adjuvant in some neurological features associated with GWI and possibly an additional role for the combination of adjuvants.”

Low dose sarin + stress affects rats

Finding: “low dose” repeat sarin + shaker stress led to delayed behavioral changes in rats and delayed endocrine effects.

Subjects: 65 Male mice

Exposures:

- **Shaker stress:** horizontal excursion of 2.9cm at 150 cycles/min x 90min/d x 7 days, as 45 2min shaking periods separated by randomized still periods of mean duration 30min (13-44min)
- **Sarin:** 64ug/kg sq x 3 days or saline control, given on shaker day 4-6 in the shaker animals

Mach 2007 J Applied Toxicol e-pub in advance of publication

Low dose sarin + stress affects rats

Test Times: 1h after 1st dose; 24h after last dose; weekly to 21d p last.

Behavioral outcomes:

1. Acoustic startle response
2. Prepulse inhibition: % inhibition of startle to noise, after give a pre-noise.

White burst noise stimulus with or without prepulse”

- **Background** 60dB
- **“Prepulse”** 70dB
- **“Pulse”** 100 or 120dB
- **Prepulse + pulse**

Each trial type 10x in 10 blocks in random order; with interval between 9-16sec

Tested in a commercial “Startle Monitor System” Version 4.0

Movements of the body (jerks) transformed into analog signal

Mach 2007 J Applied Toxicol e-pub in advance of publication

Low dose sarin + stress affects rats

Test Times: 1h after 1st dose; 24h after last dose; weekly to 21d p last.

Outcomes, continued:

3. Open field locomotion by infrared photobeams

- Locomotor activity
- Fine movement
- Rearing

4. Catecholamine determinations in homogenized adrenal glands: animals killed 7wk p last exposure. NE, Epi, DA.

Other outcomes

- Blood Cholinesterase inhibition 24h & 3wk after last sarin inj

Mach 2007 J Applied Toxicol e-pub in advance of publication

Low dose sarin + stress affects rats

Test Times: 1h after 1st dose; 24h after last dose; weekly to 21d p last.

Results:

Acoustic startle & PPI: no change (delayed, vs during AChEi w/ PB)

Activity: Sarin ↓ activity, all 3 types, $p < 0.05$. (No interaxn w stress.)

Enzymes: Sarin ↓ enz activity: ChE, AChE, BChE: all $p < 0.001$

~40% ↓ ChE, 40% ↓ BChE; 60% ↓ AChE (by graph)

Stress ↑ enzyme activity

Combination: ↓ enz activity, but less than sarin alone

Catechol content & adrenal weight: 7 wks later, homogenized adrenal

Sarin ↓ catechols: $p < .01$ NE and Epi; $p < .05$ DA

Sarin + stress increase adrenal weight vs other groups

Sarin + stress: Catechols normal

Mach 2007 J Applied Toxicol e-pub in advance of publication

Low dose sarin + stress affects rats

Test Times: 1h after 1st dose; 24h after last dose; weekly to 21d p last.

Recap:

Low dose, repeat sarin causes delayed effects, reduces rat activity; & reduces adrenal catechols

Stress modestly increases enzyme activity

Stress + sarin causes adrenal hyperplasia -- almost doubles adrenal weight, and is associated with reduced catechol activity

Elsewhere: adrenal size and catechol activity not change immediately after sarin exposure (cite their own unpublished data)

“We hypothesize that coexposure could disrupt biogenic amine balance” causing longlasting changes in autonomic fxn. (Don't seem to need coexposure, though)

18Mach 2007 J Applied Toxicol e-pub in advance of publication

AChEi Effects on Microtubules

Finding: OP decreases neuron viability – that may be associated with degradation of microtubules

“Subjects”: slice cultures of rat hippocampus and bovine tubulin

Exposure: chlorpyrifos oxon 0.1-10 μM x 1-7d

- This exposure reduces AChEi activity by 15-50%

Outcomes: assessed 1, 3, and 7 days after start of exposure

Cytotoxicity: somatic uptake of the marker propidium iodide, a “nonvital” marker; and cell damage by fluorescence microscopy

Alpha tubulin (immunoreactivity – IR) by fluorescence microscopy

Microtubulin associated protein-2 (MAP-2 IR)

Bovine microtubule outcome: Tubulin polymerization

Prendergast 2007. Microtubule associated targets in chlorpyrifos oxon hippocampal toxicity. Neuroscience 146: 330-9

AChEi Effects on microtubules

Result:

MAP: 35-45% ↓ MAP-2 (microtubule associated protein) as early as 1st measurement (1 day – 18% reduction, $p < 0.05$) and with lowest concentration 0.1 μM, dramatic after 7d, max in area CA1 & CA3 subregions of slice cultures.

Cytotoxicity: Concentration-dependent neuron injury in pyramidal cell layer of area CA1 of hippocampus and to lesser degree area CA3 and dentate cells after 3 days, at all doses, greatest after longest exposure (35% and 21% increase in PI uptake, $p < 0.005$)

Marked inhibition of polymerization of purified tubulin and MAP rich tubulin, especially the latter

No change in alpha tubulin at any time

Prendergast 2007. Microtubule associated targets in chlorpyrifos oxon hippocampal toxicity. Neuroscience 146: 330-9

AChEi Effects on brain microtubules

Conclusion:

μtubule damage was greatest in CA1-area w/ densest neurons, high energy demand
Cytotoxicity followed evidence of μ tubule injury, and *might* be related to it.

Cell death also greatest in CA1, tho ∃ higher cholinergic input to the dentate

The authors express uncertainty as to why this may be

They sugg hypotheses about AChE shown nec 4 neurite outgrowth– and speculate about apoptosis cascades sensitive to cytoskeletal integrity -- but note poor temporal assn of AChE inhibition to and increased PI uptake (24h exposure 0.1 μM not cell damage till 7 days)

They note AChEi/ CPO inhibit axon and dendrite growth at conc far below those that inhibit AChE

Comment:

CA1 especially vulnerable to cell death with energy deficits –Robert Sapolsky

Massive die-off of CA1 HC cells in mild hypoxemia coupled with stress

Possibly relevant: μ tubules transport mitochondria within the cell.

Prendergast 2007. Microtubule associated targets in chlorpyrifos oxon hippocampal toxicity. Neuroscience 146: 330-9

AChEi Effects on Learning (and cytotox)

Old Finding: “low dose” (no acute toxicity)

**repeated chlorpyrifos exposure (x14d) in rats
impaired spatial learning; inhibited axonal
transport longterm after exposure; and in cell
culture led to cell toxicity and death**

**(Exposure: CFO in peanut oil vehicle, or peanut
oil injection)**

**Terry 2003 J Pharmacology and Exp Therapeutics 305:375. Repeated exposures to
subthreshold doses of chlorpyrifos in rats: HC damage, impaired axonal transport and
deficits in spatial learning.**

Uranium and Oxidative Stress

Finding: Prooxidant effects of uranium; stress doesn't add much

Ss: Adult male rats

Exposure:

**-- Uranyl acetate dihydrate in drinking water, 0,10,20,40mg/kg/d x
34mo**

-- Restraint stress 2h/d through study in 4 of 8 groups.

**Outcome: Endogenous antioxidant capacity; oxidative damage in
several areas of the brain:**

**Reduced glutathione (GS); oxidized glutathione (GSSG);
glutathione reductase (GR); glutathione peroxidase (GPs);
superoxide dismutase (SOD); catalase (CAT); thiobarbituric acid
reactive substances (TBARS); uranium concentration**

**Linares 2007. Toxicology 236:82. Pro-oxidant effects in the brain of
rats concurrently exposed to uranium and stress.**

Uranium and Oxidative Stress

Result: U significantly accumulated in HC, c'bellum, cortex p 3 mo
UAD promoted oxidative stress in these cerebral tissues
TBARS correlated with U content in CX and Cbellum.
In Cbellum GSSG and GSH were pos and neg correlated with U
respectively.
Stress "scarcely showed additional adverse effects"

Conclusion: UAD can cause progressive perturbations on
physiological brain levels of oxidative stress markers.

Linares 2007. Toxicology 236:82. Pro-oxidant effects in the brain of
rats concurrently exposed to uranium and stress.

JP-8 Jet Fuel

Finding: JP-8 associated with GSH depletion some tissues; and promotion of
noise induced hearing loss

Background: JP-8 jet fuel = std jet fuel for US and NATO military.

Includes many compounds: toluene, xylene, nonane, undecane, octane,
ethylbenzene among many others.

Ss: 98 rats (pigmented male Long Evans)

Exposure 1: JP-8 fuel 1000mg/m³, nose only inhalation x 4hr

Current permissible exposure is 350mg/m³

Exposure 2: noise: half rats immed subjected to an octave band of noise b/n 97
dB 4h x 1 day; 97dB x 5 d and 105dB 4h x 5d

Noise alone produces a small auditory impairment

Exposure Groups:

- Neither
- Jet fuel alone
- Noise alone
- Jet fuel f/b noise

Fechter 2007 Toxicological Sciences 98: 510

JP-8 Jet Fuel

Outcomes:

Hair Cell Loss: Histology of cochlea to assess % hair cell loss (cochlea is organized tonotopically)

Oxidative stress: glutathione tissue levels

Hair cell function assessment by drop in amplitude of DPOAE = "distortion product otoacoustic emissions" (distorted tone sound energy generated in cochlea after stim with two simultaneous "primary" tones)

Hearing: CAP = compound action potentials to pure tones at ½ octave steps

Result: Jet fuel increased cochlea susceptibility to noise

GSH depleted esp in liver (antioxidant depletion)

DPOAE test especially sensitive (hair cell fxn)

Greater outer hair cell death than with noise alone.

Context: previously shown, but with longer exposure times.

Humans: toluene exposed workers had reduced auditory brainstem response vs nonexposed, Abbatae 1993; Vrea 1996 (2 yrs exposure); Morata 1997.

Rats: benzene exposed outer cell damage/ ototoxicity.

Fechter 2007 Toxicological Sciences 98: 510

Jet Fuel Context: mito mechanisms

Mitochondrial mechanisms are shown to play a role in noise induced and toxin induced hearing loss. And mitochondrial mechs in protection...

Mitochondrial dysfunction in hearing loss.

Fischel-Ghodsian 2004. Mitochondrion;4:675.

Mechanisms of noise-induced hearing loss potentiation by hypoxia.

Chen 2005. Hear Res 200:1.

Mitochondrial DNA deletion is a predisposing cause for sensorineural hearing loss. Ueda 1998. Laryngoscope 108:580.

A BAD link to mitochondrial cell death in the cochlea of mice with noise-induced hearing loss. Vicente-Torres 2006. J Neurosci Res 831:564.

Audiovestibular findings in patients with mitochondrial A1555G mutation. Noguchi 2004. Laryngoscope 114:344.

Mitochondrial role in hair cell survival after injury.

Hyde 1995. Otolaryngol Head Neck Surg 113:530.

Audiologic findings in a family with mitochondrial disorder.

Elverland 1991. Am J Otol 12:459.

Pharmacological rescue of noise induced hearing loss using N-acetylcysteine and acetyl-L-carnitine. Coleman 2007. Hear Res;226:104.

Gene-Environment

ALS vs glutathione genes

Genetic factors associated with environmental susceptibility to ALS

Ss: 186 sporadic ALS cases, 186 controls

Glutathione synthetase haplotype interacted with both metals and solvents/ chemicals to increase risk of ALS (glutathione involved in detox of both)

(Glutathione is important for protection against free radical injury/ oxidative stress; and elsewhere shown e.g. to biotransform methyl parathion, ...)

**Morahan 2007 Genetic susceptibility to environmental toxicants in ALS
Am J Med Genetics Part B: Neuropsychiatric Genetics only 14May 2007**

Recall: ALS increased in GWV

1. Armon . Excess incidence of ALS in young Gulf War veterans. *Neurology* 2004;63(10):1986-7; author reply -7.
2. Coffman. Estimating the occurrence of amyotrophic lateral sclerosis among Gulf War (1990-1991) veterans using capture-recapture methods. *Neuroepidemiology* 2005;24(3):141-50.
3. Haley. Excess incidence of ALS in young Gulf War veterans. *Neurology* 2003;61(6):750-6.
4. Horner. Prospective study of military service and mortality from ALS. *Neurology* 2005;65(1):180-1; author reply -1.
5. Horner. Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. *Neurology* 2003;61(6):742-9.
6. Weisskopf. Prospective study of military service and mortality from ALS. *Neurology* 2005;64(1):32-7.

ALS linked to metal detoxifying genes

Genetic factors associated with environmental susceptibility to ALS (186 sporadic ALS cases, 186 controls)

Metallothionein gene and metal transcription factor gene differed significantly.

Morahan 2007 Genetic susceptibility to environmental toxicants in ALS. *Am J Med Genetics Part B: Neuropsychiatric Genetics* only
14May 2007

ALS linked to PON genes

Case control: 143sALS patients and 143 matched controls

PON1 promoter allele reduces PON expression

- Strongly associated with sALS

Haplotypes associated with increased expression

- Associated with controls.

Morahan 2007 Gene environment study of PON1 gene and pesticides in ALS. *NeuroToxicology* 28: 532-40.

Prior reports link other PON polymorphisms to ALS:

- 1. Saeed M, Siddique N, Hung WY, et al. Paraoxonase cluster polymorphisms are associated with sporadic ALS. *Neurology* 2006;67(5):771-6.**
- 2. Slowik A, Tomik B, Wolkow PP, et al. Paraoxonase gene polymorphisms and sporadic ALS. *Neurology* 2006;67(5):766-70.**

And: ALS Linked to Chem Exposures

Ss: 179 sALS cases and 179 age-, ethnicity- and sex-matched controls in Australia

sALS linked to

- Solvent/chemical exposure: OR 1.9 (1.3-2.9)**
- Overall herbicide/pesticide exposure: OR 1.57 (1.03-2.4)**
- Industrial herbicide/pesticide exposure: OR 5.58 (2.1-15)**

Exposure to herbicides/pesticides showed a dose-response effect

Morahan 2006 Amyotrophic lateral sclerosis and exposure to environmental toxins: an Australian case-control study. Neuroepidemiology 27: 130

MCS and Detoxifying/ Antioxidant Genes

Ss: 521 unrelated Ss agreed to participate, of 800 Ss who answered a Q-aire of 10 items re: severity of chemical sensitivity

Genetics: Analyze variants of genes involved in detoxification of ubiquitous chemical substances for which variants have been shown to influence metabolism of ubiquitous chemicals.

N-acetyltransferases: NAT2 gene

Glutathione S-transferase: GSTM1, GSTT1, GSTP1 genes

Result: With vs w/o self-reported chemical sensitivity differ signif in distribution of gene variants for NAT2, GSTM1, GSTT1:

- NAT2 slow acetylator: OR 1.8 (1.3-2.6)**
- Homozygous deletion of GSTM1: OR 2.1, 1.5-3.0, p = 0.0001**
- Homozygous deletion of GSTT1: OR 2.8, 1.7-4.8, p = 0.0001**

Schnakenberg 2007. *Environmental Health* 6:6. A cross-sectional study of self-reported chemical-related sensitivity is associated with gene variants of drug-metabolizing enzymes. (Germany)

MCS and Genes

GST enzymes (GSTM1, GSTT1, GSTP1) protect cells and organs from oxidative stress by conjugation of glutathione: detoxify a large range of compounds generated by reactive oxygen species induced damage to intracellular molecules.

Deletion of GSTM1 or GSTT1 lead to loss of protection against oxidative stress.

N-acetylation is an important mechanisms for inactivating arylamines.

Schnakenberg 2007. *Environmental Health* 6:6. A cross-sectional study of self-reported chemical-related sensitivity is associated with gene variants of drug-metabolizing enzymes. (Germany)

MCS-Gene - Context

Complements prior finding of altered chemical detoxification in MCS¹

Complements prior study presented here

Relevance to GWV:

GWV – esp exposed to pesticides – have high rates of MCS²

1997-8 cross-sectional survey of 3 UK military cohorts

MCS in Gulf, Bosnia, Era cohorts was 1.3%, 0.3%, and 0.2%

GWV (n=3,531); Bosnia (n=2,050); Gulf Era nondeployed (n=2,614)

GWV: MCS associated pesticide exposure

adjusted OR: 12.3 95% CI: 5.1- 30.0

¹ McKeown-Eyssen 2004, Case-control study of genotypes in multiple chemical sensitivity: CYP2D6, NAT1, NAT2, PON1, PON2 and MTHFR. *Int J Epidemiol* 33(5):971-8.

² Reid 2001. Multiple chemical sensitivity and chronic fatigue syndrome in British Gulf War veterans. *Am J Epidemiol*;153(6):604-9.

Chemical Sensitivity and Genes

Cases: Hamburg, Germany 8800 randomly selected volunteers from a general practice completed the questionnaire.

Rates severity of sensitivity to each of 10 common items from 1=not at all, 2 = moderate, 3 = disabling.

Possible score: 10-30.

Score >20 defined as sensitive. Score <= 20 defined as controls.

Items: Diesel or gas engine. Tobacco smoke. Insecticide. Gasoline. Paint or paint thinner. Cleaning products such as disinfectants, bleach, bathroom cleaners or floor cleaners. Certain perfumes, air fresheners or other fragrances. Fresh tar or asphalt. Nail polish, nail polish remover, or hair spray. New furnishing, carpeting, plastic shower curtain or interior of new car.

Schnakenberg 2007. Environmental Health 6:6. A cross-sectional study of self-reported chemical-related sensitivity is associated with gene variants of drug-metabolizing enzymes. (Germany)

Chemical Sensitivity and Genes

Genotyping:

DNA extraction: DNA isolated from EDTA blood (kit).

NAT2 gene amplified: sgl nt polymorphisms (SNPs) nt481, nt590, nt857 analyzed by RFLP/PCR or real-time PCR.

Use NAT2 nomenclature of the Arylamine N-Acetyltransferase Nomenclature Committee.

Genetic variants analyzed lead to a 4-allele model of the NAT2 gene which can predict the acetylator phenotype with accuracy >95% for slow and rapid acetylation.

Multiplex PCR to detect homozygous deletions of GSTM1 and GSTT1.

Schnakenberg 2007. Environmental Health 6:6. A cross-sectional study of self-reported chemical-related sensitivity is associated with gene variants of drug-metabolizing enzymes. (Germany)

Treatment

D-ribose treatment for CFS & FM

Finding: D-ribose reportedly tolerated and helpful in 5 tested domains – but in uncontrolled open label study

Rationale: D-ribose has been shown to increase cell energy synthesis in heart and skeletal muscle

Design: Uncontrolled open-label pilot study: intervention and survey mailed to subjects once enrolled.

Ss: 41 pts with physician dx of FM (by ACR criteria) and/or CFS (by CDC criteria)

Exclusion: known “severe” med or nutrient sensitivity; prior D-ribose

Intervention: D-ribose at 5gm tid till 280g used up (19 days); then send survey

Outcome: Visual analog scales of energy, sleep, mental clarity, pain intensity and well being. Patient global assessment.

Result: 66% of subjects experienced “significant improvement” on D-ribose with average increase in energy on VAS of 45%; and average improvement in well-being

Teitelbaum 2006. J Alternative & Complementary Med 12: 857-62

D-ribose treatment for CFS & FM

Scales from 1-10

Outcome	N	Pre	Post	Difference	p-value
Energy	36	3.8 (1.1)	5.5 (1.5)	1.7 (1.1,2,2)	<0.0001
Sleep	36	4.8	6.0	1.2	0.0001
Mental clarity	36	4.9	5.7	0.8	0.003
Pain	36	4.9	5.6	0.7	0.026
Well-being	36	4.3	5.6	1.3	<0.0001

Global subjective

Much better:	14%
Somewhat better:	49%
Somewhat better/no change	2.9%
No change:	26%
No change/somewhat worse	3%
Somewhat worse	6%
Much worse	0%

Teitelbaum 2006. J Alternative & Complementary Med 12: 857-62

Effect of Treatment in FM

Ss:

30 females with primary FM by ACR criteria (Am College Rheumatology), age 37

16 "age-matched" healthy controls mean age 33

Design: uncontrolled, unblinded pre-post

Intervention: 8 wk

- amitripyline 20/d or
- sertraline 100/d

Outcomes: HAM-A; HAM-D; FIQ =FM impact Q-aire; TMS = summed 21 point pain pressure thresholds

Ozgcimen 2006 Rheumatol Int 26: 598

Effects of Treatment in FM						
	Amitriptyline N=12			Sertraline N=18		
Test	Pre	Post	P	Pre	Post	p
FIQ-pain	70	38	.008	57	35	.02
FIQ-fatigue	65	46	.12	55	27	.006
TMS	87	95	.24	88	91	.08
Ham-D	17	9	.005	17	9	.001
HAM-A	18	11	.005	21	10	.001

SOD, XO, TBAES, NO, ADA: no effect
TMS is sum of pain pressure thresholds at 21 sites
FIQ = fibromyalgia impact questionnaire
Ozgcmen 2006 Rheumatol Int 26: 598

Presentation 15 – Lea Steele

2007 RAC Report

Discussion of Recommendations

Lea Steele, Ph.D.
July 18-19,2007

☆☆☆ **RAC-GWVI**
Research Advisory Committee On Gulf Air Watershed Studies

2007 RAC Report: Recommendations

- **Comments, changes since last discussion**
- **Additional recommendations**
- **Timeline**

☆☆☆ **RAC-GWVI**
Research Advisory Committee On Gulf Air Watershed Studies

2007 RAC Report: 5 Sections

1. Overview of the issue, population research, prognosis and treatments
2. “Causes” of Gulf War illness: summary and synthesis of info on GW-related exposures
3. “Nature” of Gulf War illness
4. Federal Gulf War research programs and spending
5. Research priorities and recommendations



RAC-GWVI
Research Advisory Committee On Gulf War Veterans' Illnesses

Report: Comments, changes since last discussion

- ***Executive summary***, emphasis, take-home points
 - *Gulf War illness: a serious condition that affects a lot of people*
 - *Comprehensive review of extensive research provides consistent picture*
 - *Questions are answerable*



RAC-GWVI
Research Advisory Committee On Gulf War Veterans' Illnesses

Report: Additional Recommendations

- Need for continuing longitudinal studies ??
- Determine if chemical exposures after the war precipitate, exacerbate veterans' condition(s)?



RAC-GWVI

Research Advisory Committee On Gulf War Veterans' Health

Report: Additional Recommendations

Possible Recommendations:

- That VA continue to conduct follow-up studies of Gulf War veterans from their national sample to monitor the onset and progression of Gulf War illness and other conditions affecting Gulf War veterans.
?? At regular intervals? 5 year intervals?
- That epidemiologic studies of Gulf War veterans collect data on onset and/or exacerbation of Gulf War illness and other conditions in relation to exposure to hazardous substances subsequent to Gulf War service.
?? Name specific types of exposures? (e.g. pesticides, solvents)?



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Research Advisory Committee On Gulf War Veterans' Health

Report: Additional Recommendations

- **Recommendations re: IOM “Gulf War and Health” series**
 - **Reports mandated in 1998 by Congress in PL105-277, PL105-368**
 - **To advise Secretary of VA on decisions concerning benefits compensation, VA was directed to contract with IOM (or other appropriate scientific organization) to:**

“review and evaluate the available scientific evidence regarding associations between illnesses and exposure to toxic agents, environmental or wartime hazards, or preventive medicines or vaccines associated with Gulf War service.”



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Research Advisory Committee On Gulf War Veterans' Health

Additional Recommendations IOM “Gulf War and Health” series of reports

“Gulf War and Health” series

- **Now includes six volumes, hundreds of findings**
- **Methodology for preparing reports based on IOM series that reviewed evidence re: Agent Orange and diseases in Vietnam veterans**



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Additional Recommendations IOM "Gulf War and Health" series of reports

Goal of the process is to assign the level of evidence linking individual exposures with individual diseases

1. "Sufficient evidence of causal relationship"
2. "Sufficient evidence of an association"
3. "Limited/suggestive evidence of association"
4. "Inadequate/insufficient evidence of association"
5. "Limited/suggestive evidence of no association"



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Additional Recommendations IOM "Gulf War and Health" series of reports

Charge to VA/IOM, as directed by Congress (PL 105-277, PL-368)

Sec. 1603 c) Identify Agents and Illnesses

- A. Identify hazardous substances to which Gulf War military personnel were exposed
- B. Identify illnesses (including diagnosed and undiagnosed illnesses) that occur at higher prevalence in Gulf War veterans



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Additional Recommendations IOM "Gulf War and Health" series of reports

Approach directed by Congress (PL 105-277, PL-368)

Sec. 1603 e) Determination of Assoc Between Agents and Illnesses

- A. Determine if there is a statistical association between the exposure and the illness**
- B. Determine if there is an increased risk of illness in human or animal populations exposed to the hazardous substance**
- C. Determine if there is a plausible biological mechanism or other evidence of a causal relationship between exposure and illness**



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Additional Recommendations IOM "Gulf War and Health" series of reports

Approach used by IOM in preparing reports

- Generated numerous conclusions determining strength of evidence re: associations between individual exposures and many diagnosed medical conditions**
- Determinations re: levels of evidence rely exclusively on human studies (primarily occupational studies)**
- Almost no information re: exposures in relation to conditions that do (or might) affect Gulf War veterans at excess rates: GWI, ALS, symptom complexes, migraines, seizures, etc**



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Additional Recommendations IOM "Gulf War and Health" series of reports

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Additional Recommendations IOM "Gulf War and Health" series of reports

Findings from Vols 1 – 3 (DU, PB, Sarin & Vaccines, Solvents & Pesticides, Fuel Combustion)

231 conclusions: 134 related to cancers (all types: e.g., childhood cancers, breast cancer, leukemia)

- * 3 findings indicating "sufficient evidence of causal relationship"
 - *Benzene and aplastic anemia*
 - *Benzene and acute leukemia*
 - *Sarin and acute cholinergic syndrome*
- * 6 findings indicating "sufficient evidence of an association"
- * 22 findings indicating "limited/suggestive evidence of association"



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Additional Recommendations IOM "Gulf War and Health" series of reports

Major Problems

- Lengthy reports with lots of findings, but few directly relevant to health problems associated with Gulf War service
- Findings based on human studies only
- Selective reporting of available studies

Statute not followed: reports largely peripheral to the purpose for which they were mandated

- Problems due to restrictions in the approach used, studies considered (occupational studies of dx diseases)



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Additional Recommendations IOM "Gulf War and Health" series of reports

Examples

- Updated sarin report requested by Sec. Principi due to new info from animal studies; but panel did not consider animal studies in drawing conclusions
- Reports do not consider findings from epidemiologic studies of Gulf War veterans re: associations of GWI w/ exposures
- Prevalence of "multisymptom illness" reported from one selected study



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IOM “Gulf War and Health” series of reports Possible Recommendations:

The Institute of Medicine’s “Gulf War and Health” series of reports, as commissioned by VA, have not adhered to requirements set forth by Congress in mandating the reports. As a result, they have not comprehensively addressed key questions regarding Gulf War-related health conditions in relation to Gulf War exposures.

The Committee therefore recommends:



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Research Advisory Committee On Gulf War Veterans' Health

IOM “Gulf War and Health” series of reports Possible Recommendations:

- > That VA, in commissioning reports mandated by Congress in PL 105-277 and 105-368, substantially change the approach used for reviewing scientific information and preparing the reports. As directed by Congress, conclusions should be based on findings from the full range of human and animal studies that provide information on effects of Gulf War-related exposures, as well as both diagnosed and undiagnosed illnesses affecting Gulf War veterans.
- > That VA contract with the Institute of Medicine, or other appropriate scientific organization, to redo previously completed Gulf War and Health reports to adhere to requirements set forth by Congress
- > That responsibility for contracting reports mandated by PL 105-277 and PL 105-368 be reassigned from VA's Office of Public Health and Environmental Hazards to VA's Office of Research and Development.



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Research Advisory Committee On Gulf War Veterans' Health

2007 RAC Report

- Comments, changes since last discussion
- Additional recommendations
- **Timeline**



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Research Advisory Committee On Gulf War Veterans' Illnesses