

# **WRIISC-CA**

# **research update**

**J. Wesson Ashford, MD, PhD**

**War-Related Injuries and Illnesses Study Center  
(WRIISC)**

**Palo Alto VA Health Care System**

**[wes.ashford@va.gov](mailto:wes.ashford@va.gov)**

**March 1, 2011**

# Most Frequent Symptoms of Veterans from the First Gulf War

Frequency of Symptoms of 53,835 Participants in VA Registry  
(1992–1997)

Symptom	Percentage
• Fatigue	20.5
• Skin rash	18.4
• Headache	18.0
• Muscle and joint pain	16.8
• Loss of memory	14.0
• Shortness of breath	7.9
• Sleep disturbances	5.9

*(Continued)*

# Most Frequent Symptoms (cont'd)

## - affected systems

Symptom	Percentage
• Musculoskeletal and connective tissue	25.4
• Mental disorders	14.7
• Respiratory system	14.0
• Skin and subcutaneous tissue	13.4
• Digestive system	11.1
• Chest pain	3.5

SOURCE: Murphy et al., 1999.

## 39 year old male Veteran – evaluated at WRIISC-CA February, 2011

Veteran was in good health prior to deployment to Persian Gulf in August, 1990.

Veteran flew into Saudi Arabia, deployed within a week to the IRAQ border.

Was with the 82 Airborne, in an engineer battalion.

During Operation Desert Shield - did mostly training (“blowing things up”), preparation.

- Veteran developed diarrhea within 2 weeks (eating local food - water, fruits, vegetables - vendors would be selling food), which did not last more than 2-3 weeks. Meds included Immodium (does not recall anti-biotics).
- Heard chemical weapons alarms go off x 2, put on MOP suit 2-3 times.
- Saw SCUD missiles fly overhead, never saw one explode.

During Operation Desert Storm, Veteran supported the infantry – “blowing things up”, disarming mines. Was at the weapons dump at Khamisiyah and was responsible for the destruction of this facility between March 3-10, 1991.

He reports or believes that he was exposed to:

- o Sand, Smoke from oil-well fires,
- o Insecticides (DEET, permethrin), Organophosphate nerve agents, Pyridostigmine bromide (PB)
- o Paints, Solvents, Petroleum fuels and their combustion products,
- o Anthrax botulinum toxoid vaccinations, Infectious diseases
- o Psychological and physiological stress
- o C4, TNT, mines (direct handling).
- o Was near large radar trucks.

Veteran recalls no other symptoms before returning to the US in April, 1991. On return, Veteran experienced anger, got into fights, irritability, problems with concentration, difficulty with interpersonal relationships (ended relationship with girl-friend from before War), diarrhea and constipation. Veteran avoided social situations and crowds.

Major symptoms subsequently were:

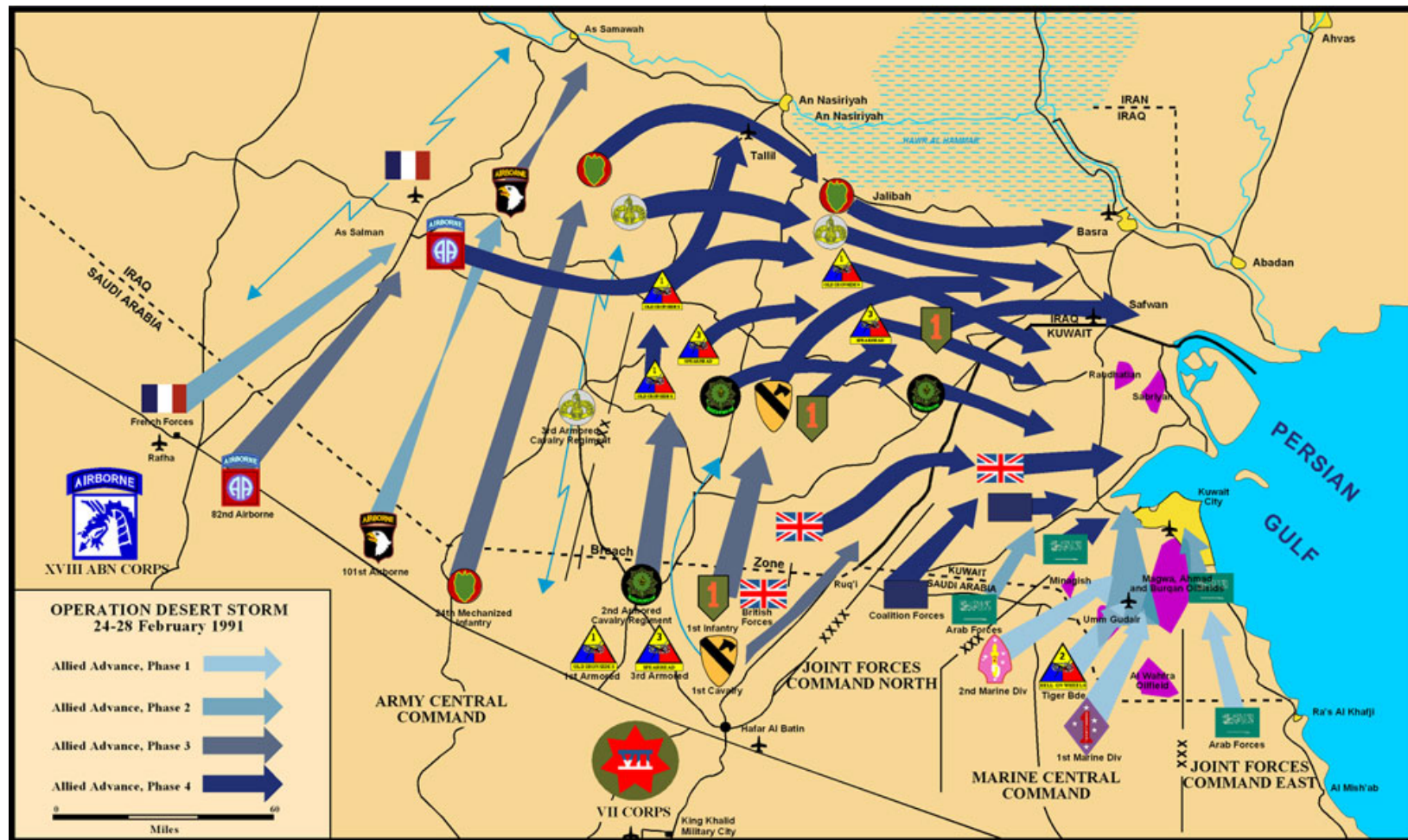
- > Chronic fatigue
- > Muscle and joint pain
- > Headache
- > Skin rashes first 2 years after return
- > Sleep disturbances
- > GI disturbances
- > Loss of concentration
- > Forgetfulness, loss of memory

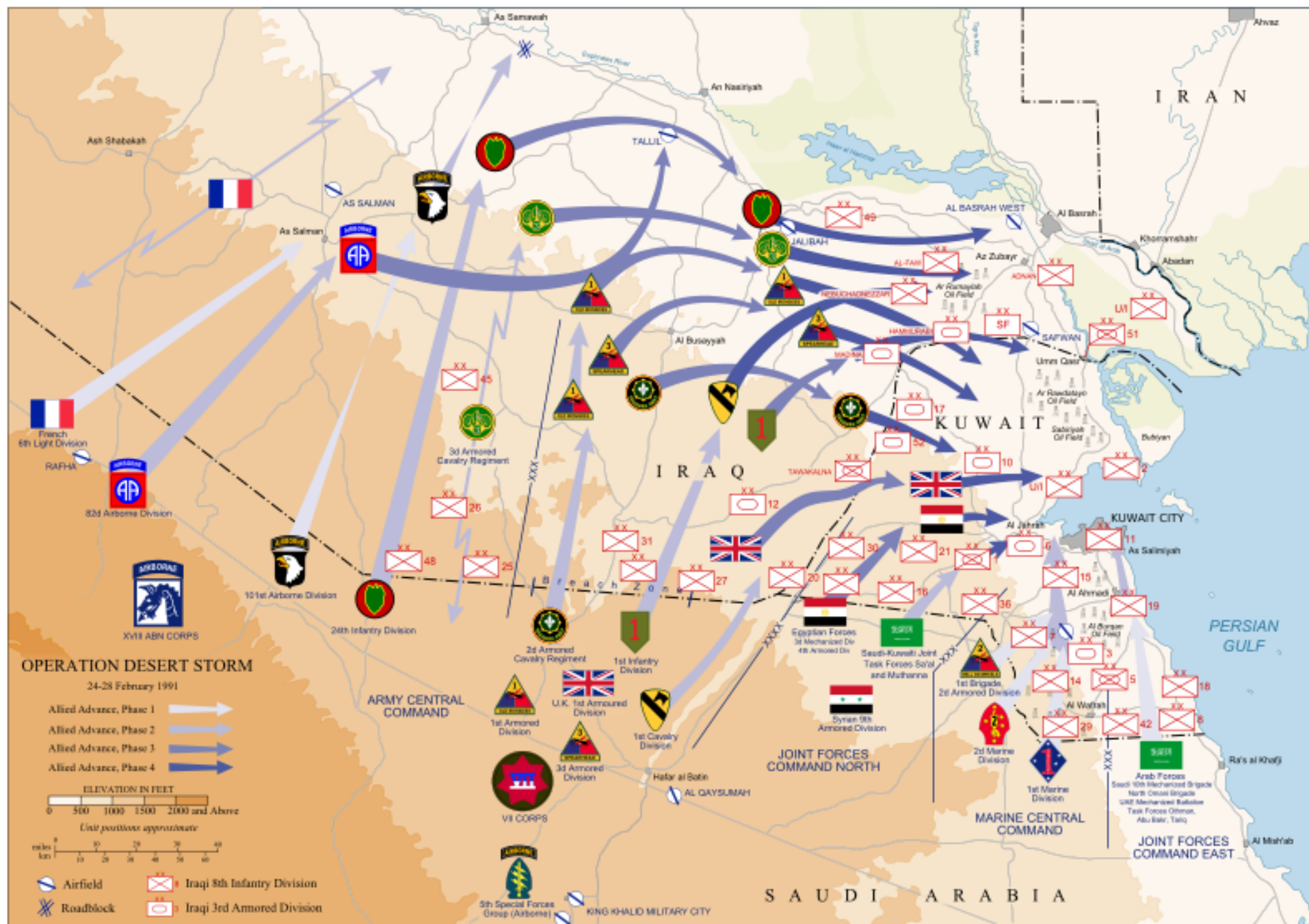
Some of these symptoms have been stable (muscle, joint pain), but most have gotten progressively worse.

Veteran has 4 combat comrades who had similar problems.

Veteran has had TBI x 2 times, major - Fort Bragg, parachuting. Knocked unconscious for 5 - 10 seconds (witnessed). Some dizziness, no other residual.

# Summary of the Offensive Ground Campaign





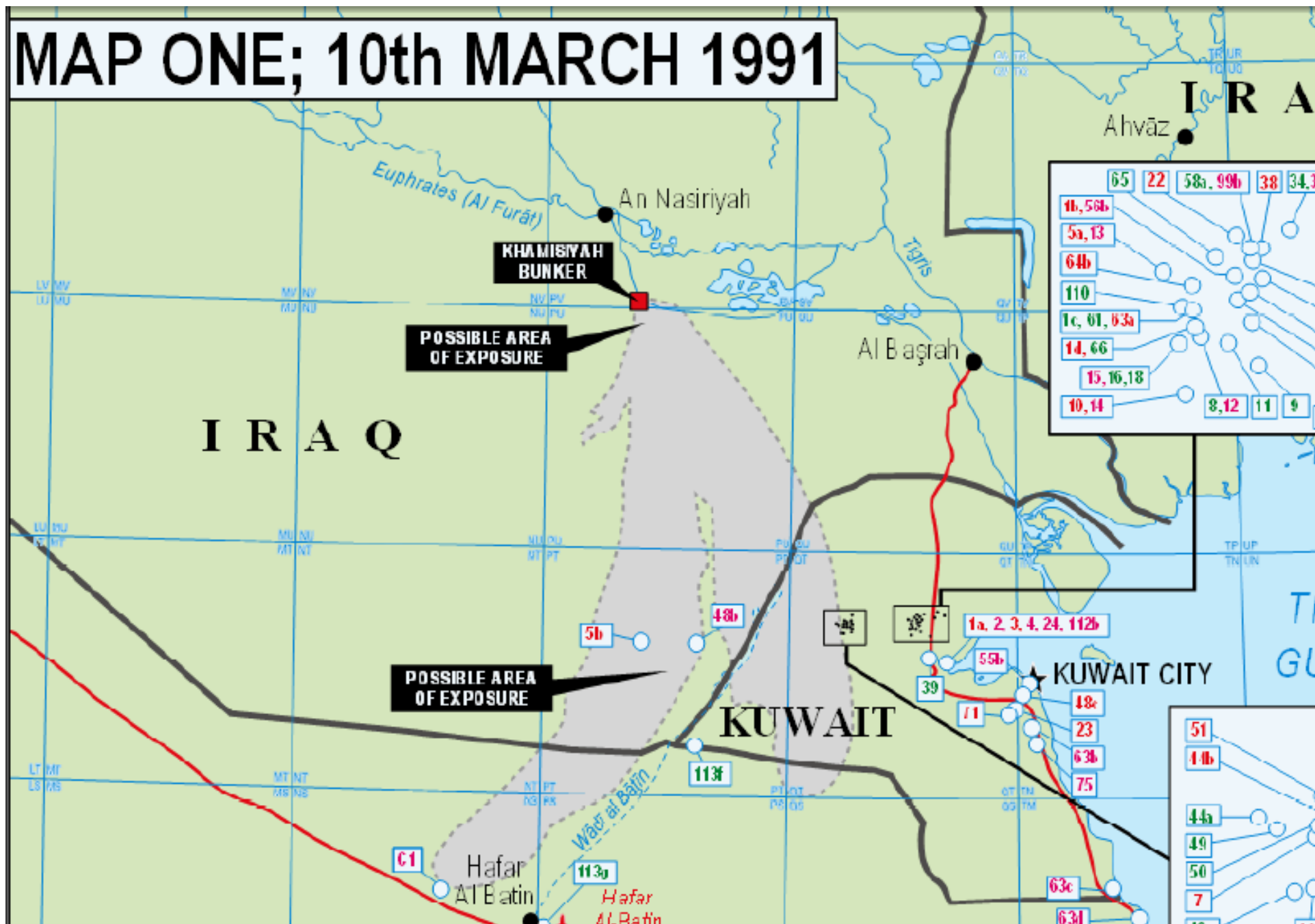


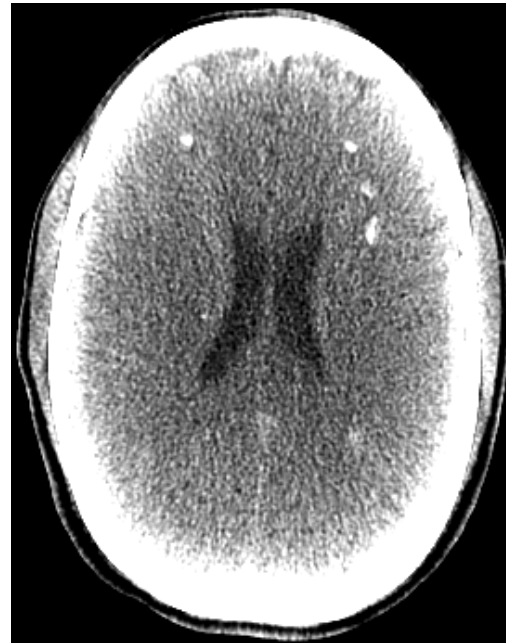
# MAP ONE; 10th MARCH 1991





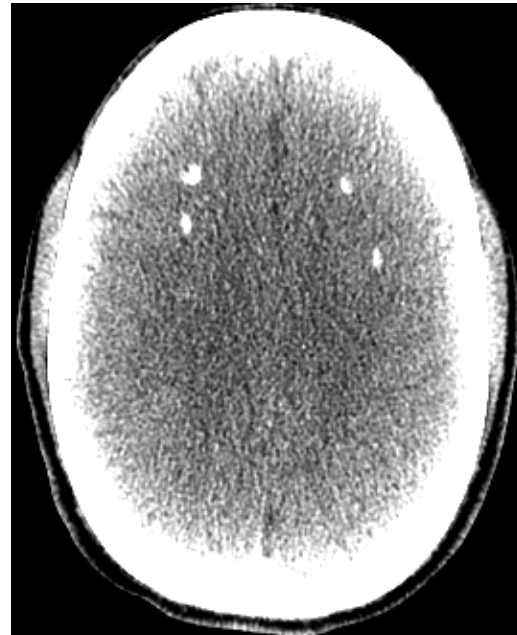
# MAP ONE; 10th MARCH 1991





39 year old veteran (GW1)  
Parachute jumper with 2  
episodes of brief LOC.

Neuropsychological testing  
was abnormal, showing  
multiple areas of  
dysfunction, most related to  
variable performance.

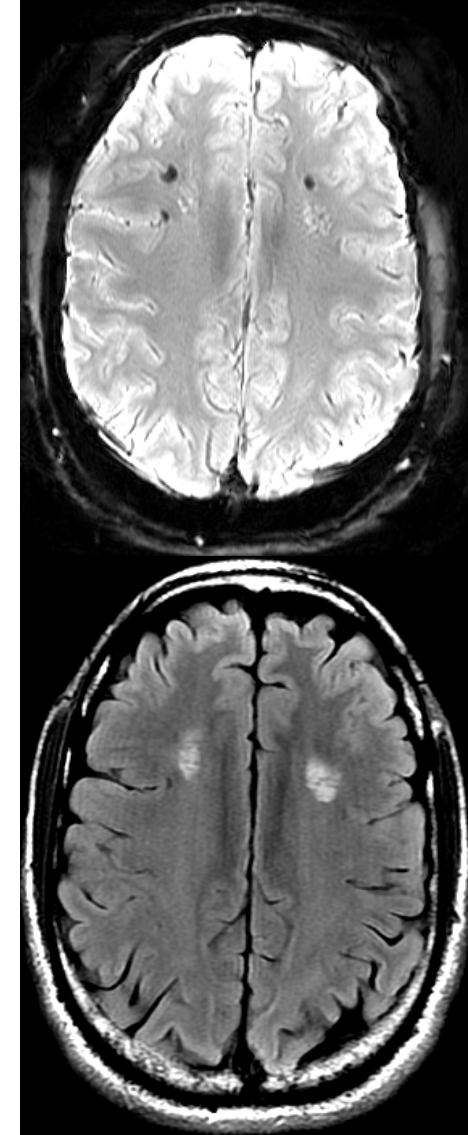
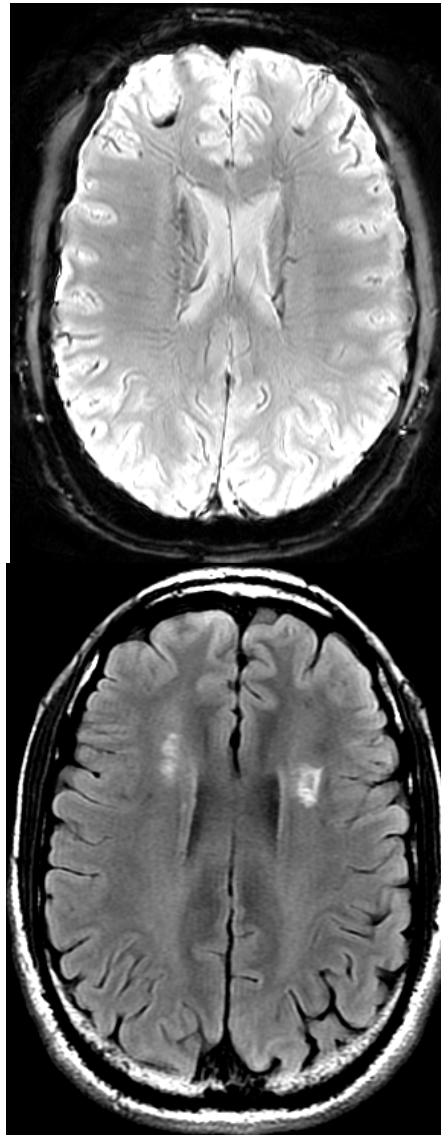
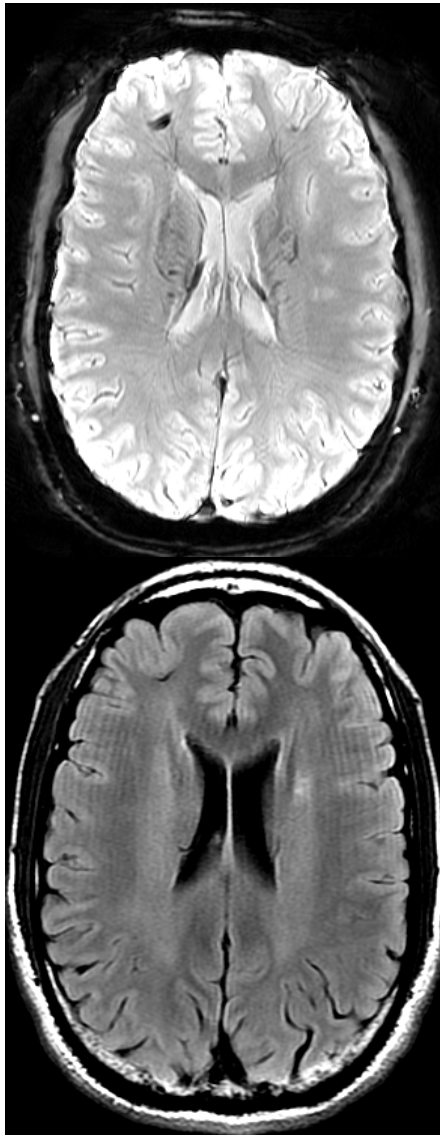


Internal Medicine notes  
migraine, occipital  
neuralgia, irritable bowel  
syndrome, PTSD

CT scan showing multiple  
areas of calcification.

39 y/o Veteran of first Gulf War,  
demolitions engineer at Khamasiyah.

Axial MRI scans – 3T – SWI above, FLAIR below



# Cerebral Cortical Perfusion Defects on 3-D-SPECT in First Gulf War Veterans

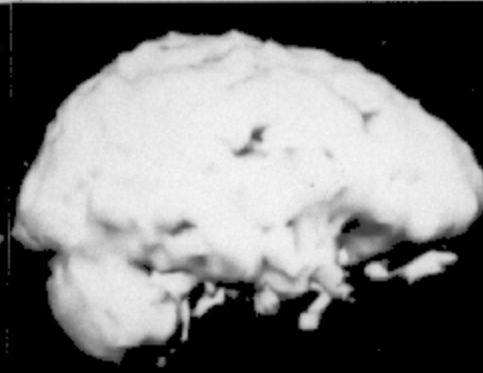
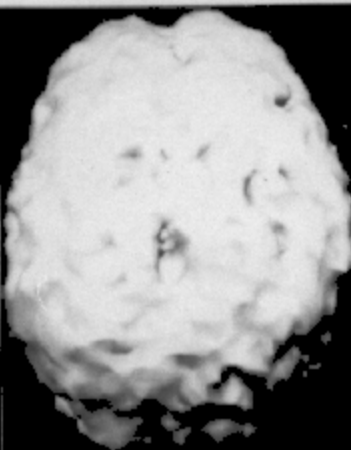
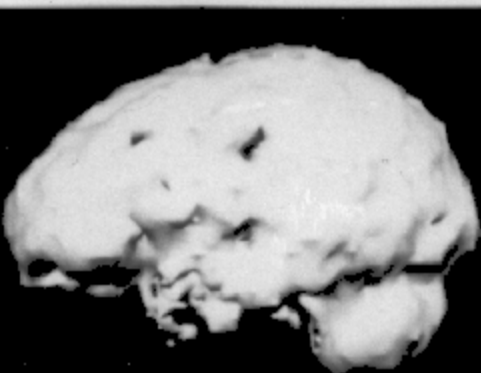
- Examination of 49 Veterans of the First Gulf War with symptoms primarily in the mood and cognitive spectrum who presented to the Lexington Veterans Affairs Medical Center (between 1996 and 2000).
- These Veterans were referred from the Primary Care Clinic with credible memory complaints (e.g., concerns expressed by spouses, family members, and employers).
- All participants were administered a routine dementia evaluation, which included the Mini-Mental State Exam (MMSE), animal naming in one minute, and MRI and SPECT brain scanning.
- These Veterans were scanned with SPECT using a three-headed camera, 99mTC-ECD, and 3-D computer analysis.
- One of these participants had a second SPECT 11 months later to confirm an abnormal finding, and another had a repeat scan 12 months later.

LL

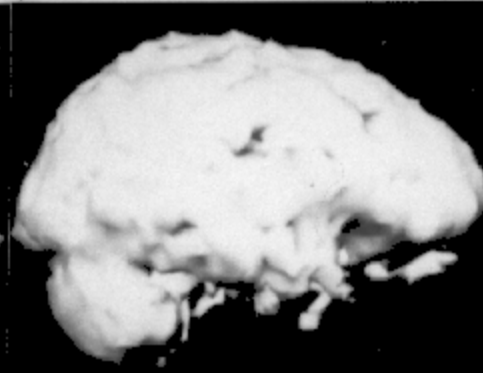
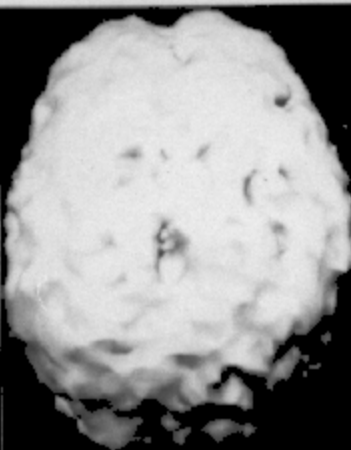
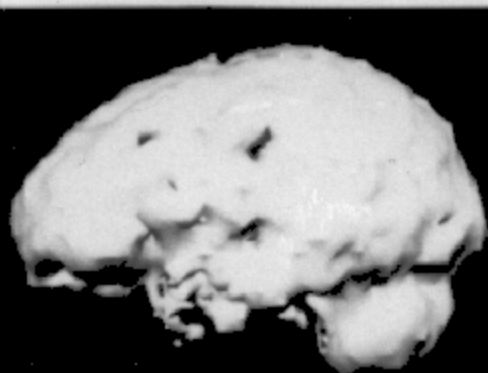
VX

RL

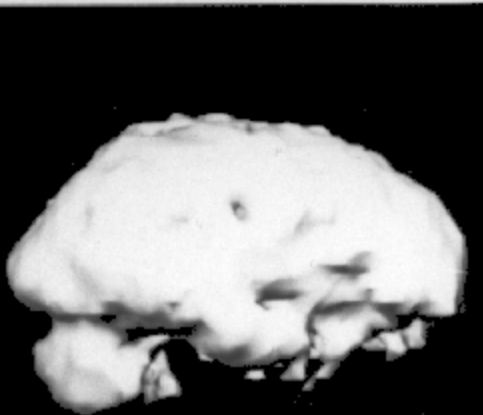
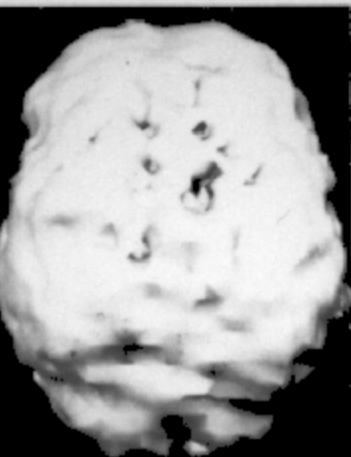
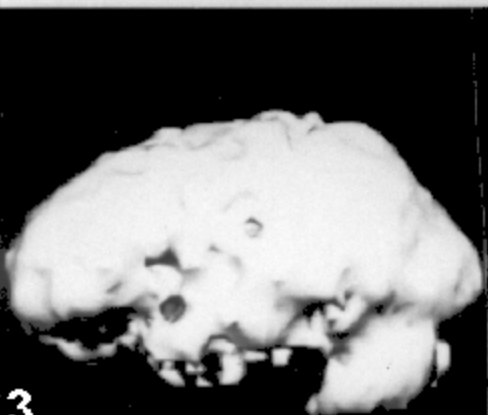
1



2



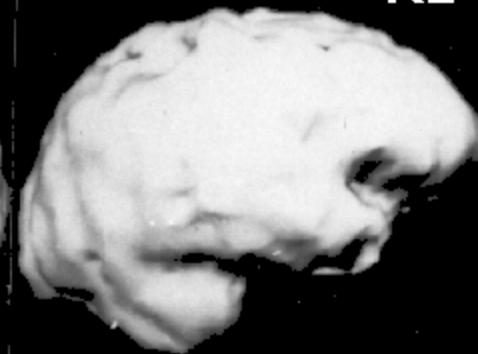
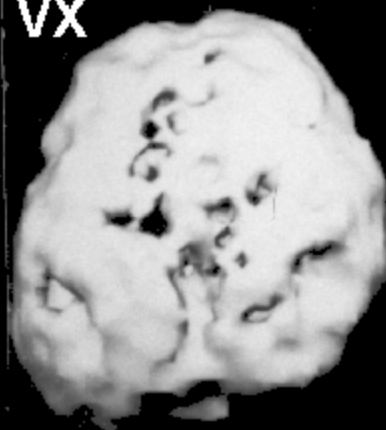
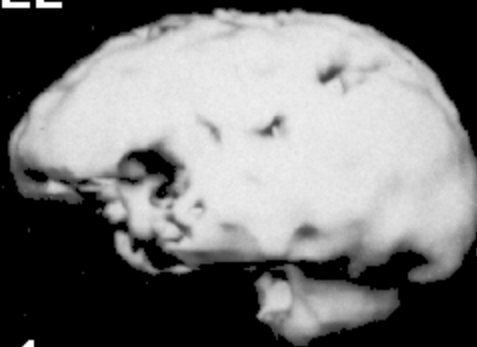
3



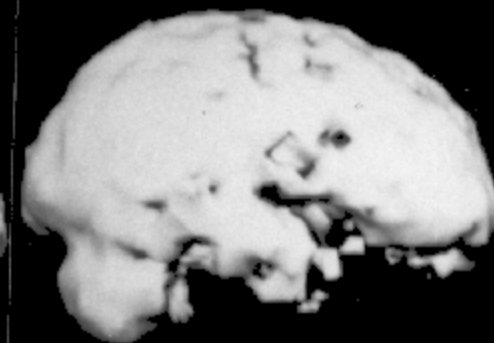
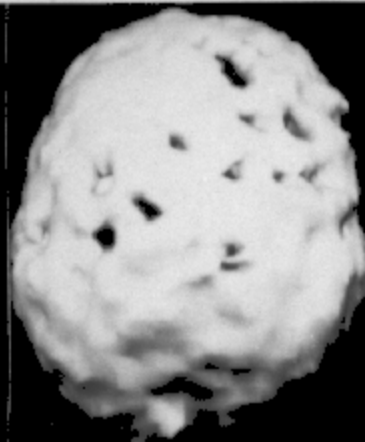
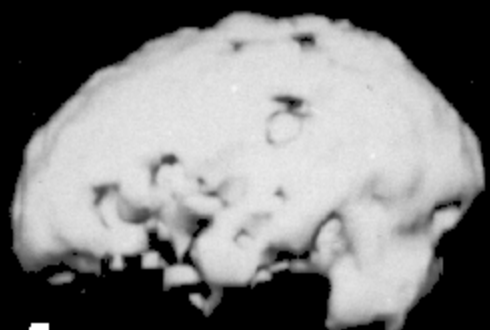
LL

VX

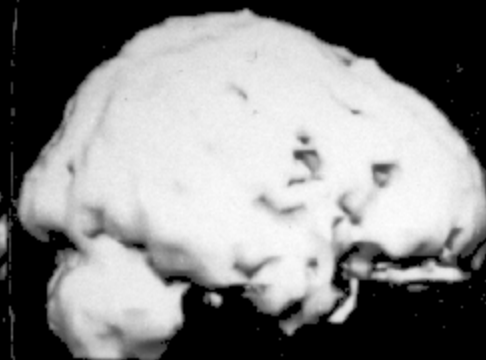
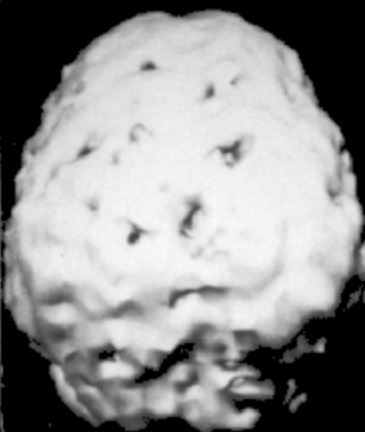
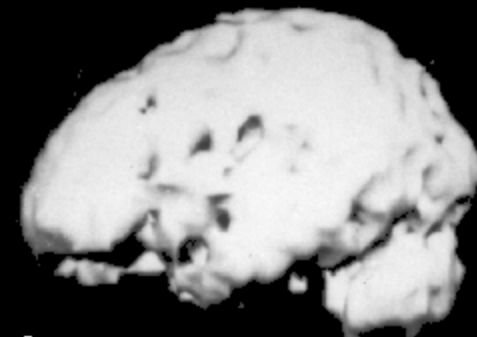
RL



4



5



6

LL

VX

RL

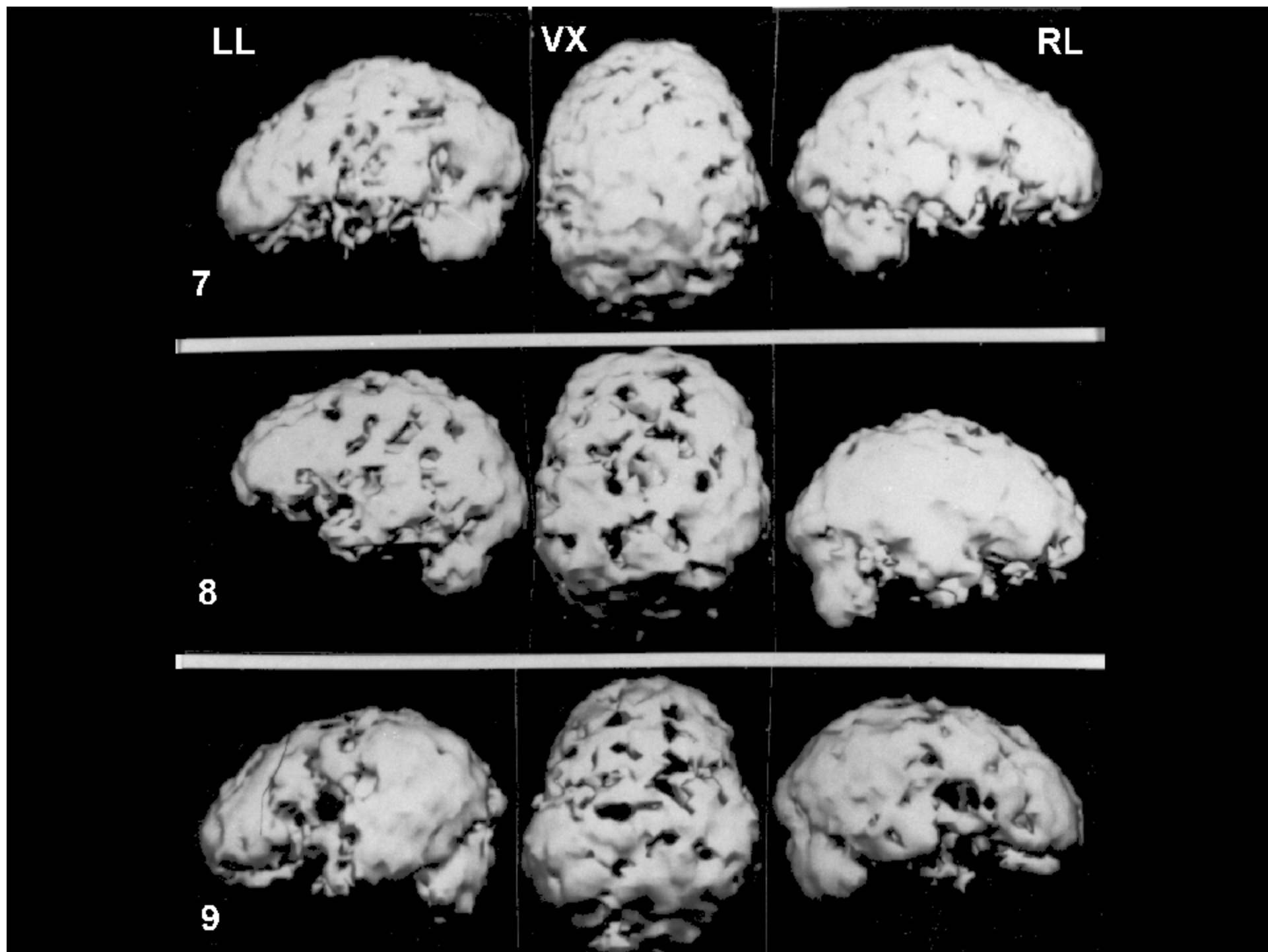
7



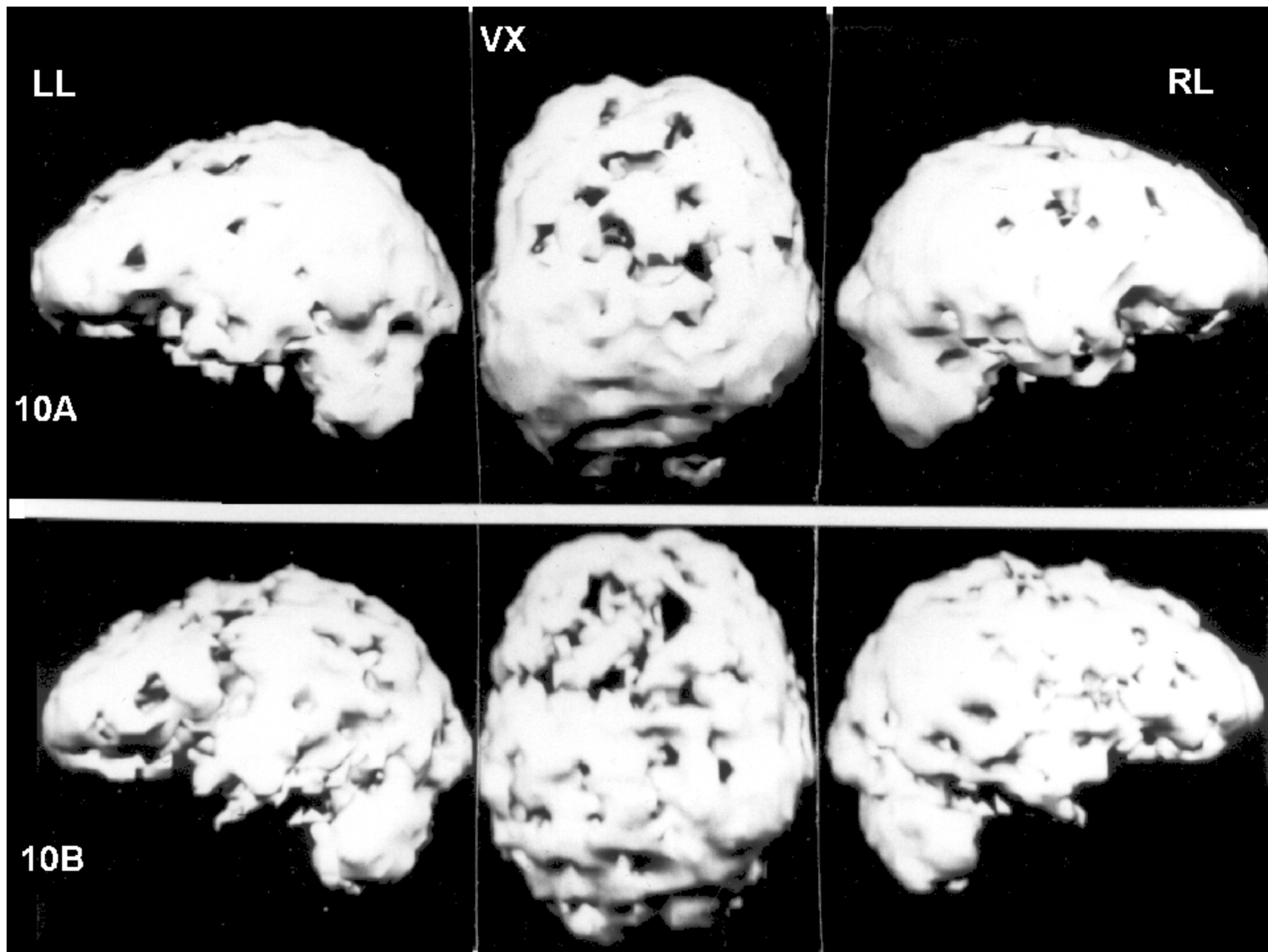
8



9





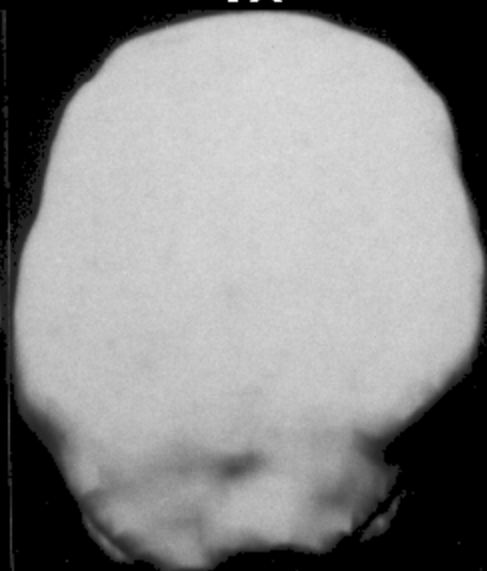


# Reference Populations

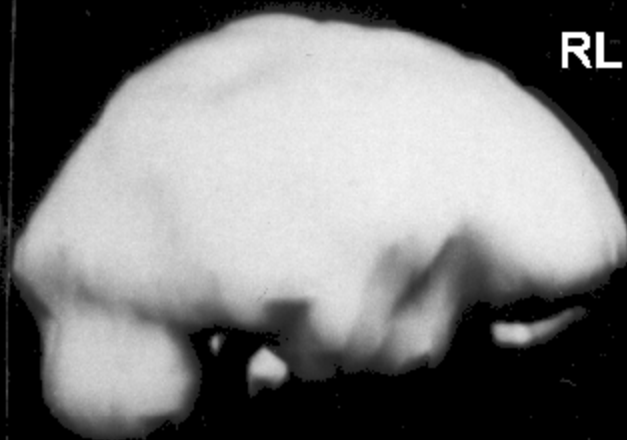
- Normal individuals
- PTSD patients
- Dementia patients with Alzheimer diagnoses
- Memory disorder (including alcohol use)

**24 y/o male, normal  
VX**

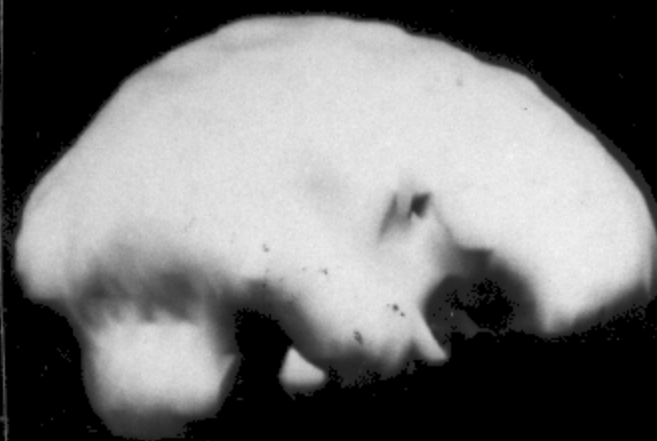
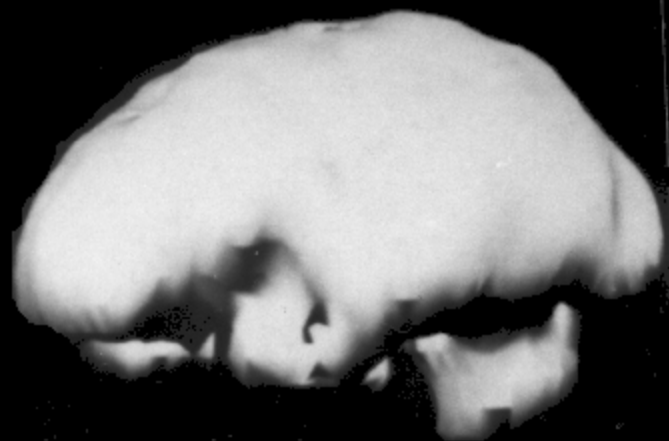
**LL**



**RL**

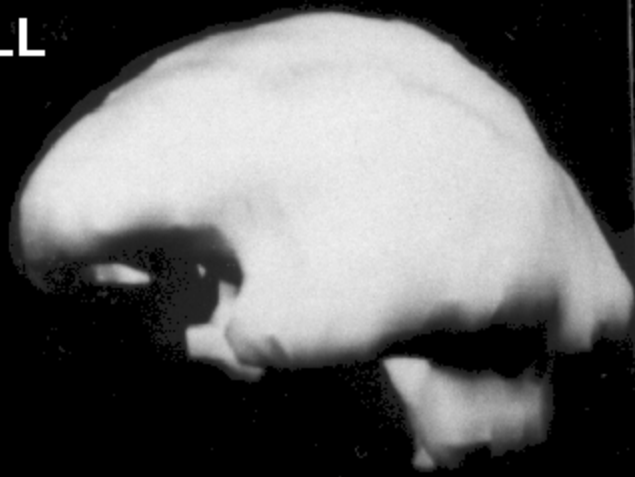


**46 y/o male, post-traumatic stress disorder**

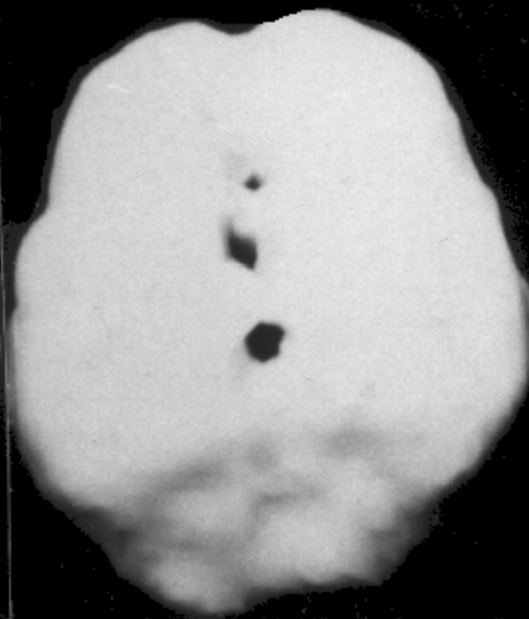


**79 y/o male , probable Alzheimer's disease**

**LL**



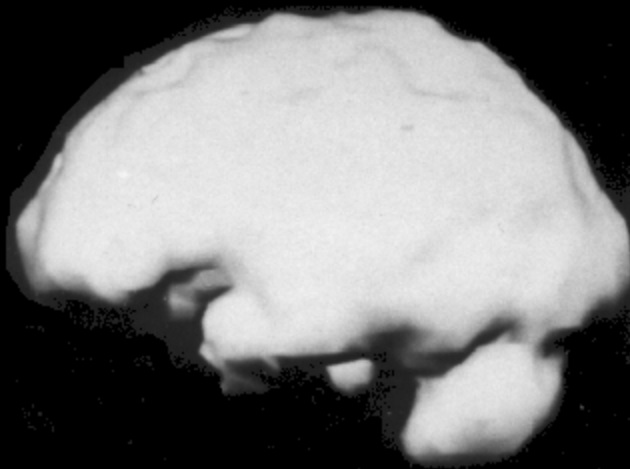
**near normal = 1**



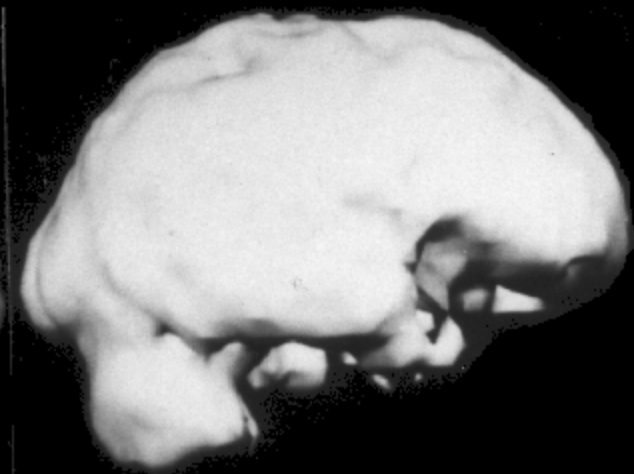
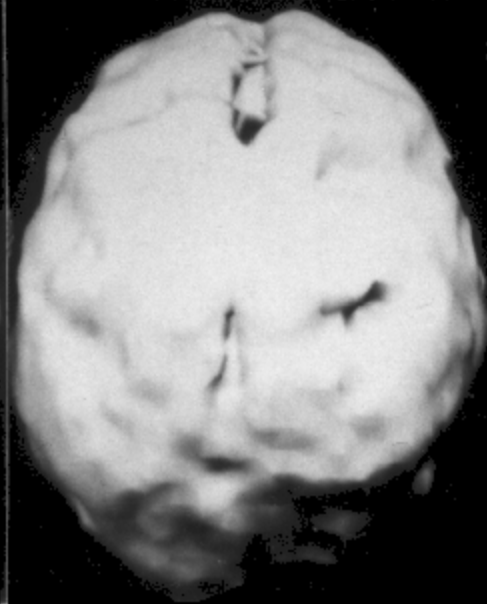
**RL**



**MMSE = 16**



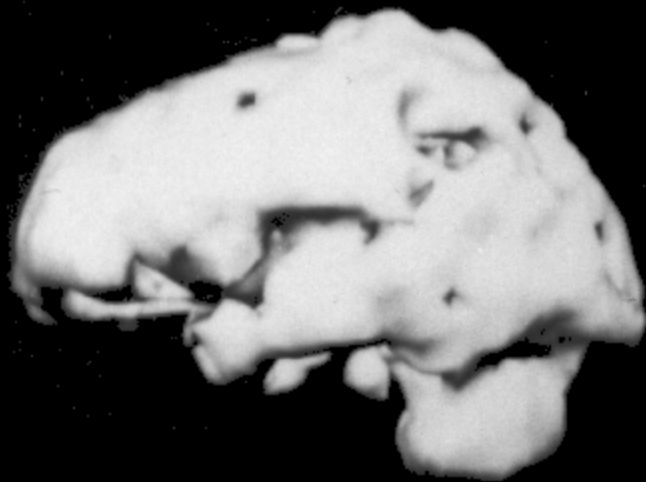
**mild = 2**



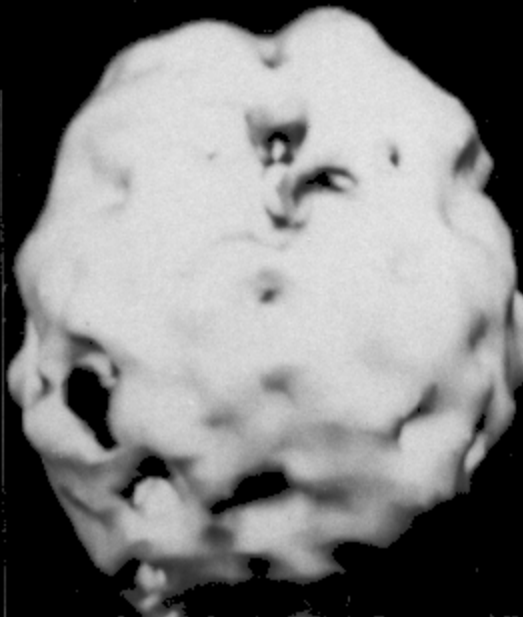
**16 months later  
MMSE = 14**

**74 y/o male with autopsy confirmed Alzheimer's disease**

**LL**



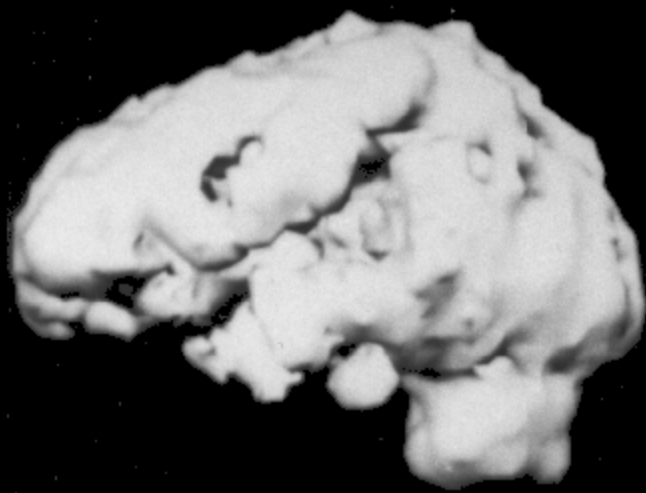
**mild to moderate = 3**



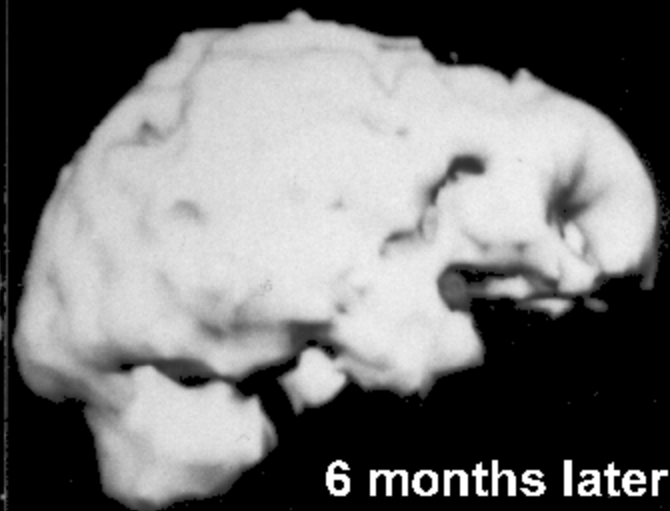
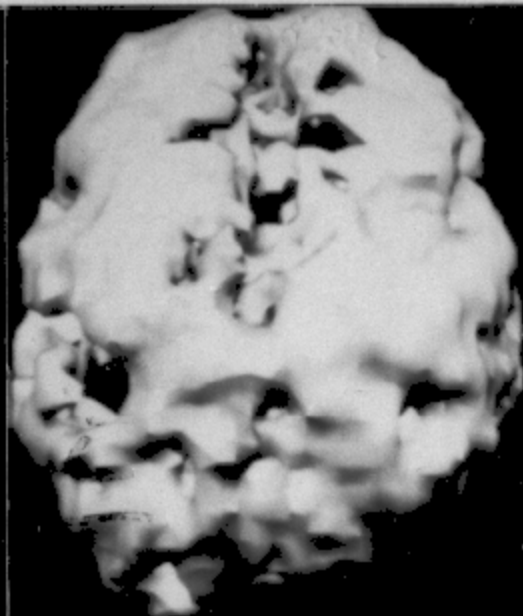
**RL**



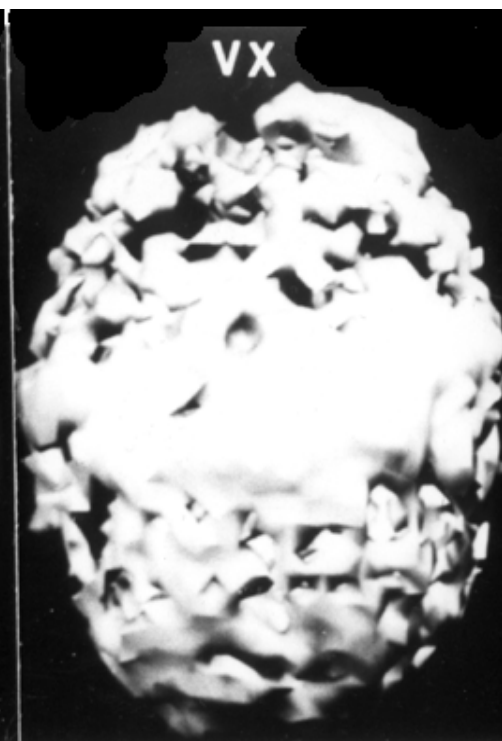
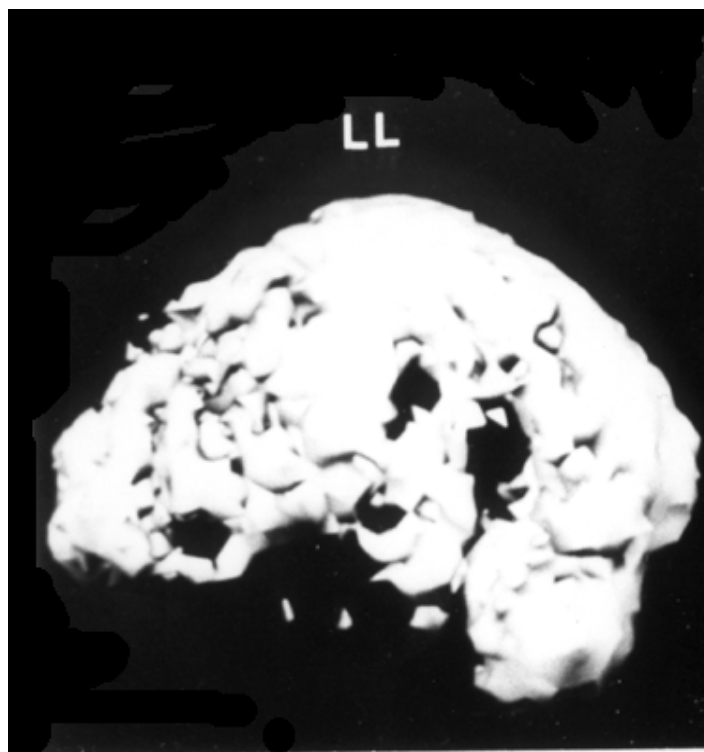
**MMSE = 13**



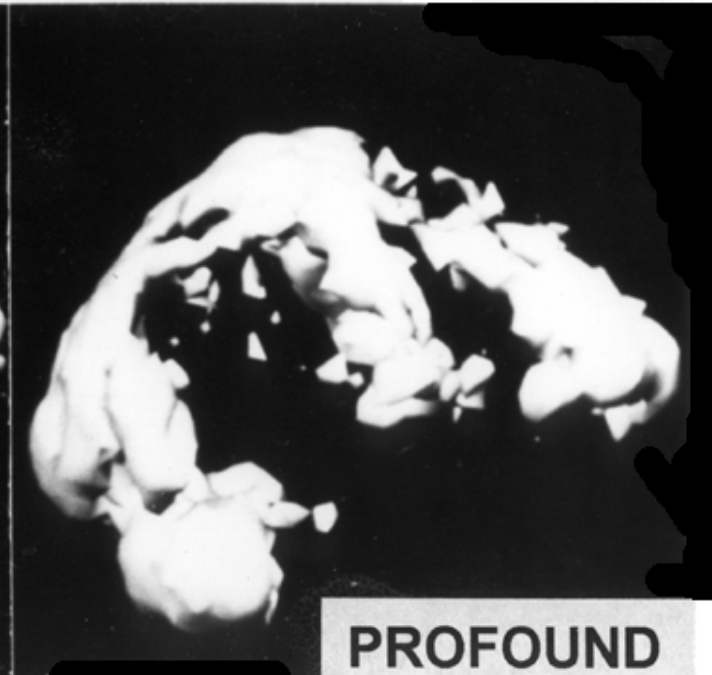
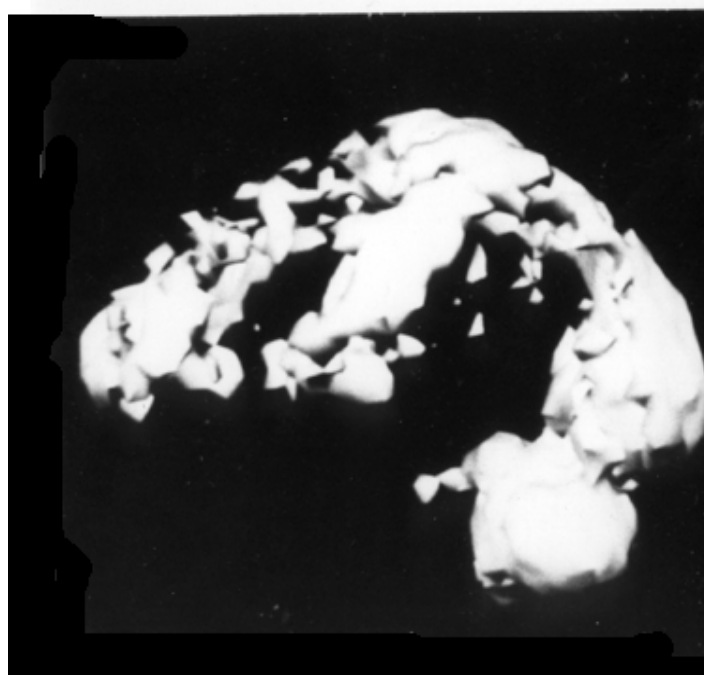
**moderate = 4**



**6 months later  
MMSE = 2**



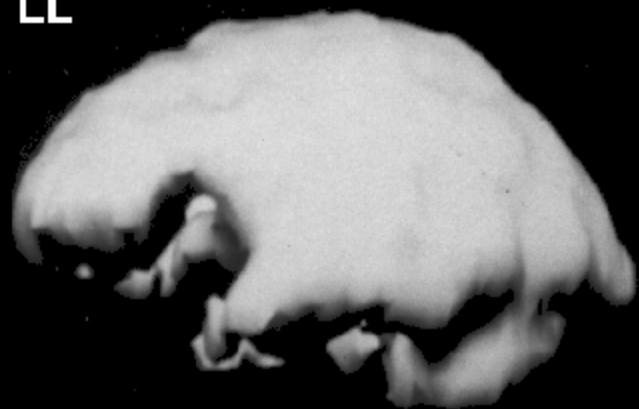
**SEVERE**



**PROFOUND**

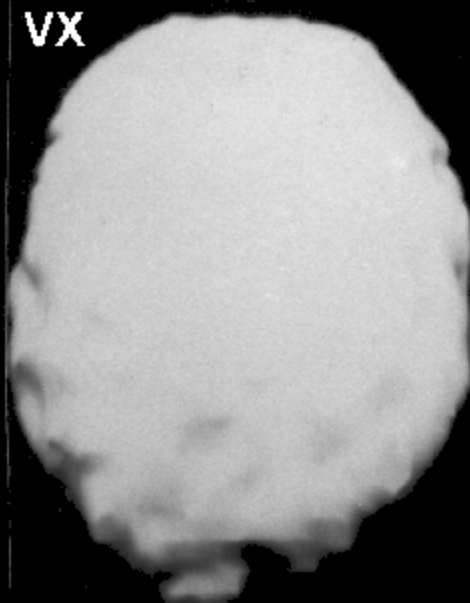
**50 y/o male with memory loss after a bout of EtOH abuse**

**LL**

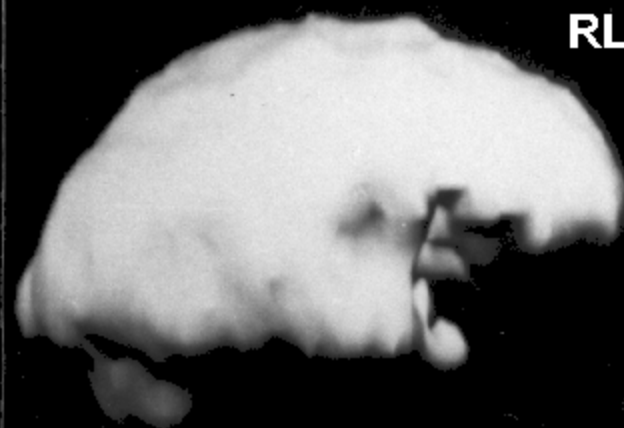


**normal = 0**

**VX**



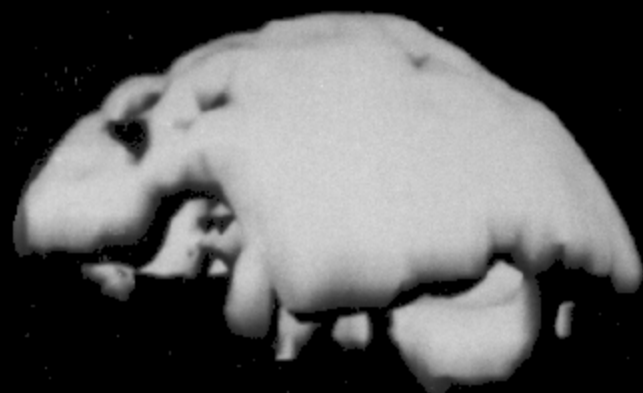
**RL**



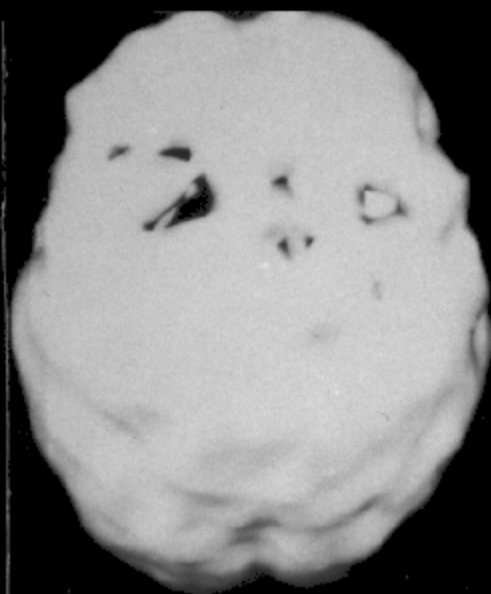
**MMSE = 23**

---

**62 y/o male with memory loss after a bout of EtOH abuse**



**near normal = 1**

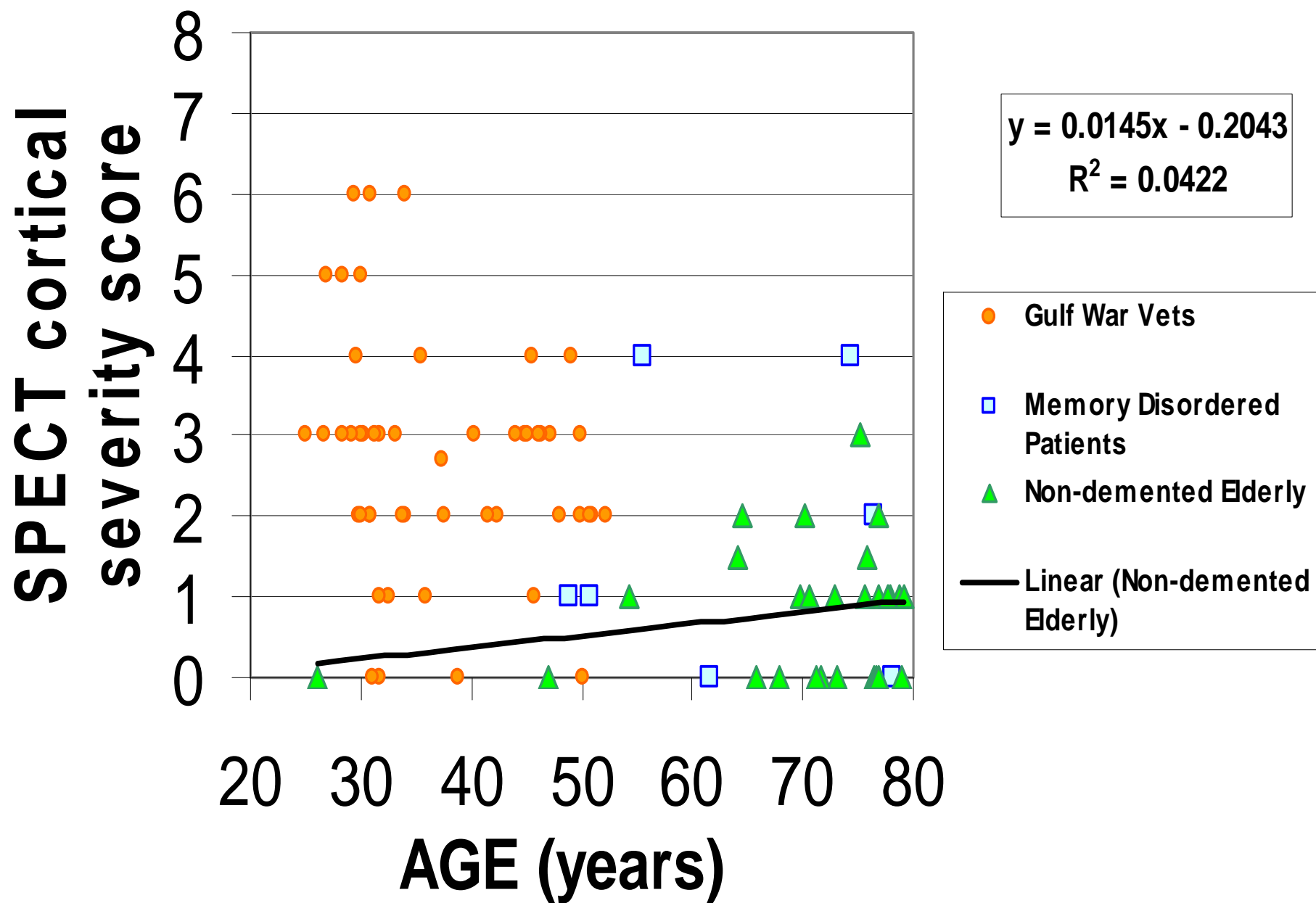


**MMSE = 14**  
**(23 months later, MMSE = 23)**



# Gulf Veteran SPECT gradations

<u>SPECT grade</u>	<u>N</u>	<u>average age</u>
• 0 (normal)	4	38 years
• 1 (near norm)	4	36
• 2 (mild)	14	40
• 3 (mild-mod)	17	36
• 4 (moderate)	4	40
• 5 (mod-severe)	3	29
• 6 (severe)	3	31



# Significance of SPECT changes in Gulf Vets with memory complaints

- Cortical gradations relative to normals:
  - $p < 10^{-9}$  (with respect to age)
- The pattern of changes in the cortex involve all cortical regions, including primary cortex
  - unlike Alzheimer's disease.
- Decreased perfusion in thalamus, basal ganglia
- Changes may be due to patient selection, normal variation of cortical blood flow.

# Findings in Gulf War Veterans with Multi-symptom Conditions

- Somatic Medical - normal x-rays of joints
- Neurological -
  - peripheral electrophysiological abnormalities
  - normal MRI scans
  - abnormal SPECT, MR spectroscopy
- Psychiatric -
  - depression
  - neuropsychological dysfunction - borderline

# FUNDAMENTAL PROBLEMS

- Gulf War Illness is considered to exist
  - (Institute of Medicine, 2009)
- There is no recognized “Gulf War Syndrome”
- There have been many dozen explanations that have been considered, but none has yielded an acceptable explanation

# What is this Multi-Symptom Illness?

- Could it be due to compensation neurosis?
- Could it be a conspiracy among Gulf Veterans?
- Could it be mass hysteria? (like other wars)
- Could functional brain changes be induced by psychological phenomena?
- Is there a relation to chronic fatigue syndrome, fibromyalgia, multiple chemical sensitivity?
- Are the brain abnormalities caused by:
  - an unknown agent,
  - due to unrelated pathology,
  - or are the abnormalities really normal variants inadvertently found on high-tech exams?

# Some of the Causes Considered

- Chemical Weapons and other chemical exposures
  - Sarin and Cyclosarin, Pyridostigmine Bromide, Organophosphate Pesticides, other chemical pesticides, CARC - Chemical Agent Resistant Coating, fuel, decontamination solution, oil fires
- Infectious Diseases
  - Leishmaniasis, travelers diarrhea, sandfly fever, malaria, and viscerotropic leishmaniasis found in 12 U.S. veterans
- Multiple vaccinations
  - Anthrax vaccine containing squalene as an adjuvant
- Depleted Uranium
- Aspartame/Methanol Poisoning
  - At 85 °F, aspartame breaks down into methanol which then breaks down into formaldehyde
- Biological Weapons
  - mycoplasma fermentans – may be combined with part of the AIDS virus



# Idiopathic Small Fiber Neuropathy

## (an example of a possible explanation)

- Caused by diabetes, HIV, Erythromelalgia, postherpetic neuralgia, CRPS, alcoholism, and many other nerve pain conditions
- Cause is also commonly idiopathic
- There are no known causes for most cases and most tests do not identify it
- Peripheral nerve fibers that can be affected include peripheral autonomic neurons (acetylcholine, epinephrine), pain fibers (substance P) (like causalgia)
- Central small nerve fibers could also be affected (acetylcholine, norepinephrine, serotonin, others)
- Cholinergic fibers supplying cerebral blood vessel could be the a major, vulnerable system

# Plausible biological explanations for small nerve fiber damage

- Anti-cholinesterase agents (insecticides, DEET, permethryn, flea collar stories, sarin exposure, combinations, PB predisposal or potentiation - blocks peripheral, not central AChE).
- Spider Bites – toxin, not infectious agent, but a biological toxin that could damage small neurons
- RADAR (radio-frequency injury to neurons – has extensive literature, not considered a problem under normal circumstances, but there was a tremendous amount of radar in use in the First Gulf War) – heat may increase sensitivity
- Immunological response – chronic response to infectious agent attacking small neurons (like Guillan-Barre syndrome)
- Reaction of body to severe diarrhea or agent that caused severe diarrhea (local fruits, vegetables given to soldiers deployed early, those soldiers deployed later did not seem to get the condition)

There are no approaches for treating  
idiopathic small fiber neuropathy

Single cause or multiple causes of the  
multiple symptoms of the Veterans  
from the First Gulf War may never be  
determined

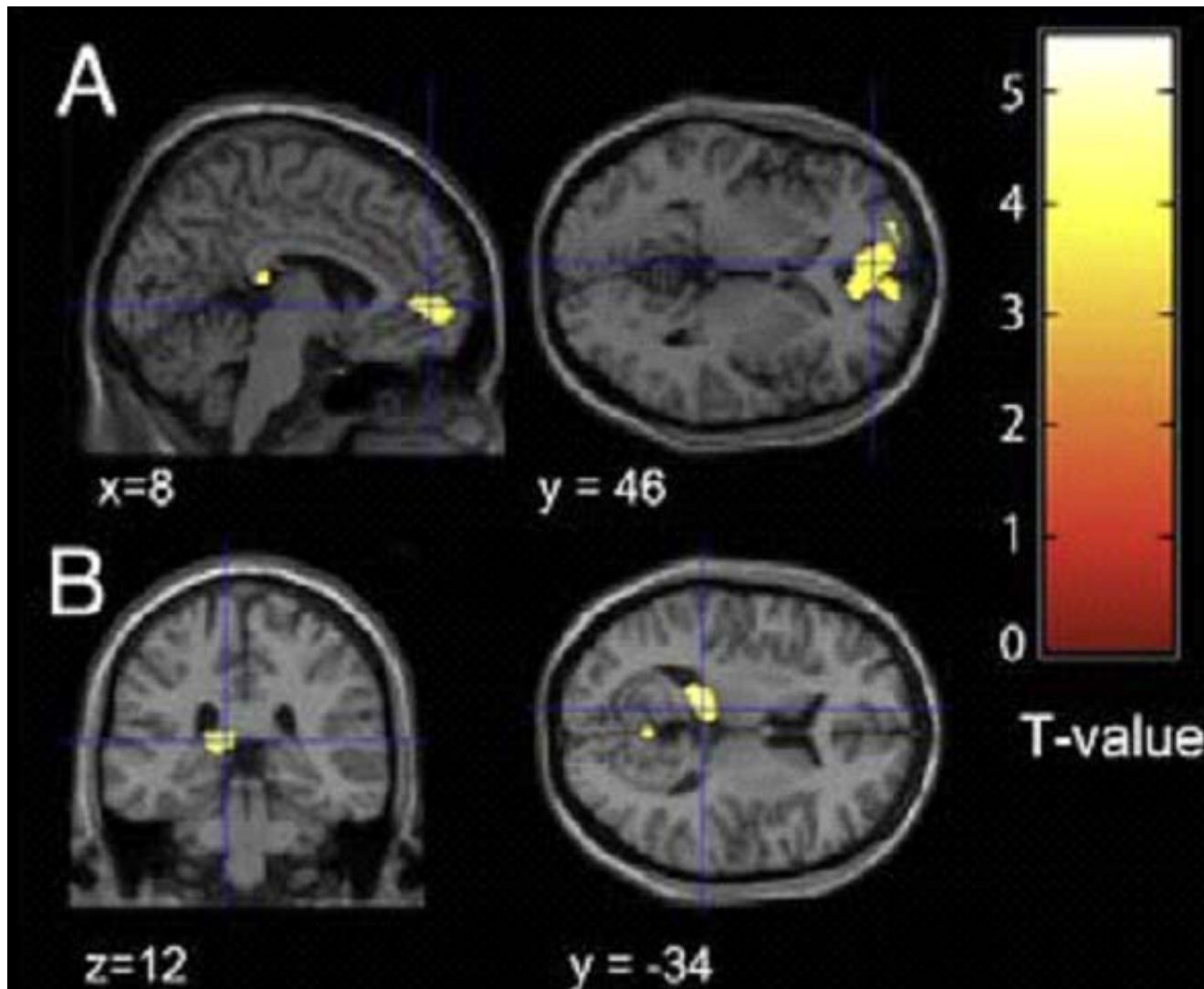
Treatments must address the  
symptoms of the Veterans, minimize  
their discomfort, and maximize their  
function

# Results of Iowa Study – 3,695 Veterans:

Symptoms, % Prevalence

	Non-GW			
	GW Veterans		Veterans	
Fibromyalgia	19.2		9.6	
Cognitive Dysfunction	18.7		7.6	
Alcohol Abuse	17.4		12.6	
Depression	17.0		10.9	
Asthma	7.2		4.1	
PTSD	1.9		0.8	
Sexual Discomfort	1.5		1.1	
Chronic fatigue	1.5		0.3	

Iowa Persian Gulf Study Group, 1997



Regions of the brain where healthy controls have higher activity the Fibromyalgia Syndrome patients during subjectively calibrated painful stimulation minus sensory stimulation.

- Clusters corresponding to (A) the rACC, and (B) the pulvinar nucleus of thalamus.
- The exact locations (x,y,z) are given in MNI coordinates.

Jensen et al., 2009

# rTMS for the Treatment of Chronic Pain in GW1 Veterans

(repetitive Transcranial Magnetic Stimulation)

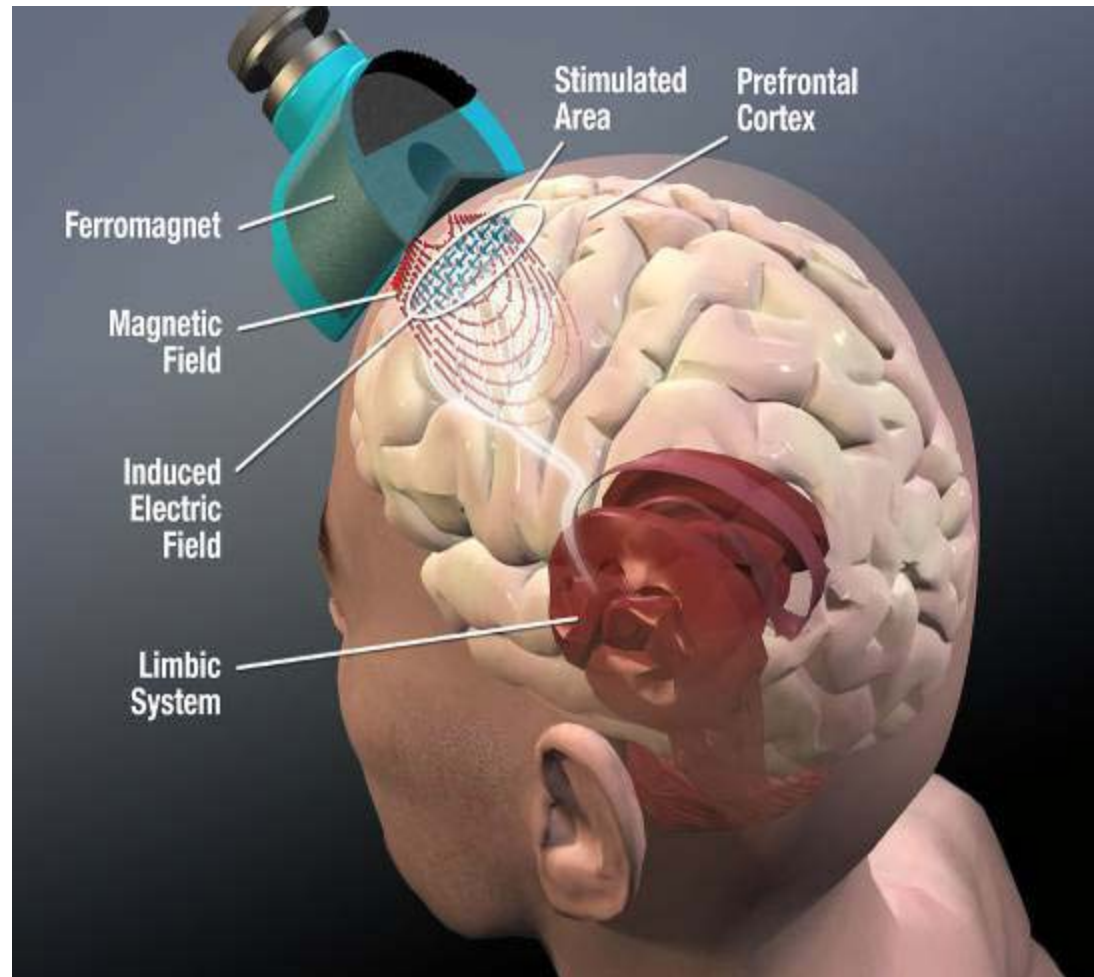
(proposal submitted for  
VA Merit Review System,  
2010)

This project will study 206 Veterans with Gulf War Illness (GWI) whose symptoms include chronic pain. The first aspect of this study will evaluate a series of Gulf War One (GW1) veterans to identify individuals with these symptoms which in addition to chronic pain may include respiratory difficulty, gastrointestinal problems, dermatologic problems, chronic fatigue, depression, substance abuse, anxiety, cognitive problems and posttraumatic stress disorder (PTSD). Following screening to determine eligibility and informed consent, Veterans will be randomly assigned to treatment or sham (placebo) for the study. Additional examinations will compare brain imaging (PET-FDG) across participants. Also, genetic data will be gathered for a pilot sub-study analysis that examines gene relationships with GWI symptomatology

To determine whether repetitive Transcranial Magnetic Stimulation (rTMS) can be effective in treating the symptoms of chronic pain among Veterans with GWI, this project will evaluate the efficacy, safety, durability of benefits and cost-effectiveness of rTMS in the rehabilitation of Veterans with chronic pain in the context of multiple GWI symptoms. We will specifically compare 103 patients receiving rTMS with 103 sham treated patients. Care will be taken to account for common conditions associated with GWI, including fatigue, gastrointestinal problems, dermatologic problems, respiratory problems, cognitive dysfunction, depression, anxiety disorders, substance abuse, and PTSD.

It is the intent of this study to determine if the newly FDA-approved treatment for depression, rTMS, may have some benefit to Veterans with GWI and chronic pain.

Diagram of simulated rTMS delivery





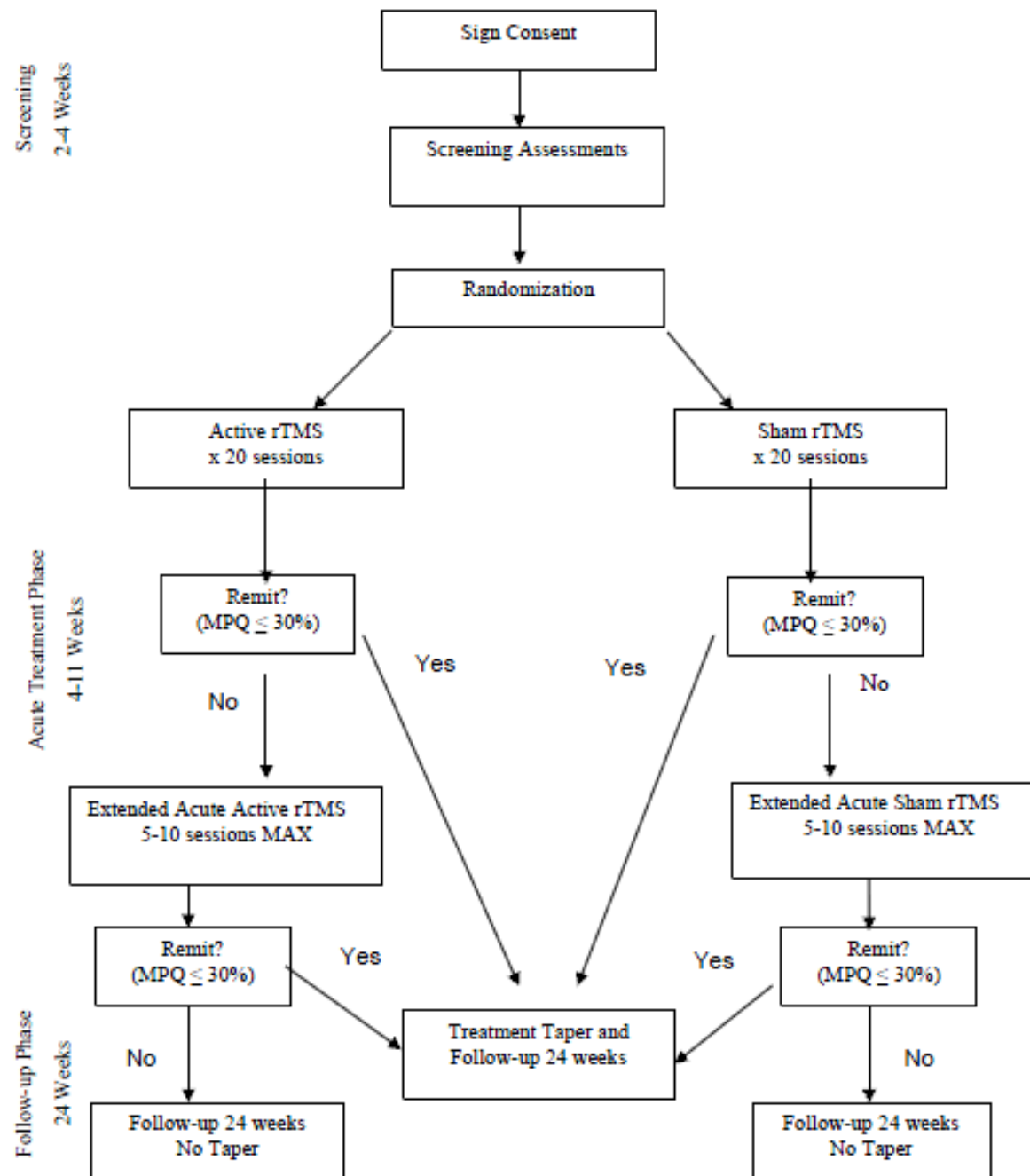


Figure 5: Overview of Research Design

# Other Possible Treatments for Pain and other Symptoms of Veterans from the First Gulf War

- More exercise – non-impact:
  - Swimming pools (arthritic water temperature – need more)
  - CAM, YOGA
  - Elliptical exercise machines
  - Stretching routines
  - Many hours per day
- Need to focus on helping Veterans:
  - symptomatic therapies

# References

- 1. Murphy FM, Kang H, Dalager NA, et al.: The health status of Gulf War veterans: lessons learned from the Department of Veterans Affairs Health Registry. *Mil Med.* 164(5), 327-31 (1999).
- 2. Iowa Persian Gulf Study Group: Self-reported illness and health status among Gulf War veterans. A population-based study. The Iowa Persian Gulf Study Group. *Jama.* 277(3), 238-45 (1997).
- 3. Jensen KB, Kosek E, Petzke F, et al.: Evidence of dysfunctional pain inhibition in Fibromyalgia reflected in rACC during provoked pain. *Pain.* 144(1-2), 95-100 (2009).