#### Using Multiple Brain Imaging Approaches to Understand How the Brain is Failing When GW Veterans Have Symptoms

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# **Typical Symptoms of Gulf War Syndrome**

- Chronic fatigue
- Cognitive problems (memory, attention, word-finding)
- Personality change (depression, anger, hyperarousal)
- Sensory changes (joint pain, paresthesias, headaches)
- Balance disturbances (vertigo attacks)
- Autonomic dysregulation (diarrhea, hot flashes)
- Unrefreshing sleep
- Skin rash (folliculitis over chest)
- Sexual dysfunction

Mostly subjective symptoms without objective signs.

# **Environmental Exposures** in the 1991 Gulf War\*

- OP chemical warfare agents (sarin, cyclosarin)\*\*
- OP pesticide spraying
- **OP pesticides on uniforms**
- **DEET insect repellants**
- Pyridostigmine bromide
- Ciprofloxacin
- Chloroquine
- Multiple immunization including anthrax vaccine

- Smoke from oil well fires
- Fumes from jet fuel sprayed on roads
- Fumes from burning jet fuel in tent stoves
- Petroleum in drinking water
- Depleted uranium
- CARC pain
- Combat stress/PTSD

\*Defense Science Board 1994; NIH Consensus Conference 1994; etc. \*\*Pentagon officially denied that chemical weapons were in theater. Conducted a Survey in a Reserve Seabees Battalion 24<sup>th</sup> Reserve Naval Mobile Construction Battalion\* December 1994 – February 1995

	PAR PAR PAR PAR PAR PAR PAR PAR PAR PAR	<u>P4R</u>
Name Tag Number	Name Tag Number	L STATUS
Survey of Symptoms and Exposures In Veterans of the Persian Gulf War	vey of Symptoms and Exposures elerans of the Persian Gulf War	
Part 1. Exposure Survey	Part 2. Symptom Survey	
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Knoxville Birmingham Winston-Salem Charlotte Atlanta

\*Seabees uniquely go all over the theater, and this was the only Reserve seabees battalion.

#### Factor Analysis of 52 Symptom Scales Identifying 6 Possible Gulf War Syndromes



Syndrome			
actor	<b>Description</b>	N	
1	Impaired		
	Cognition	12	
2	<b>Confusion-</b>		
	Ataxia	21	
3	<b>Central Pain</b>	22	
<b>4-6</b>	Subtypes of		
	Syn 2	36	
		()	

Total syndromic63Ill but not syndromic116Remained well70

JAMA 1997;277:215-222.

Structure of Gulf War Syndrome in Two Different GW Veteran Samples

JAMA 1997;277:215-222. Psych Res 2001;102:175-200.



# Comparison of Syndromes On Percentage Employed in 1995 (N=249)



Functional Status (MOS SF-36) of 22 III GW Veterans vs 16 Well Veterans (Top) and 6 Reference Medical Conditions (Bottom)



Am J Public Health 2001;45:121-2.

### **Epidemiologic Study of Risk Factors for Haley Gulf War Syndromes (N=249)**

<u>Syndrome</u>	<b>Exposure</b>	<u>RR</u>	<u>P value</u>
1	Wore flea collar (chlorpyrifos)	8.2	.001
Impaired cognition	Military security	6.4	.007
2	Chemical nerve agent exposure	7.8	<.0001
Confusion-ataxia	Many advanced side effects of PB	32.4	<.0001
	N.E. Saudi on 4 <sup>th</sup> day of Air War*	4.3	.004
3	Many advanced side effects of PB	5.1	<.0001
Central pain	Index of DEET insect repellant use	7.8	<.0001
*Paths cross	ed near Khafji on Jan. 19-20, 1991.		

JAMA 1997;277:215-222.

# Soldiers who were near Khafji on 19-20 Jan. had the highest rate of Gulf War illness (Syndrome 2).



The 4 main U.S. troop concentrations during the Air War From the 249 Surveyed Veterans Selected Smaller Samples for Case-Control Studies of Brain Function and Serologic Markers

• 23 ill veterans ("cases") **5** Syndrome 1 **13 Syndrome 2 5** Syndrome **3** • 20 well veterans ("controls") (from the same battalion and age-sex-education-matched to cases)

# Positive Results On Neurophysiologic Tests



JAMA 1997;277:2223-230.

# Jan. 15, 1997 Issue of JAMA

Reprinted from JAMA @ The Journal of the American Medical Association January 15, 1997 Volume 277 Copyright 1997, American Medical Association

#### **Original Contributions**

#### Is There a Gulf War Syndrome?

Searching for Syndromes by Factor Analysis of Symptoms

Robert W. Haley, MD; Thomas L. Kurt, MD, MPH; Jim Hom, PhD

# Evaluation of Neurologic Function in Gulf War Veterans

#### A Blinded Case-Control Study

Robert W. Haley, MD; Jim Hom, PhD; Peter S. Roland, MD; Wilson W. Bryan, MD; Paul C. Van Ness, MD; Frederick J. Bonte, MD; Michael D. Devous, Sr, PhD; Dana Mathews, PhD, MD; James L. Fleckenstein, MD; Frank H. Wians, Jr, PhD; Gil I. Wolfe, MD; Thomas L. Kurt, MD, MPH

#### Self-reported Exposure to Neurotoxic Chemical Combinations in the Gulf War

A Cross-sectional Epidemiologic Study

Robert W. Haley, MD; Thomas L. Kurt, MD, MPH

# **Genetic Predisposition: Paraoxonase (PON1) Enzyme Assay**





Dr. Bert La Du U. of Michigan

# Lower PON1 Type Q Allozyme Levels in Blood of III Gulf War Veterans than Controls





Con Syn 1 Syn 2 Syn 3 Patient Group *Toxicol Appl Pharmacol* 1999; 157: 227-233 Brain Scanning with Nuclear Magnetic Resonance Spectroscopy (MRS Scan)



# **3 Brain Regions Scanned by MRS**

### Left BG

# **Right BG**

### **Brain stem**







Rear view

Side view

## Chemical Analysis from an MRS Scan Of Normal Brain



# Chemical Analysis of Right Basal Ganglia In Control and Ill Gulf War Veteran



### **NAA Concentration in Basal Ganglia** Haley Syndromes 1-3 vs Controls



#### **Tests of Autonomic Function**

Embargo Date: September 27, 2004, 5:00 a.m. EST October 1, 2004, The American Journal of Medicine, Volume 117, No. 7

#### Blunted Circadian Variation in Autonomic Regulation of Sinus Node Function in Veterans with Gulf War Syndrome

Robert W. Haley, MD, Wanpen Vongpatanasin, MD, Gil I. Wolfe, MD, Wilson W. Bryan, MD, Roseanne Armitage, PhD, Robert F. Hoffmann, PhD, Frederick Petty, PhD, MD, Timothy S. Callahan, PhD, Elizabeth Charuvastra, RN, William E. Shell, MD, W. Wesley Marshall, MD, Ronald G. Victor, MD





# Gulf War Illness Research Program 2006-2012



## 1. National Survey and Tissue Bank

#### • National Survey

- Data collection completed with approx. 8,000 responses
- Data analysis begun
- Factor analysis case definition shows good fit to new data.
  - Three factor model fits best.

 Ready to select random subsamples of Syndromes 1-3 and well veterans for the Phase 2 Neuroimaging and Biomarker Study

# 1. National Survey and Tissue Bank

#### • Tissue Bank

- Present goal: collect serum, DNA, RNA from 2,092 survey participants (all syndromic and sample of well)
- Suffered a 12 month work stoppage due to unanticipated VA contract requirements.
- Resumed blood collections in November 2008
- Have collected blood, DNA from 1500 participants
- Project completion of 2,092 by fall
- Considering enlarging sample to all survey participants for genomewide association study

#### **Paraoxonase Laboratory**

- Established Paraoxonase Laboratory in 2006 (John Teiber, PhD)
- Developed automated, high throughput assays for:
  - Paraoxonase
  - Arylesterase
  - Diazononase
  - Butyryl-cholinesterase (BChE)
  - PCR genotyping of PON1, PON2, PON3 genes
  - Validated Q/R interpolation method for heterozygotes
- Completed experiments testing whether Gulf War chemicals might reduce PON enzyme activity.
- Will soon apply for CLIA Certification and begin PON/BChE assays on GW serum.

### 2. Neuroimaging and Biomarker Studies

- Purposes of the Neuroimaging studies
  - To understand the neurological basis of GWI
    - Measure brain pathology from different perspectives, all in the same group of ill and well veterans, to develop a *mosaic of evidence*.
  - To develop an objective diagnostic test for GWI
    - VA needs a brief, cost-effective set of tests to decide who has GWI for service connection and treatment.
    - Researchers need an objective measure to create groups homogeneous for a given illness to allow efficient clinical trials of treatment

– Suggest mechanisms at which to target treatment.

**Designed New Brain Imaging Tests to Probe GWV's Deficits and Respective Brain Regions** 



### **Operational Plan**

- Three phases of Neuroimaging and Biomarker Study
  - A long series of developmental pilots in normals (2005-Present)
  - Formal pilot study in 50 seabees studied in '96 & '98 (2008-9)
  - Confirmatory study in a population representative sample (Future)
- Formal Pilot Study in Seabees Battalion
  - July 2008 April 2009
  - Sample: 24<sup>th</sup> Reserve Naval Mobile Construction Battalion
    - Factor Sd 1 10
    - Factor Sd 2 14
    - Factor Sd 3 10
    - Controls 16 Total 50 (47 completed)

- Researchers still blinded to group membership

Confirmatory Neuroimaging Study in population sample (2009-2010)
– Random subsamples of syndromes and well from National Survey

### **3. Preclinical Studies Leading to Treatment**

- Originally proposed 17 basic neuroscience projects to aggressively explore the intracellular mechanisms by which GW chemicals damage brain cells to cause chronic illnesses.
- These projects were the last to be processed through the contracting process and only began in the last quarter of 2008.
- No results obtained yet

#### **3. Preclinical Studies Leading to Treatment**

- Studies funded by VA 10
- Studies to be submitted to VA soon 3
- Studies to be reviewed by MRG 2
- Studies presently on hold or withdrawn 5

### **3. Preclinical Studies Leading to Treatment**

5.0 Effects of OPs on behavior and clinical/neuroimaging parameters (MRG) 5.1 Effects of Ops/vaccines on the immunologic system (W/D) 5.2 Fate of OP-protein conjugates by proteomic analysis (MRG) **5.3 Effects of OPs on phosphorylation signaling in striatum 5.4 Effects of Ops on plasticity of cholinergic signaling** 5.5 Effects of OPs on calcium signaling in mitochondria 5.7 Effects of OPs on neuro-inflammation and NF-kB activation 5.8 Effects of OPs on neuro-inflammation and cytotoxicity **5.9 Effects of OPs on neuronal and mitochondrial physiology** 5.10 Role of Klotho in Neurotoxicity (On hold)

### 3. Preclinical Studies Leading to Treatment Funded Projects

- 5.11 Role of the xenobiotic nuclear hormone receptor PXR (On hold)
- **5.12 Effects of OPs on hippocampal cognitive function in mice**
- **5.13 Effects of OPs on a mouse model of Motor Neuron Disease**
- **5.14 Effects of OPs on a mouse model of Glioblastoma brain cancer**
- **5.15 Effects of OPS on autonomic nervous system function**
- 5.16 Effects of parental OP exposure on brain development of fetus (MRG)
- 5.17 Effects of OPs on fear conditioning (On hold)

#### **Neuroimaging and Biomarker Study**

**The Problem:** 

Since 1991 Gulf War Veterans Have Had a Characteristic Set of Symptoms That Disable Many.

# **Typical Symptoms of Gulf War Syndrome**

- Can't remember things
- Can't concentrate or pay attention
- Can't find the right word
- Constant body pain, tingling or numbness
- Feeling tired, fatigued all the time
- Feeling depressed, easily angered, irritable

# **Operational Plan**

- Three phases of neuroimaging
  - Long series of developmental pilots in normals (2001 2008).
  - Formal pilot study in 50 Seabees studied in 1996, 1998 and 2008.
  - Confirmatory study in a population random sample (2009 –2010).
- Seabees Pilot Study (July 2008 April 2009)
  - Objectives: 1) 10-year followup, and 2) Pilot new MR imaging tests.
  - Sample: 24th Reserve Naval Mobile Construction Battalion
    - Factor Sd 1 10
    - Factor Sd 2 13
    - Factor Sd 3 10
    - Controls 15
  - Researchers still blinded to group membership
    - Presently comparing Groups A (?) and B (?)
# **Organization of Tests**

- Neuropsychological/Psychological Tests
- fMRI of Memory
  - Memory encoding, Memory associations
- fMRI of Executive Functions and Language
  - Attention/concentration, Working memory, Word-finding, Complex verbal function
- fMRI of Affective Functions
  - Emotional response to threat, Fronto-striatal circuits involved in depression
- fMRI of Sensory Perception
  - Warming threshold and heat pain
- Quantitative EEG
  - General level of arousal, add temporal resolution to fMRI's spatial resolution
- fMRI of Functional Connectivity
  - General level of inter-regional traffic, test integrity of specific pathways
- Studies of Global Brain Integrity
  - MR spectroscopy, Volumetrics, DTI, Cholinergic challenge with SPECT, Dexamethasone Suppression Test



# **Basic Brain Anatomy**



Part 1. Studies to Discover What the Brain is Doing When GW Veterans Have Symptoms

# **Typical Symptoms of Gulf War Syndrome**

- Can't find the right word
- Can't remember things
- Can't concentrate or pay attention
- Constant body pain, tingling or numbness
- Feeling tired, fatigued all the time
- Feeling depressed , easily angered, irritable

Symptom: "Can't Find the Right Word"

# "Can't find the right word" fMRI of Word Generation Test

**B.** Crosson, K. Gopinath

In scanner, subjects given a category (e.g., birds) and asked to generate as many words in the category (e.g., sparrow) as they can.



Well Veterans

 $t_{9/11} = +10$ 



**Test of group difference in basal ganglia:** p<10<sup>-6</sup> (corrected)

## "Can't find the right word" fMRI of Word Generation Test



Well Veterans



### Sick Veterans

### **Test of group difference in thalamus: p<10<sup>-6</sup> (corrected)**

# **"Can't find the right word" fMRI of Word Generation Test: Group Comparison**





Comparison of Sick vs Well Groups: Sick < Well in bilateral thalamus (red) Sick > Well in right hippocampus (blue)



 $t_{21} = -10$ 

Symptom: "Can't Remember Things"

Study 1

### "Can't remember things" fMRI Task of Learning and Remembering Words, Objects, Faces and Nature Scenes W. Ringe

STIMULI	LEARN	SEEN MANY	SEEN ONCE
WORDS	FACT	NIGHT	FACT
OBJECTS	Ż		Ż
FACES			
NATURE SCENES			

### **"Can't remember things" fMRI** Task of Learning and Remembering Words, Objects, Faces and Nature Scenes

### Well Veterans

Right Hippocampus: Medial-to-Lateral



### Sick Veterans

Well veterans showed activation in Right Hippocampal head and body. Sick veterans showed less activation and more de-activation. Symptom: "Can't Remember Things"

Study 2

### "Can't remember things" fMRI Task of Learning/Remembering Faces & Names T. Odegard



**Test Phase** 

## "Can't remember things" fMRI Task of Learning/Remembering Faces & Names

Studied: Faces Tested: Recall of face only





Group A < B in Left Posterior Hippocampus

Group A < B in Left Middle Hippocampus

Studied: Face-Name Pairs Tested: Knows name of face



Group A < B in Left Anterior Hippocampus

Symptom: "Can't Remember Things"

Study 3

### "Can't remember things" fMRI of Working Memory and Executive Function B. Rypma, M. Motes

- Commonly reported symptoms in GW illness:
  - Impaired concentration
  - Impaired "short-term memory" (executive working memory functions)
- These symptoms may be due to:
  - Cholinergic system damage
    - Disproportionally affects the frontoparietal circuit, which is known to mediate working memory.

## **"Can't remember things" fMRI of Working Memory and Executive Function**

Method: In scanner, subjects given a set of 2, 4 or 6 letters to remember over a brief delay (8s), and then scan is done while they recall whether a probe letter was in the memory set.

**Result:** Well veterans use executive function in dorsal PFC and parietal storage. Sick veterans use ventral PFC for rehearsing (workaround).



# Symptom: "Can't Concentrate or Pay Attention"

# "Can't concentrate or pay attention" fMRI of Continuous Performance Test (CPT)\*

\*Conners' Continuous Performance Test (CPT)

### CPT Not-X Task

- In scanner, subject presses a button at every letter, but at not "X."
- Group A failed to inhibit at "X" significantly more often than Group B.



Group A < B in basal ganglia

Symptom: "Constant Body Pain, Tingling or Numbness"

## "Constant body pain, tingling or numbress" fMRI of Heat Pain Stimulation

K. Gopinath



 $p < 1 \times 10^{-6}$ 

Well Veterans





 $p < 1 \times 10^{-6}$ 

Sick Veterans

### **"Constant body pain, tingling or numbness" fMRI of Heat Pain Stimulation: Group Comparison**



t<sub>20</sub>= +10

 $t_{20} = -10$ 



Sick > Well Groups in:

Insular cortex, S1, S2, superior temporal gyrus and posterior parietal cortex, in left hemisphere Bilateral cingulate gyrus, SMA, medial frontal cortex and right amygdala Symptom: "Feeling Tired or Fatigued All the Time"

Study 1

## **"Feeling tired, fatigued all the time"** Quantitative Electroencephalography (QEEG) T. Ferree, J. Hart





### **QEEG Shows Global Slowing of Brain Waves**

A sign seen in many brain diseases and injuries



Suggests reduced signaling from the Reticular Activating System through the Thalamus, thus retarding the usual diffuse arousal state. Eyes open condition.

# QEEG Shows Reduced Alpha Suppression by Eyes Opening



	$f_{ m alpha}$	$\Delta P_{alpha}(dB)$
Sick	8.91	.070
Well	8.27	.274
Р	0.10	0.022

Alpha activity characterizes the resting state.

When eyes open, in well veterans *alpha* decreases as neural activity increases. In sick veterans, opening eyes does not suppress alpha as much. Also compatible with reduced signaling from the RAS through the Thalamus. Symptom: **'Feeling Tired or Fatigued** All the Time''

Study 2

### **"Feeling tired, fatigued all the time" fMRI of Functional Connectivity in Resting State** R. Briggs, K. Gopinath

- Series of MR scans taken with subject in resting state.
- Analysis places a "seed" in a given brain structure and measures correlation of activation of other brain structures with the "seed" structure.
- Reveals the amount of interaction between the "seed" structure and the other brain structures.

# **"Feeling tired, fatigued all the time" fMRI of Functional Connectivity in Resting State** Seed in: Left Dorsal Striatum (Group Comparison)



 $t_{16} = +10$   $t_{16} = -10$ 

Sick > Well: Increased connectivity (blue) with medial frontal cortex, parietal cortex, sup. temp. gyrus, post-central gyrus and insula. Sick < Well: Decreased connectivity (red) with right thalamus **'Feeling tired, fatigued all the time'' fMRI of Functional Connectivity in Resting State** Seed in: Left Ventral Striatum (Group Comparison)  $t_{72}=+10$ 











Sick > Well : Increased connectivity (blue) with ventrolateral prefrontal cortex, insula, precentral, cingulate, SMA and sup. frontal

*Sick < Well : Decreased connectivity (red) with bilateral thalamus* 

Indicates constant hyper-arousal / hyper-vigilance

Symptom: "Feeling Depressed, Easily Angered, Irritable"

### **"Feeling depressed" fMRI of Fronto-Striatal Systems in Mood States** W. Ringe

- In scanner, subjects view positive, neutral and negative pictures (right).
- MRI scans taken during periodic self-rated mood checks.



### **"Feeling depressed" fMRI of Fronto-Striatal Systems in Mood States** W. Ringe

- In scanner subjects view positive, neutral and negative pictures
- MRI scans taken during periodic self-rated mood checks
- Usual findings:
  - Non-depressed subjects activate the Dorsal Striatum – Dorso-Lateral PFC pathway (DSDL)



 Depressed subjects activate the Ventral Striatum – Ventro-Medial PFC pathway (VSVM)



## **"Feeling depressed" fMRI of Fronto-Striatal Systems in Mood States**

#### Well Veterans



Sick Veterans



*Well Veterans activate the DSDL, and Sick Veterans the VSVM. Will correlate this with other findings to try to explain the depression.* 

## **"Feeling depressed" fMRI of Fronto-Striatal Systems in Mood States**

Well Veterans

**Sick Veterans** 



In Well Veterans the stimulus activates the Amygdala bilaterally, part of the VSVM. In Sick Veterans the same stimulus does not activate the Amygdala (P < 0.05).

*Currently running MDD patients through this paradigm. The literature says that MDD patients show Amygdala hyperactivity, not hypoactivity as in GWS subjects.*
### Part 2.

Studies to Explain the Basis for the Brain Dysfunction Underlying the GW Veterans' Symptoms

MR Spectroscopy (MRS)
Brain Volume Measurements
Diffusion Tensor Imaging (DTI)
Cholinergic Challenge with SPECT
Arterial Spin Labeling (ASL)

## Nuclear Magnetic Resonance Spectroscopy (MRS Scan), 1998 and 2008 S. Cheshkov, R. Briggs



# NAA Concentration in Basal Ganglia (NAA level measures health of neurons.)

### **Basal Ganglia and Hippocampus**

N-acetyl-aspartate (NAA) is a chemical found only in brain neurons. Neuronal injury reduces NAA.



	LBG NAA/Cr (STDEV)	RBG NAA/Cr (STDEV)
Sick Veterans	1.30(0.12)	1.13(0.10)
Well Veterans	1.40(0.17)	1.20(0.09)
p-value (t-test)	0.11	0.06
p-value (non-param.)	0.017	0.07

	LHP NAA/Cr (STDEV)	RHP NAA/Cr (STDEV)
Sick Veterans	1.08(0.11)	1.19(0.28)
Well Veterans	1.18(0.16)	1.16(0.17)
p-value (t-test)	0.064	0.72
p-value (non-param.)	0.05	0.79

**Rear view** 

### **Brain Volumes:** Measuring Volume of WM vs GM vs CSF D. Woolston



• Brains of Sick Veterans have significantly less white matter volume than Well Veterans (p=0.01).

### Diffusion Tensor Imaging (DTI): Why Is White Matter Shrunken? R. McColl



- **Parallel Diffusion:** Sick = Well
- Perpendicular Diffusion: Sick > Well (p =0.05)
- Suggests demyelination rather than axonal degeneration

# SPECT 1998: Regional Cerebral Blood Flow (rCBF) R. Haley, J. Spence et al.

Hypothesis: If soldiers suffered brain cell damage from sarin nerve gas (a cholinergic stimulant), we might expect to see an abnormal brain cell response to an experimental cholinergic challenge.

- So in 1998 we performed an experiment to see how the cholinergic stimulant *physostigmine* would affect regional cerebral blood flow (rCBF) measured by 99mTc-HMPAO-SPECT scans.
- 21 cases (5, 11, 5) and 17 controls

Haley RW et al. Abnormal brain response to cholinergic challenge in chronic encephalopathy from the 1991 Gulf War *Psychiatry Research: Neuroimaging* 2009 (March); 171:207-220.

## **Cholinergic Challenge Experiment**

Session 1









60 minute infusion\*

99mTc-HMPAO injection





Session 2 (3 days later)









60 minute infusion\*

99mTc-HMPAO injection

SPECT Scan†

SPECT image

21 GWS and 17 Controls

\* Profile of Mood States

<sup>†</sup> Picker 3-headed high resolution scanner

### **Global Hypothesis Test (1998)**



Test of change in rCBF with cholinergic challenge: Group-by-structure interaction P = 0.005 Blocks with Significant Physostigmine Effect on nrCBF









# **Physostigmine Effects in the Amygdala**



**SPECT 1998:** Predicting clinical groups with discriminant function of activation in 17 small brain areas.

Sensitivity = 0.95 Specificity = 0.82



# **SPECT and ASL: 1998 and 2008** Measuring Regional Cerebral Blood Flow (rCBF)

J. Spence, R. Briggs, X. Li, D. Buhner, R. Haley



- Group B responds normally and Group A abnormally to physostigmine (p=0.01).
- MRI-ASL gives same results as SPECT, but more significant.

### Using Multiple Brain Imaging Approaches to Understand How the Brain is Failing When GW Veterans Have Symptoms

Robert W. Haley, M.D. Department of Internal Medicine University of Texas Southwestern Medical Center Dallas, Texas





# humps

### SEMANTIC OBJECT RETRIEVAL

#### CORRECT RETRIEVAL PAIRS

#### CORRECT <u>NON</u>RETRIEVAL PAIRS



Kraut et al., 2002a

# Thalamic Depth and Scalp Electrode Placement





Slotnick et al., 2002











# Word Finding/Semantic Memory Project

- Reported word finding problem that neuropsych did not consistently detect
- Developed Semantic Object Retrieval Task for clinical measures and fMRI and EEG measures of how brain performs
  - Word-Word Object SORT
  - Picture-Word Object SORT
  - Semantic Object Inhibition Task

### Word-Word SORT

#### WWB Binds vs. Fixations Group B, p<.0001



#### Well Veterans

WWB Binds vs. Fixations Group A, p<.05

**Absence of** 

(associated

with 25 Hz

rhythm) in

**Group** A

binding

**BA6** activation



**Sick Veterans** 



Sick Veterans

Well Veterans

Red bar is post vs. pre stimulus Group B 25 Hz power in midline frontal region; blue bar in negative is Group A

### Semantic Object Inhibition



### **Conclusions**

- Significant number of clinical SORT impairments in group A and significantly slower reaction times to retrieve a memory
- Absent fMRI signal in thalamus for Group A (Sick)
- Absence of midline frontal brain region and its associated 25 Hz binding rhythm
- Inability to choose or inhibit correct memory on P3 ERP

# **Emotional Memory Circuit Project**

- Hyperarousal to emotional stimuli is a reported problem
- Patients have met criteria for PTSD but acknowledge that they don't have it
- They have the hyperarousal component but not the traumatic, life threatening experience or "flashback"
- We term this "PTSD without the T"
- Assessed hyperarousal to emotional stimuli on Mississippi PTSD scale
- Threat stimuli fMRI and ERP studies also conducted









# Threat vs. Nonthreat



# Threat vs. Nonthreat ROI of Amygdala






















# Visual Object Semantic Memory

# Threatening > Nonthreatening Normal Young Controls



### VISUAL ITEM SEMANTIC MEMORY **Threatening > Nonthreatening** Group B (Well)

#### Group A (Sick)







SPM{T<sub>12</sub>}

SPMresults: /THREAT VS NONTHREAT 1 leight threshold T = 3,929633 (p<0.001 (unc.)) ktent threshold k = 3 voxels

#### **Absence of** activation in what system threat area

**Typical activation in** what system threat area







SPM{T<sub>10</sub>}

SPMresults: JHREAT\_VS\_NONTHREAT\_1 Height threshold T = 4,143701 (p<0.001 (unc.)) Extent threshold k = 3 voxels

### Visual Threat ERP

### Group B (Well) - P3a (black) < P3b (red) $\rightarrow$ typical Group A (Sick) - P3a (black) > P3b (red) $\rightarrow$ hyper-arousal



#### Black - unattended threat oddball (combat scenes) Red - attended threat target (dangerous and nondangerous animals)

# Summary of Findings

- Significant difference with more reported hyperarousal to threat in Group A (p < .0001)</li>
- Absence of typical activation in visual threat memory area for Group A
- Hyperarousal P3 response to all threatening stimuli, not just combat- related for Group A



## **Take-Home Points**

- 1. Virtually every Neuroimaging study shows substantial differences between Sick and Well Groups.
  - a. Due to:
    - 1) The strategy for developing the imaging tests by targeting veterans' symptomatic deficits and the related brain regions.
    - 2) The homogeneous phenotyping from the Factor case definition.
  - b. Suggests that brain imaging might explain most symptoms.
  - c. Provides rich mosaic of evidence to explain mechanisms.
- 2. The evidence does not yet favor one mechanism
  - a. White matter is clearly abnormal, but deep gray matter also abnormal (Pain not a symptom of WM disease.)
  - b. Gray matter abnormalities appear bilaterally asymmetrical.
  - c. White matter abnormality appears to involve myelin rather than axonal degeneration.

## **Take-Home Points**

- 3. Besides explaining the specific deficits, the mosaic of evidence points to certain general findings:
  - a. Structures activating during a task in Well Veterans often do not activate in Sick Veterans, but other structures do
    - 1) Probably the brain's attempts to compensate for deficits
  - b. The brain in Sick Veterans appears to be hyper-aroused and hyper-responsive to stimuli.
    - 1) The brain working hard to overcome deficits?
    - 2) May explain the chronic fatigue
    - 3) May explain the emotional lability and hyper-reactivity
- 4. Optimism that this multi-perspective testing protocol might lead to objective phenotyping and diagnosis
  - a. For developing an objective diagnostic testing protocol
  - b. For providing homogeneous groups for clinical trials