Presentation 4 – Robert Haley

UT Southwestern Research on Gulf War Syndrome

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Typical Symptoms of Gulf War Syndrome

- **Chronic fatigue**
- **Cognitive problems (attention, concentration, confusion)**
- **Personality change**
- **Constant body pain, paresthesias and hypesthesias (without arthritis)**
- **Balance disturbances, vertigo attacks**
- **Unrefreshing sleep and insomnia**
- **Hot flashes and night sweats**
- **Watery diarrhea alternating with constipation**

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.

The Epidemiologist's Rule Number 1

The first step in investigating a new disease is: Establish a Case Definition*

*Gregg et al. *Field Epidemiology*. Oxford University Press:1996

The Epidemiologist's Rule Number 1

The first step in investigating
a new disease is:
Establish a Case Definition*

And if you can't:
then
Establish a Case Definition!

*Gregg et al. *Field Epidemiology*. Oxford University Press:1996

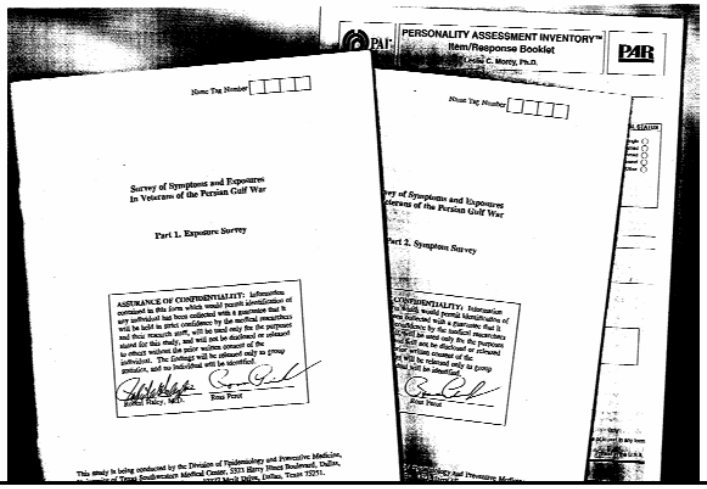
Development of a Case Definition

- **One of Mr. Perot's aides had developed a "registry" of over 2,000 ill Gulf War veterans.**
- **I requested medical records of the 60 "sickest veterans."**
- **Two weeks later I received 60 medical records.**
- **Review of the records identified the "10 sickest veterans" with no other possible explanation.**
- **The Perot Foundation paid for full evaluation of these 10 at Mayo Clinic.**
- **The Mayo evaluation ruled out all known diseases.**
- **I built their symptoms into a survey questionnaire.**

Conducted a Survey in a Reserve Seabees Battalion

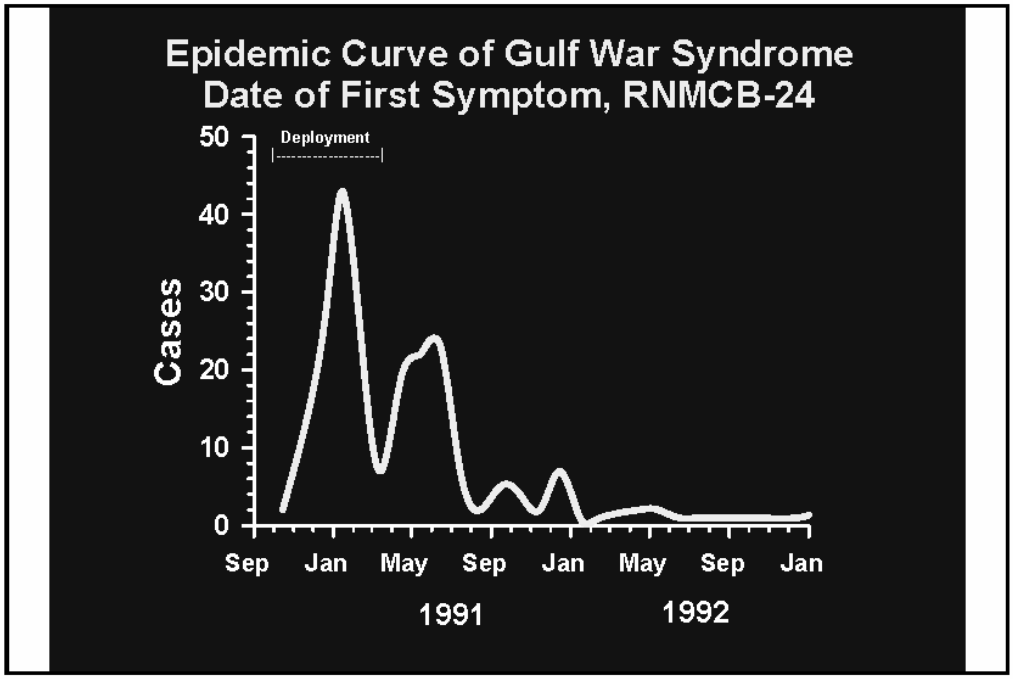
24th Reserve Naval Mobile Construction Battalion*

December 1994 – February 1995



Knoxville
Birmingham
Winston-Salem
Charlotte
Atlanta

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



Haley Symptom Questionnaire: Example Question on Paresthesias

2-stage factor analysis
- **Symptom factors**
- **Syndrome factors**

4. In the past 5 years, have you experienced *tingling, burning or stinging pain* in any part of your body *lasting all day* and continuing for *at least a month*? *(Do not count feelings that come and go quickly and are not present continuously.)*

CIRCLE ONE

Yes 1
No 2

If you answered "Yes," answer Question #4A.
If you answered "No," skip to Question #5.

4A. Please indicate what part of your body was affected by this pain, in what month and year it began, and whether it is still a problem for you.

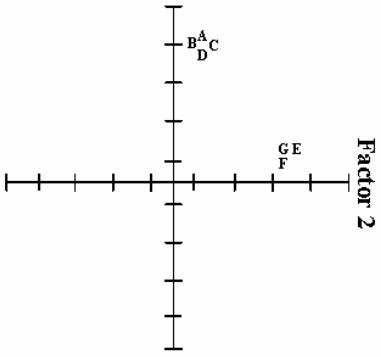
	Was this area involved? YES	NO	If yes, in what month/year did it begin? MONTH	YEAR	Is it still a problem? YES	NO
Scalp	1	2	/		1	2
Face	1	2	/		1	2
Lips	1	2	/		1	2
Tongue	1	2	/		1	2
Chest	1	2	/		1	2
Back	1	2	/		1	2
Hands	1	2	/		1	2
Arms	1	2	/		1	2
Abdomen	1	2	/		1	2
Groin	1	2	/		1	2
Genital area	1	2	/		1	2
Rectal area	1	2	/		1	2
Thighs	1	2	/		1	2
Calves	1	2	/		1	2
Feet	1	2	/		1	2
Other	1	2	/		1	2

specify _____

-6-

Stage 1 Factor Analysis of 7 Anatomical Sites of Symptom "Tingling/Numbness" (249 veterans)

Rotated Factor

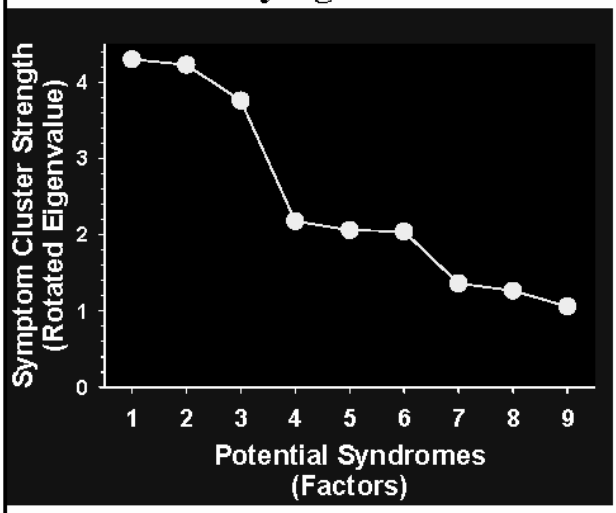


Anatomic location of paresthesias	Correlation with: Symptom Factor 1	Symptom Factor 2
A. Arms	.84*	.19
B. Feet	.82*	.17
C. Hands	.79*	.21
D. Calves	.78*	.19
E. Face	.21	.74*
F. Tongue	.18	.69*
G. Lips	.14	.67*

JAMA 1997;277:215-222.

Separate factor analyses of 21 ambiguous symptoms yielded 52 unambiguous symptom factors.

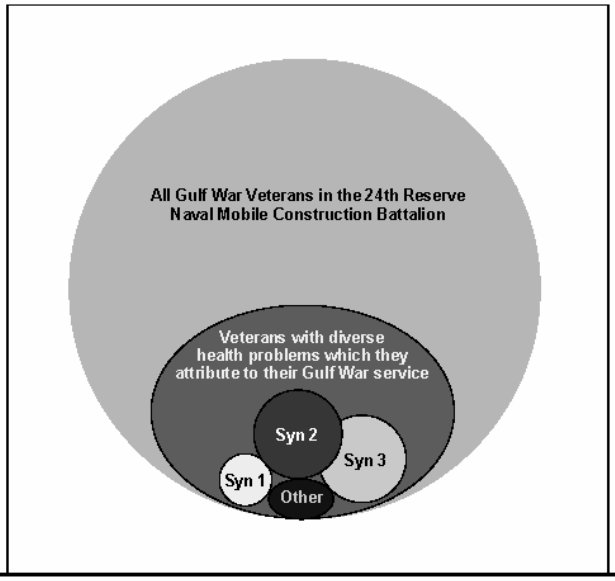
Factor Analysis of 52 Symptom Scales Identifying 6 Possible Gulf War Syndromes



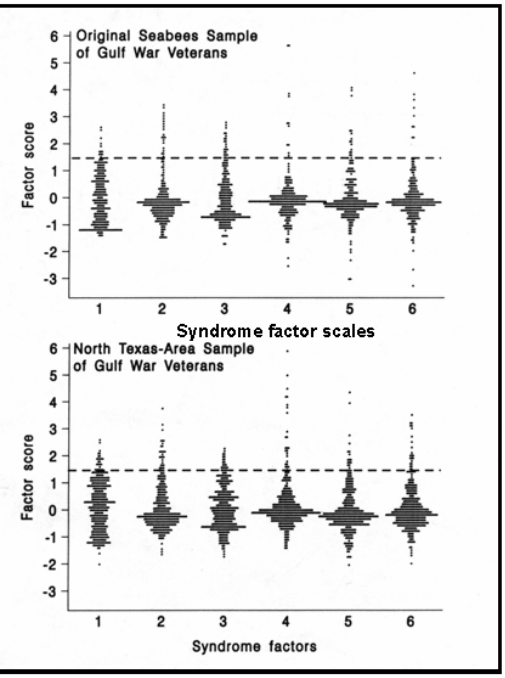
Syndrome Factor	Description	N
1	Impaired Cognition	12
2	Confusion-Ataxia	21
3	Central Pain	22
4-6	Subtypes of Syn 2	36
	Total syndromic	63
	Ill but not syndromic	116
	Remained well	70

JAMA 1997;277:215-222.

Clinical Subgroups of Gulf War Veterans

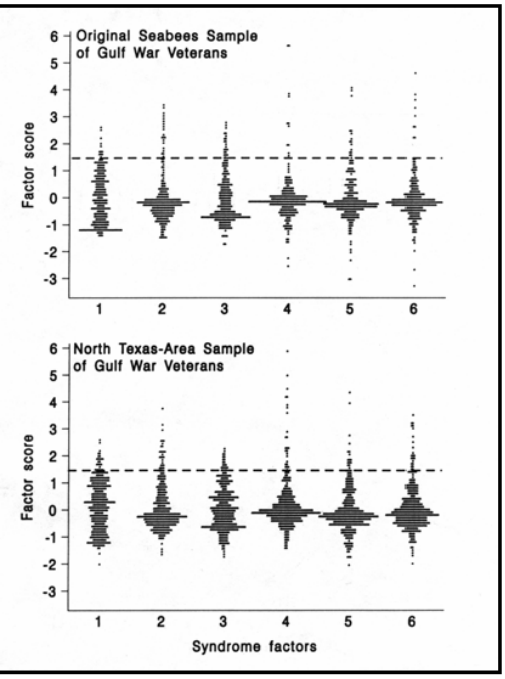


Distribution of the 249 Naval Reservists on each of 6 Syndrome Factor Scales

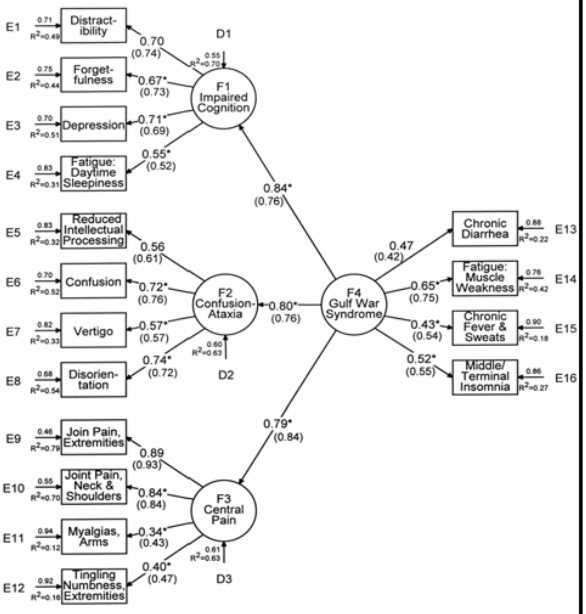


Validation of the Case Definition on 335 Army Veterans Surveyed at the Dallas VA 1997- 1998

Distribution of 2 Independent Samples of GW Veterans on 6 Factor Scales of GW Syndrome



Structure of Gulf War Syndrome in Two Different GW Veteran Samples



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

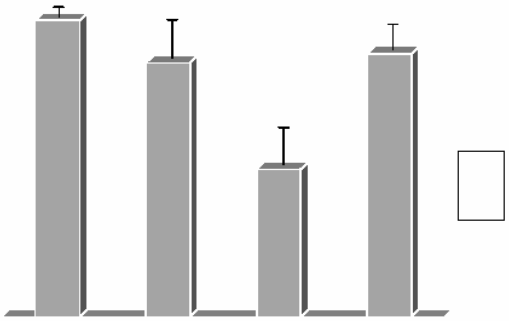
Comparison of Factor Models from Symptom Surveys of Gulf War Veterans

Year	Author	Cognitive	Neurologic	Pain/sensory
1997	Haley	F1	F2	F3
1998	Fukuda	F1	---*	F2
1999	Ismail	F1	---*	F3
2001	Cherry	F1	F3	F2
2002	Kang	F1	F2	F3

*Did not measure the symptoms of the neurologic factor.

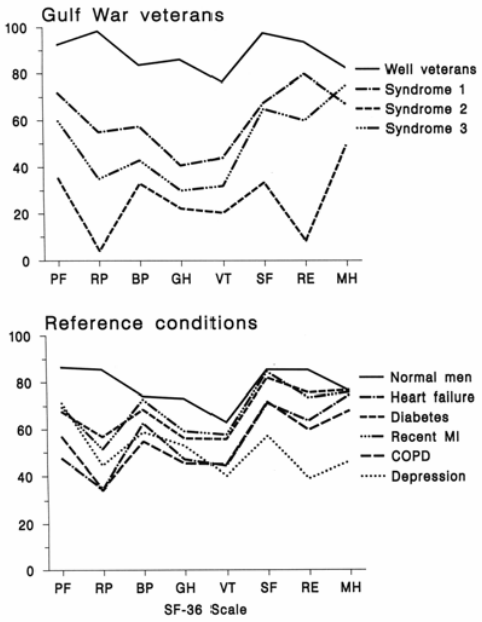
The surveys of Knoke (2000) and Doebbeling (2000) measured symptoms of standard psychiatric conditions and thus found none of the syndrome factors found by the other groups.

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



JAMA 1997;277:215-222.

Functional Status (MOS SF-36) of 22 Ill 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)

Syndrome	Exposure	RR	P value
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 4th 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 crossed 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

Hypothesis Regarding The Nature of Gulf War Syndrome

- There is a Gulf War *syndrome* with 3 variants, or subgroups.
- It is due to brain cell damage or destruction in deep brain structures (basal ganglia and brainstem).
- The symptoms resemble those of well understood diseases of these deep brain structures (early Parkinson's, Huntington's).

Hypothesis Regarding The Cause of Gulf War Syndrome

- The most likely causes include low-level sarin, possibly in combination with OP pesticides, pyridostigmine tablets, pesticides, DEET, etc., caused cellular damage in deep brain structures
- Probably more pronounced in those soldiers with low natural resistance to OP effects (blood esterase activity).

Undertook a Series of Clinical Case-Control Studies

Purpose: To attempt to validate the case definition

Research Question: Do the syndromes differ from controls and among themselves on objective biological parameters?

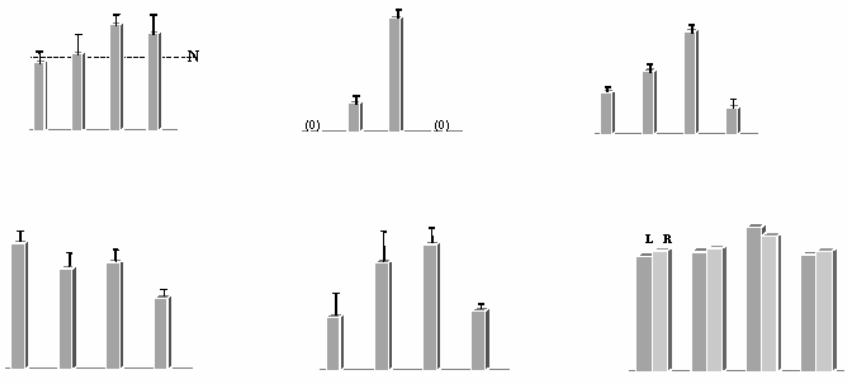
From the 249 Surveyed Veterans Selected Smaller Samples for Case-Control Studies of Brain Function and Serologic Markers

- 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)

Negative Results
No Significant Group Differences

- Clinical neurologic examination
- Clinical interpretation of brain MRI and resting HMPAO-SPECT scans (read blindly by 3 radiologists)
- Routine blood work (CBC, chemistries, glucose, ESR)
- Creatine kinase
- Serum protein electrophoresis
- Serum cholinesterase levels and variant phenotypes
- ANA, RF, immunoglobulins, C3/C4
- Anti-double stranded DNA, acetylcholine receptor antibodies

Positive Results
On Neurophysiologic Tests



JAMA 1997;277:2223-230.

Jan. 15, 1997 Issue of JAMA

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

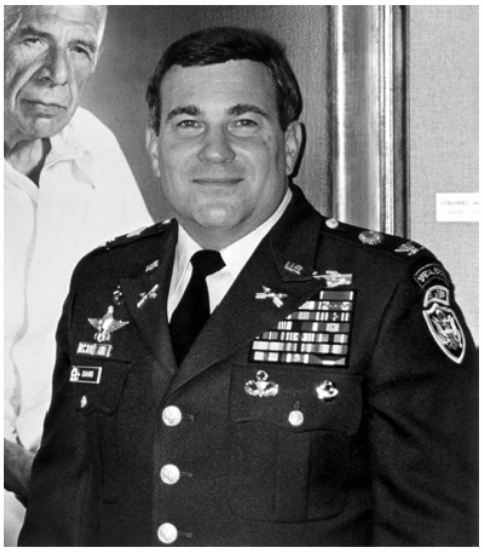
Robert W. Haley, MD; Jim Hom, PhD; Peter S. Roland, MD; Wilson W. Bryan, MD; Paul C. Van Ness, MD; Frederick J. Bonte, MD; Michael D. Devous, Sr., PhD; Dana Mathews, PhD, MD; James L. Fleckenstein, MD; Frank H. Wians, Jr., PhD; Gil I. Wolfe, MD; Thomas L. Kurt, MD, MPH

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

Pilot Study with Col. Bill Davis



U. S. Army Special Forces
- Army Ranger
- HALO/Scuba

Commander, 5th Special Forces Group in the 1991 Gulf War
- Commanded border salient
- Rescued downed fliers
- Let Coalition forces in assault on Kuwait City

Developed Gulf War neurological illness soon after returning from the Gulf War.

Col. Bill Davis had a twin!

Clinical Evaluation of the Davis Twins

- **Identical twins are ideal because they normally perform identically on most medical tests; any differences would suggest pathology underlying Gulf War illness.**
- **They visited UT Southwestern Medical Center 4 times.**
- **First performed genetic tests to confirm monozygosity.**
- **Then performed many sophisticated medical tests sensitive to subtle abnormalities in brain function.**
- **Spent over 20 hours in MRI, SPECT and PET scanners to develop brain scanning approaches that showed differences in brain function.**
- **Tests showing differences were then run on 23 cases and 20 controls selected from the earlier study.**

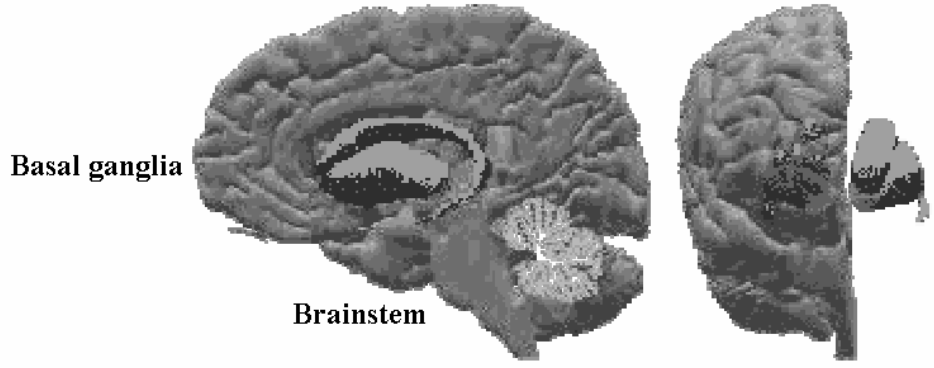
January-June 1998

Second Clinical Case-Control Study with More Advanced Tests of Brain Function and Genetic Predisposition

- 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)

Hypothesis to Be Addressed in the Second Clinical Case-Control Study

Gulf War syndrome variants represent neurotoxic injury to brain cells in deep brain structures involved in well understood diseases that present with similar symptoms: Huntington's, Wilson's, Farr's.



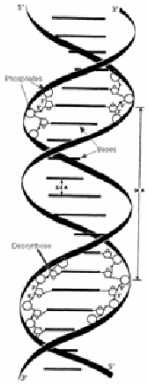
May 29 - June 5 -- Veteran A — Revised 6/1/98

Time	Friday 29	Saturday 30	Sunday 31	Monday 1	Tuesday 2	Wednesday 3	Thursday 4	Friday 5
6:00		Wake at 6:00	Wake at 6:00	Wake at 6:00	Wake at 6:00	Wake at 6:00	Wake at 6:00	Wake at 6:00
		Breakfast 6:30	Breakfast 6:30 Void at 7:00	Breakfast in Sleep Lab Void at 7:00	Breakfast 6:30 Void at 7:00	No Breakfast Void at 7:00	Breakfast 6:30	Breakfast 6:30
7:00			Start 1st 24urine	Start 2nd 24urine Waking EEG (J4)	Start 3rd 24 urine	Blood Drawng (Aston 5)		
8:00		MR Spectroscopy (Rogers)				SEP Neurophys. (PMH 8)		Joint X-Ray (Aston 9)
9:00				Neuro-Psychology			Audio-Vestibular (Aston 7)	
10:00			Psychiatric	(CS4)		Proprioception		
11:00			Interview (GCRC)		Neuro-Muscular (Aston 4)	(MRAL) 9705 Harry Hines		End 48hBP
12:00		Lunch	Lunch	Metabolic Wt.	Pat Brings Lunch	Lunch	Liquid Lunch	Lunch
		Tu E6.120		Liquid Lunch			To E6.120	Limo 12:30
1:00		HMPAO Inj.					HMPAO Inj.	
2:00				Micro-Neurography (GCRC)		Neuro-Psychology (CS4)		Plane 2:16
3:00								
4:00		SPECT (1st)					SPECT (2nd)	
5:00					Dinner			
		Dinner	Dinner	Dinner	Cab 5:15	Dinner	Dinner	
6:00						Start 48 hr BP		
7:00			End Holter Monitor		Joint MRI (Rogers)			
8:00	Plane 8:40pm	Start Holter Monitor	Send Breakfast to Sleep Lab					
9:00	GCRC	Sleep Lab 1 (J4)	Sleep Lab 2 (J4)	Sleep Lab 3 (J4)	Sleep Lab 4 (J4)	GCRC	GCRC	

GCRC Protocol for Cases and Controls

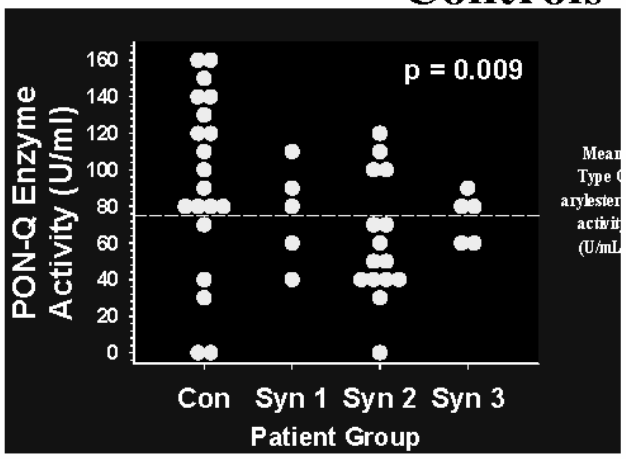
- Low tyrosine diet
- Brain MR spectroscopy scans
- Autonomic evaluation
- Neurophysiologic tests
- Quantitative sensory tests
- Psychiatric/neuropsychological evaluation
- Sleep studies over 4 nights
- Blood tests for dopamine metabolites
- Brain SPECT scans with cholinergic challenge
- Etc.

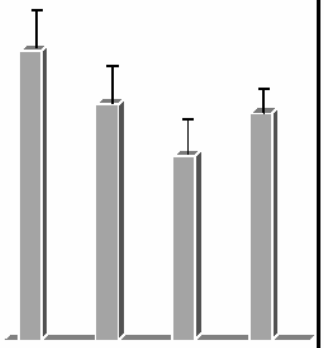
Genetic Predisposition: Paraoxonase (PON1) Enzyme Assay



Dr. Bert La Du
U. of Michigan

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



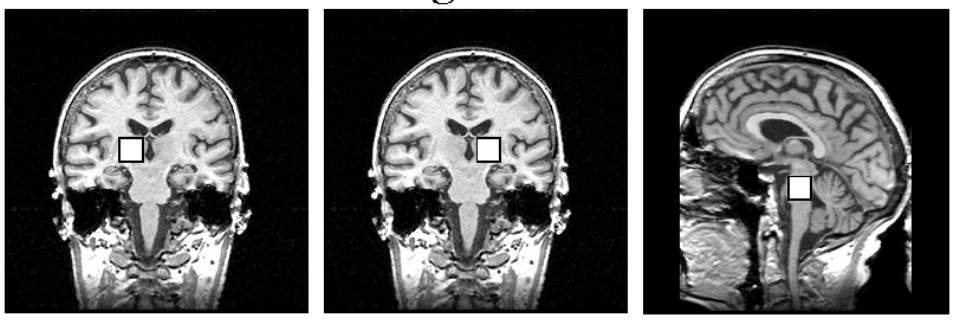


Toxicol Appl Pharmacol 1999; 157: 227-233

Brain Scanning with Nuclear Magnetic Resonance Spectroscopy (MRS Scan)

3 Brain Regions Scanned by MRS

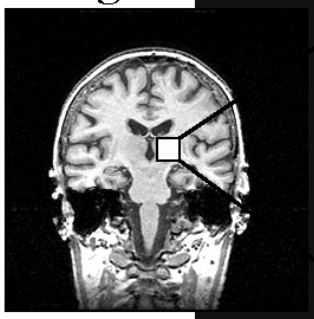
Left BG **Right BG** **Brain stem**



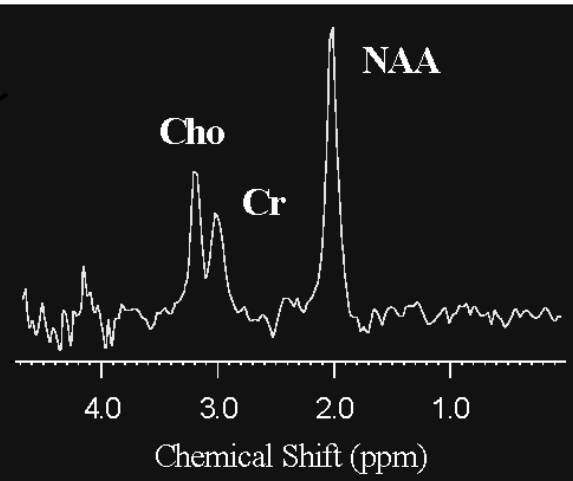
Rear view *Side view*

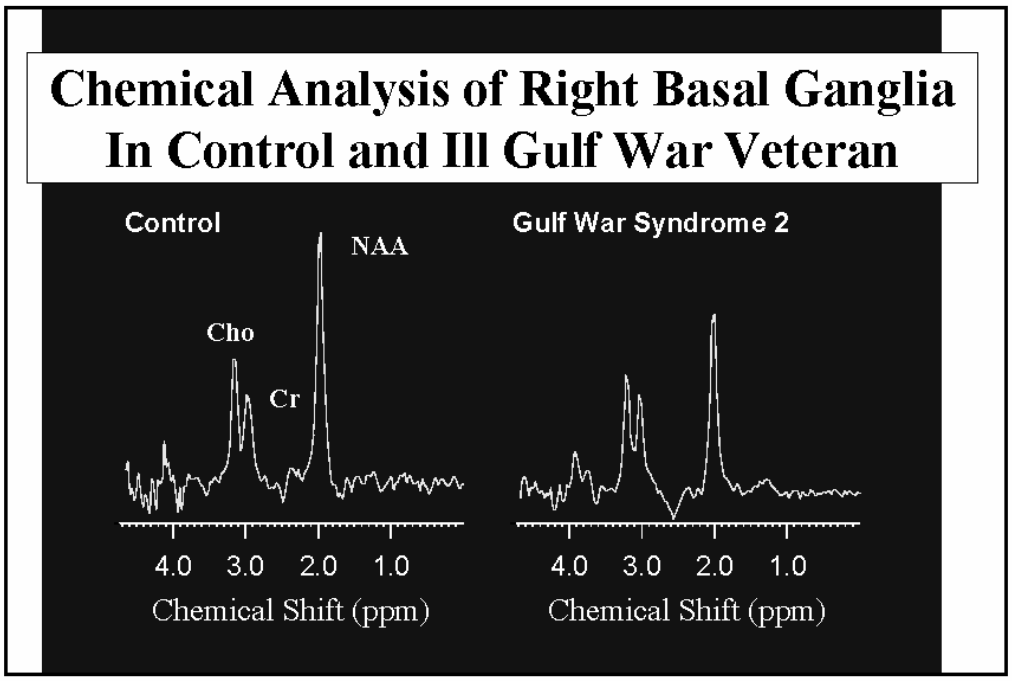
Chemical Analysis from an MRS Scan Of Normal Brain

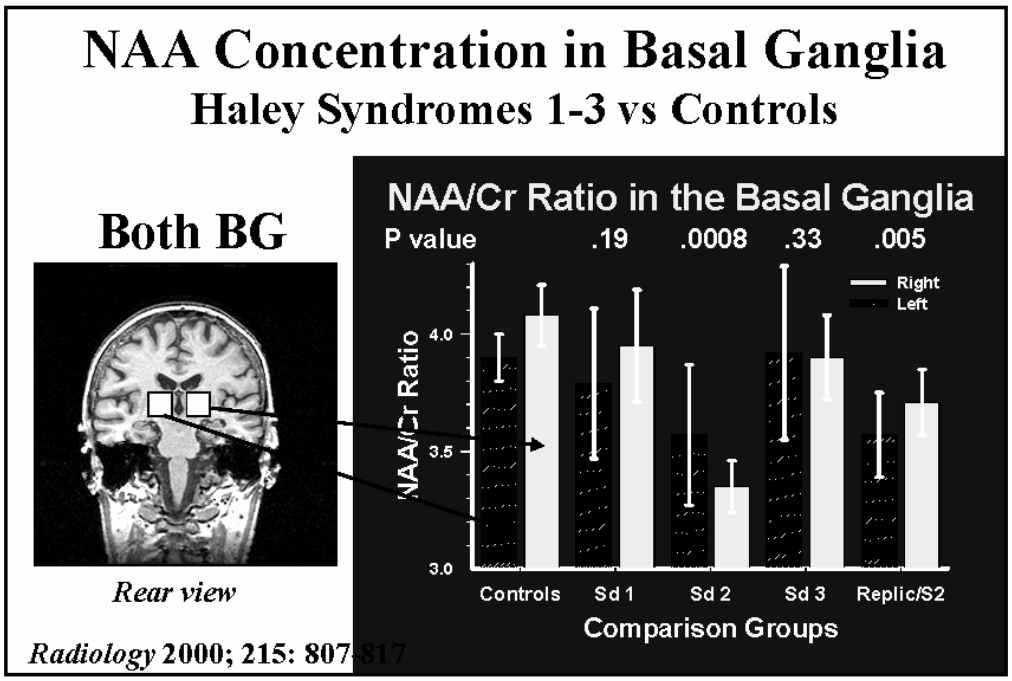
Right BG



Rear view



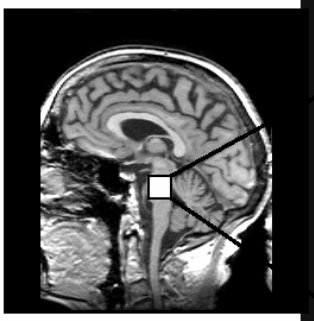

Chemical Analysis of Right Basal Ganglia
In Control and Ill Gulf War Veteran
Control
Gulf War Syndrome 2
NAA
Cho
Cr
4.0 3.0 2.0 1.0
Chemical Shift (ppm)
4.0 3.0 2.0 1.0
Chemical Shift (ppm)


NAA Concentration in Basal Ganglia
Haley Syndromes 1-3 vs Controls
Both BG
Rear view
NAA/Cr Ratio in the Basal Ganglia
P value .19 .0008 .33 .005
Right
Left
NAA/Cr Ratio
4.0
3.5
3.0
Controls
Sd 1
Sd 2
Sd 3
Replic/S2
Comparison Groups
Radiology 2000; 215: 807-817

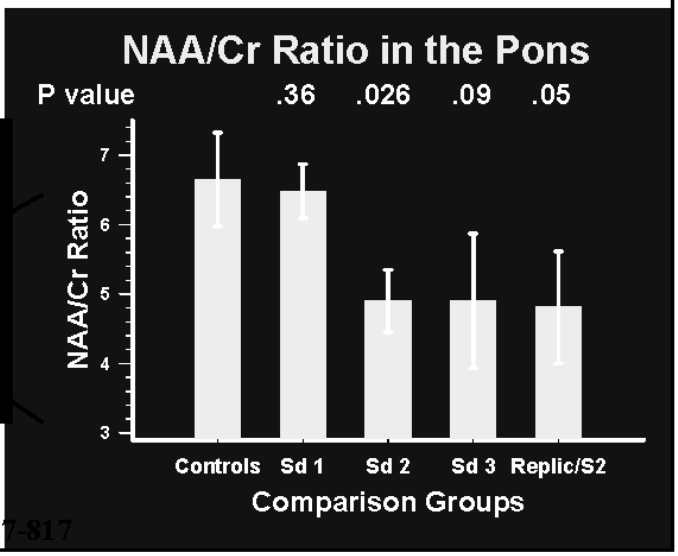
NAA Concentration in Brain Stem

Haley Syndromes 1-3 vs Controls

Brain stem

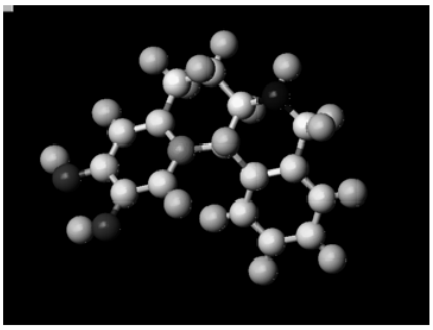


Side view

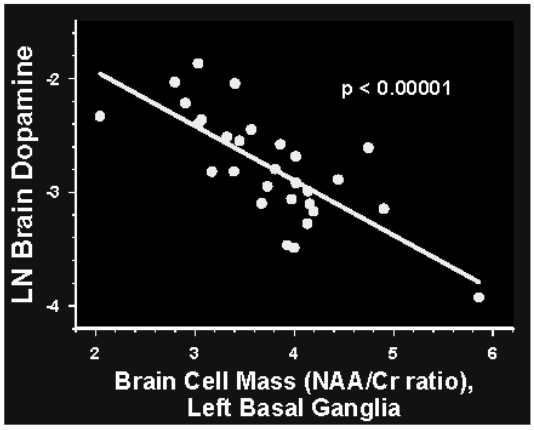


Radiology **2000; 215: 807-817**

Brain Chemistry:
Dopamine Production Rate
(Homovanillic Acid / MHPG)

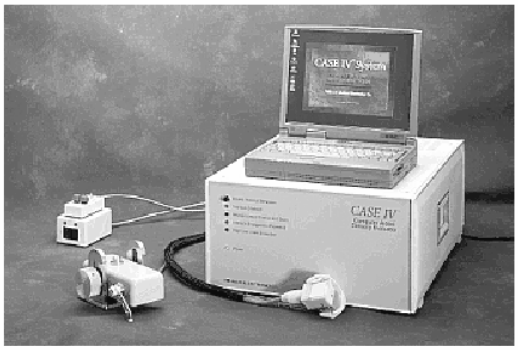


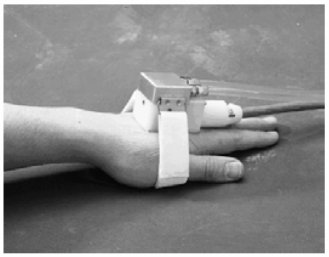
Increased Brain Dopamine Production with Brain Cell Damage



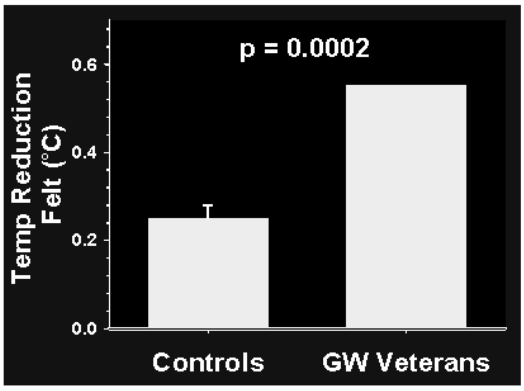
Archives of Neurology **2000; 57: 1280-1285**

Quantitative Sensory Testing: Cooling Threshold





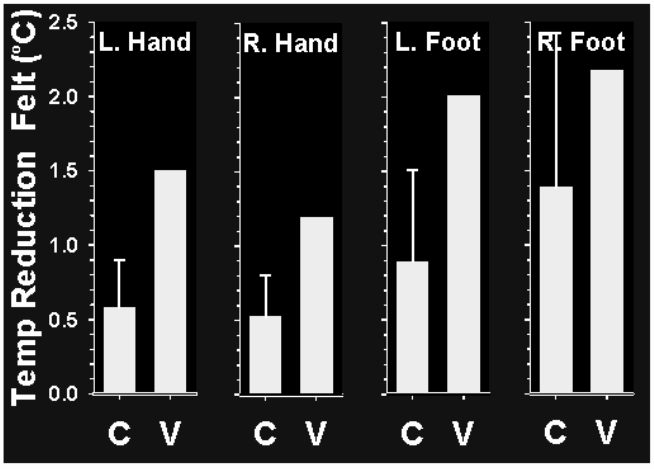
Jamal et al. 1996 Study: Abnormal Ability to Sense Changes in Temperature



J Neurol, Neurosurg, & Psychiatr 1996; 60: 499-451

Impaired Cooling Perception Threshold*

R. Haley, G. Wolfe, MD, W. Bryan et al.



Global Test:
P < 0.0001

C = Control
V = GW Veteran

*Similar findings for warming threshold but not vibratory

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

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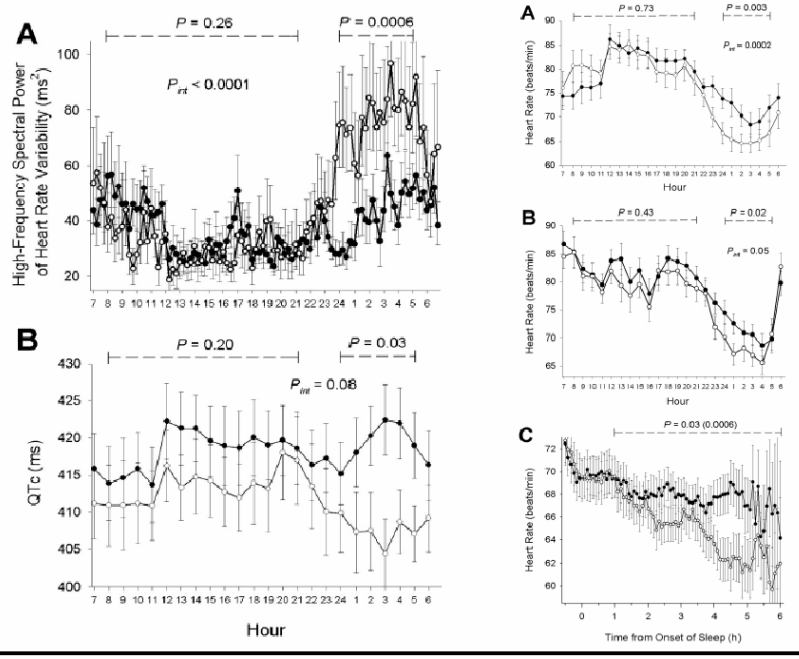

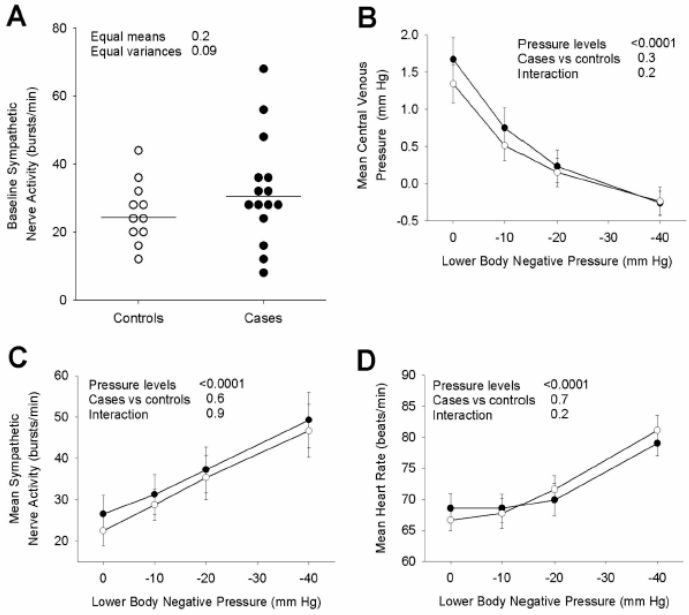

Neuropsychological Findings

- Psychological scales of the *MMPI (1, 2 and 4)* and *PAI* are elevated in ill veterans but not in the well veterans.
- SCID interviews show high rate of depression, little PTSD.
- A few sicker veterans have mild psychotic features.
- Inability to perform skills easily done before the war.
- WAIS *Verbal IQ*, but not Performance IQ, is significantly lower, as are *Arithmetic* and *Vocabulary* subtests.
- The *Halstead Impairment Index*, *Connors Continuous Performance Test (CPT),* and other tests of *attention-concentration* best distinguish ill from well veterans.
- In general, many tests of subcortical function are slightly skewed in the abnormal direction in ill veterans but not significantly.

April 22, 2001 ISMRM Meeting in Scotland

Replication of Our MR Spectroscopy Finding

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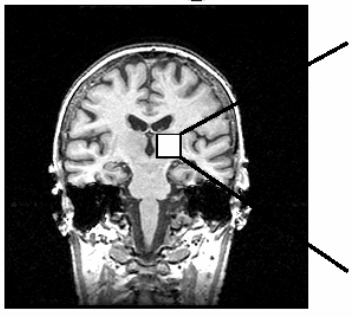
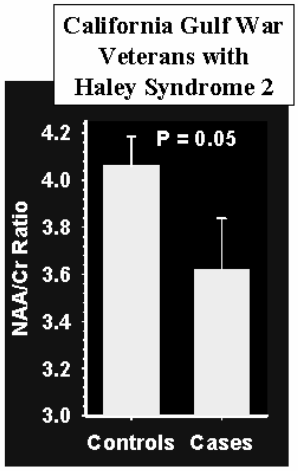
First Replication by Weiner et al. : NAA Concentration in Right BG

MRS of Right BG



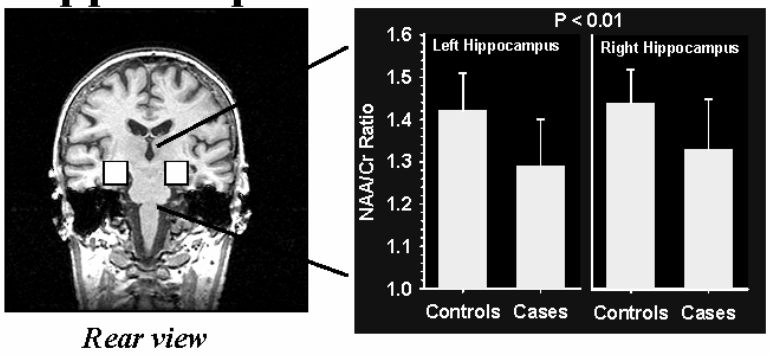
Rear view



Proc Intl Soc Mag Reson Med **2001; 9: 994.**

Second Replication by Menon et al. : NAA Concentration in the Hippocampus Left and Right Hippocampus

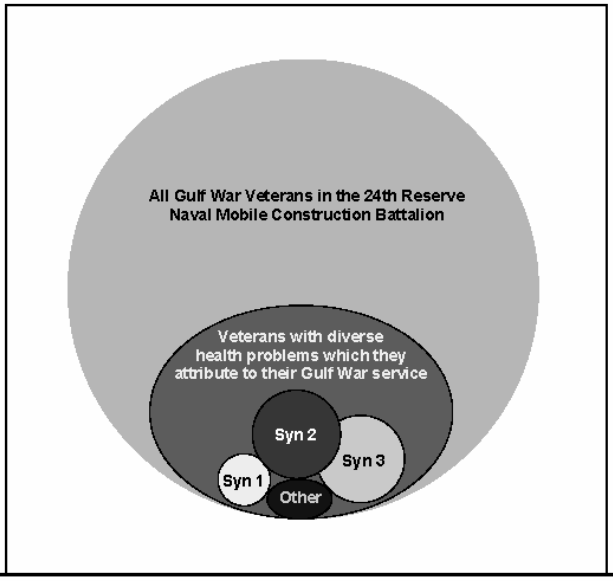
Mississippi Gulf War Veterans with Gulf War Illness



Rear view

Brain Research **2004; 1009: 189-194.**

Clinical Subgroups of Gulf War Veterans



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Alteration of Cholinergic Receptors in Rats by Low-Level Sarin

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Henderson et al. *Toxicology Applied Pharmacology* 2002;184:67-87

Toxicology and Applied Pharmacology **184,** 67–76 (2002)
doi:10.1006/taap.2002.9495

Response of Rats to Low Levels of Sarin

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Toxicology and Applied Pharmacology **184,** 82–87 (2002)
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Subclinical Doses of the Nerve Gas Sarin Impair T Cell Responses through the Autonomic Nervous System

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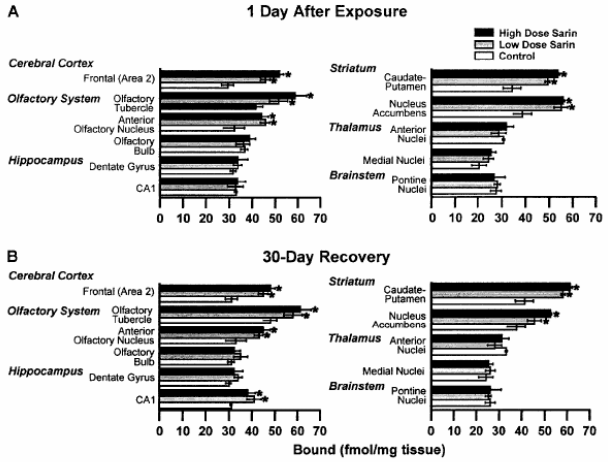
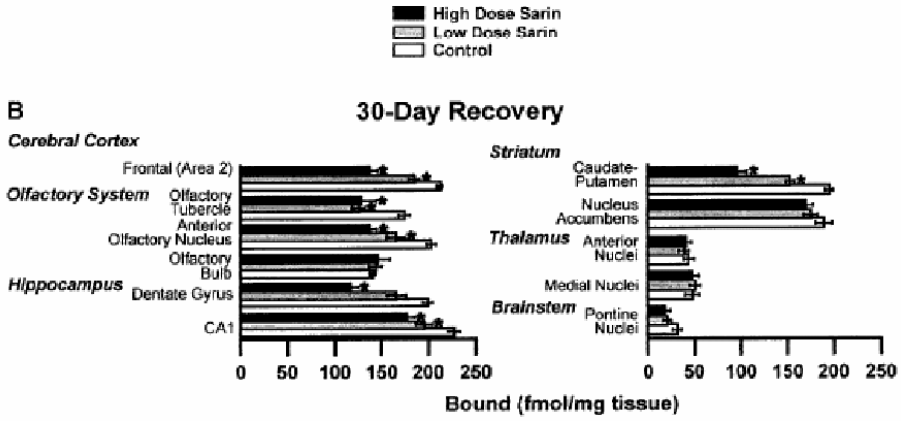
Up-regulation of M3 Receptors at 1 and 30 Days After Inhalation of Sarin for 5 Days



Henderson et al. ***Toxicology Applied Pharmacology*** 2002;184:67-87

Down-regulation of M1 Receptors 30 Days After Inhalation of Sarin for 5 Days



Henderson et al. ***Toxicology Applied Pharmacology*** 2002;184:67-87