

Research Advisory Committee on Gulf War Veterans' Illnesses



DR. J. WESSON ASHFORD

War Related Illness and Injury Study Center (WRIISC) CA
VA Palo Alto Health Care System
Stanford University

Gulf War Illnesses (GWI)

Acetyl-cholinesterase inhibitor withdrawal hypothesis: Tardive Dysautonomia

**Research Advisory Committee on Gulf War
August 4, 2021**

J. Wesson Ashford, MD, PhD
Director, WRIISC-CA
VA Palo Alto Health Care System
wes.ashford@va.gov
www.warrelatedillness.va.gov

What is Gulf War Illness (GWI)?

- A condition that affects 30-40% of Veterans who were deployed to Operations Desert Shield/Storm/Sabre (ODS/S/S)
- Collection of symptoms
- Weak diagnostic criteria
- No accepted pathophysiological explanation
- Variety of unestablished biomarkers
- No specific treatment

Results of Iowa Study – 3,695 Veterans:

Symptoms, % Prevalence

	GW Veterans	Non-GW 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

Most Frequent Symptoms, Affected Systems of Veterans from Gulf War 1

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

Symptoms

– 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

Percentage

Systems

– Musculoskeletal and connective tissue	25.4
– Mental disorders	14.7
– Respiratory system	14.0
– Skin and subcutaneous tissue	13.4
– Digestive system (irritable bowel syndrome)	11.1
– Chest pain	3.5

SOURCE: Murphy et al., 1999

- Symptoms of fibromyalgia

2012-2013 VA Follow-up Study on 30,000 Gulf War Veterans

- 44% still reported symptoms consistent with unexplained multi-symptom illness
- Deployed Veterans continue to report:
 - Joint stiffness and chronic pain (fibromyalgia?)
 - Fatigue (chronic fatigue syndrome?)
 - Gastrointestinal (irritable bowel syndrome?)
 - Respiratory concerns (shortness of breath, asthma, respiratory concerns)
 - Skin rashes
 - Sleep issues (insomnia, loss of circadian rhythm, waking during the night)
 - Mental Health (depression, anxiety, mood changes)
 - Cognitive dysfunction and memory complaints

Gulf War Illness criteria for In-Depth Study (NIH/WRIISC DC)

CDC	KANSAS	MODIFIED KANSAS
<p>One symptom required in at least two of the following domains:</p> <ol style="list-style-type: none"> 1) fatigue 2) mood and cognition (feeling depressed, difficulty remembering/concentrating, feeling moody, anxious, trouble finding words, difficulty sleeping) 3) musculoskeletal (joint pain, joint stiffness, muscle pain) <p>No exclusions.</p> <p>Severity not included in determining case.</p>	<p>Multiple moderately severe symptoms (>=6 months) in at least 3 of the 6 symptom domains:</p> <ol style="list-style-type: none"> 1) fatigue and sleep problems 2) somatic pain symptoms 3) neurologic/cognitive/mood symptoms 4) gastrointestinal symptoms 5) respiratory symptoms 6) skin symptoms <p>Exclusions: Any serious medical or psychiatric diagnosis that accounts for symptoms, or prevents accurate symptom reporting.</p> <p>Must have at least 1 moderately severe symptom or 2 or more symptoms within each symptom domain.</p> <p>Symptoms developed as a consequence of deployment to Operation Desert Shield/Desert Storm, August, 1990 – June, 1991.</p>	<p>Kansas definition that also meets the CDC case definition, and includes the following modifications / allowances:</p> <p>Common diseases of aging, such as hypertension and type II diabetes, if the conditions are treated, demonstrably stable, and within normal range at the time of screening and assessment.</p> <p>Stable comorbid conditions, such as PTSD, MDD and mild TBI, that have not required hospitalization in the five years prior to recruitment.</p>

IOM 2014 CMI Case Definition Report recommended VA use CDC and Kansas case definitions because they capture the most commonly reported symptoms of Gulf War Illness (National Academies Report, 2014).

Clinical evaluation requires a thorough physical exam, mental status exam, minimum battery of lab tests. Symptoms should be assessed systematically using standardized instruments that assess functional status and symptom domains. Some medical conditions will resolve or are adequately managed with treatment and should therefore be considered temporary exclusions (Reeves et al., 2003).

Gulf War Illness Findings

No Identified Diagnostic Entity

- **Somatic Medical** – chronic pain (normal x-rays of joints)
- **Gastro-intestinal** – irritable bowel syndrome (no path changes)
- **Psychiatric** –
 - Chronic Fatigue, Sleep Problems, Depression (brainstem disorders)
 - neuropsychological dysfunction – borderline but complaints common
- **Neurological** -
 - peripheral electrophysiological abnormalities
 - normal MRI, PET scans
 - abnormal SPECT, MR spectroscopy, DTI of brain stem
- **Possible relation to other conditions**
 - chronic fatigue syndrome, fibromyalgia, multiple chemical sensitivity

Operation Desert Shield/Desert Storm Exposures

- CARC Paint
- Chemical and Biological Weapons
- Depleted Uranium
- Harsh living conditions
- Incoming fire, explosive events
- Industrial solvents and chemicals
- Infections
- Injuries, musculoskeletal wear and tear
- Oil Well Fires, Smoke, and Petroleum
- Loud noises
- Pesticides
- Physical and Mental Stressors
- Pyridostigmine Bromide
- Sand, Dust, Airborne Particulate Matter
- Vaccinations
 - Multiple in short period of time

REF: WRIISC Clinical Reports

Possible ODS/S/S Chemical Weapon Exposures

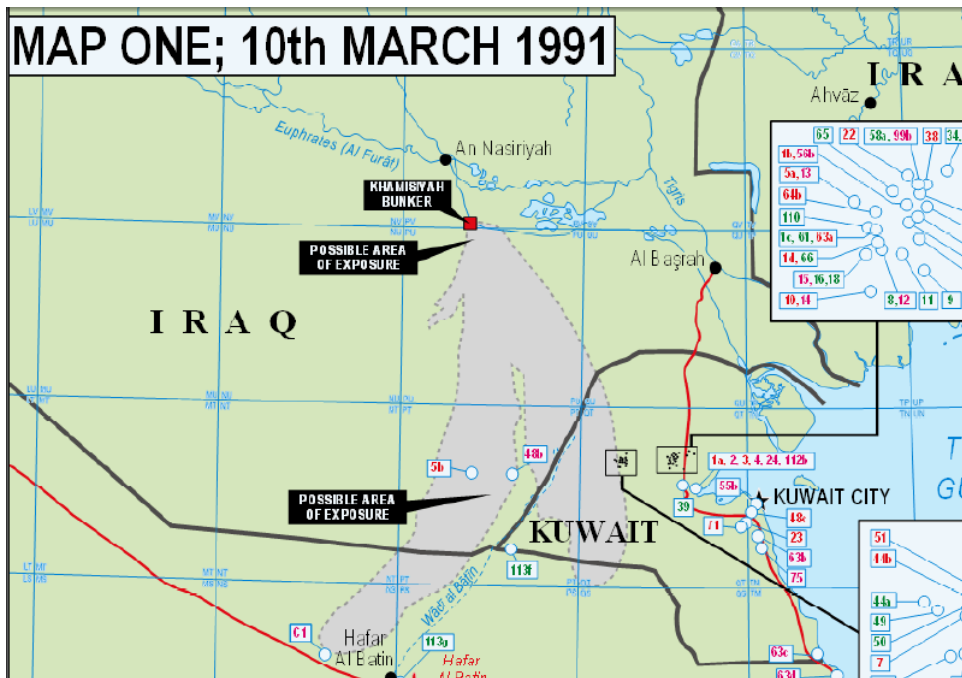
Many chemical alarms sounded, troops told to put on MOPP suits as protection – feared life-threatening attacks

- Anecdotal reports of isolated chemical weapon exposures to nerve agents, however no cases of acute poisoning were documented
- U. S. destroyed ammunition depot in Khamisiyah containing sarin and cyclosarin nerve agents
 - DoD notified 100,000 Veterans that they may have been exposed to low levels of chemical agents
 - There were several detonations
- No specific tests available to detect sarin or cyclosarin exposure

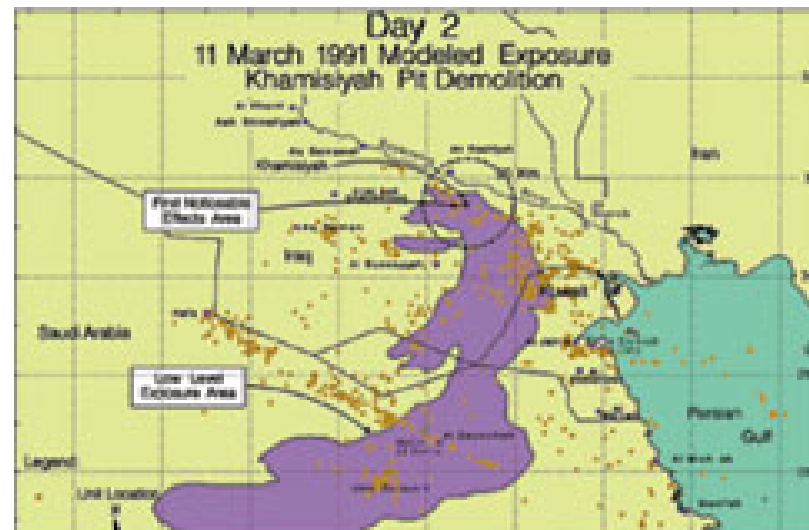


Initial Cloud from Khamisiyah Explosion

Model of Sarin Exposure from Khamisiyah



DGIA Ministry of Defense, UK, 2004
(several detonations in March)



Models of chemical exposure were developed using data supplied by NRL from the Coupled Ocean/Atmosphere Mesoscale Prediction System (COAMPS). COAMPS, which generates high resolution numerical models of the atmosphere, is an analysis-nowcast and forecast tool applicable for any given region of the earth.

Due to the fear of sarin exposure, pyridostigmine bromide (PB pills) was given emergency approval for use as a nerve-gas protection and was widely used in this same region.
PB is commonly used as a treatment for myasthenia gravis by neurologists.

Some of the Causes Considered

- Chemical Weapons and other chemical exposures
 - Acetyl-cholinesterase inhibitors: Sarin and Cyclosarin, Pyridostigmine Bromide (PB), Organophosphate Pesticides, other chemical pesticides
 - Other potentially neurotoxic agents: CARC - Chemical Agent Resistant Coating, fuel, decontamination solutions, oil fire smoke
- Infectious Diseases
 - Leishmaniasis, traveler's diarrhea, sandfly fever, malaria, and viscerotropic leishmaniasis found in 12 U.S. veterans
- Multiple vaccinations
 - Anthrax vaccine containing squalene as an adjuvant (normal skin fat)
 - Many vaccinations given close together inducing neural inflammation
- Depleted Uranium (no evidence or plausible link)
- Aspartame/Methanol Poisoning
 - At 85 °F, aspartame breaks down into methanol, formaldehyde
- Biological Weapons
 - mycoplasma fermentans – may be combined with part of the AIDS virus
 - (cover of Popular Science Magazine April 1999 – no support since 2002)

FUNDAMENTAL PROBLEMS

- Gulf War Illness is considered to exist
 - (Institute of Medicine, 2009)
- There has been no recognized “Gulf War Syndrome” since there is no known disease process
 - Definition of “syndrome”: “a combination of symptoms and signs that together represent a disease process”
- There have been at least 40 theories that have been considered, but none has yielded an acceptable explanation

Nervous System Sites as Possible Attack-points of Gulf War Illness Pathophysiology

- Peripheral nerves – sensory, pain, small fiber neuropathy
- Autonomic Nervous System - dysautonomia
 - Parasympathetic: brainstem (esp: vagus nerve), base of spinal cord
 - Sympathetic – spinal cord
- Brainstem - Central control of body energy
 - Energy feelings/motivation/fatigue/sleep
 - Respiration control, respiration during sleep (OSA), lung management
 - Cardiac, blood pressure control, blood flow control including brain
 - Bowel activity (note highly sensitive to cholinergic, anti-cholinergic drugs)
 - Temperature control, skin dilation, blood flow to skin, sweating
 - Pain management, control (peri-aqueductal gray)
 - Management of anxiety, mood, memory
 - Vigilance, awareness of the environment, consciousness (dorsal, RAS, PTSD)
- Cortex, basal ganglia
 - Direct injury versus compromise of blood flow

Small Fiber Neuropathy

- Can be 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)
- Central small nerve fibers could also be affected (acetylcholine, norepinephrine, serotonin)

Plausible biological explanations for small nerve fiber damage

- **Anti-cholinesterase agents** (sarin exposure, combinations, PB predisposal, insecticides, flea collar use, not permethryn).
- **Spider Bites** – biological toxin that could damage small neurons (not infectious agent)
- **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)

Dysautonomia

- Dysautonomia is common in fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome, raising the possibility that such dysautonomia could be their common clustering underlying pathogenesis.
- **BUT**, GWI occurs late in Gulf War Veterans, usually after return (tardive; not a dystrophy –may be an excess of connections)
- The Gulf War Veterans have many symptoms
 - usually unexplained (most have possible autonomic relationship)
 - conditions with a clear cause get specific treatment recommendations)
- The autonomic nervous system is under control of the brain stem, so dysautonomia can be caused by disruption of the brain stem.

Tardive Dysautonomia in GWI

Acetyl-cholinesterase inhibitor withdrawal hypothesis:

- **Dysautonomia can account for all GWI symptoms**
- Since the autonomic nervous system is controlled by the brain stem, any condition affecting the brainstem could explain the condition
- Tardive means developing later (tardy), and this term describes the late onset of symptoms associated with GWI, i.e., weeks, months, or even years after return
- Acetyl-cholinesterase is an enzyme which breaks down the neurotransmitter acetylcholine, which is the primary neurotransmitter of the autonomic nervous system (including the Vagus Nerve), the neurons which innervate all muscles (including smooth muscles).
- There are acetylcholine neuronal cell bodies in several nuclei of the brainstem and the basal ganglia
- Many ODS/S/S soldiers took pyridostigmine bromide (PB tablets) a peripherally acting inhibitor of acetyl-cholinesterase (to protect against fatality if exposed to sarin nerve gas, also a cholinesterase inhibitor), including most of those reporting symptoms suggestive of GWI. Some of the insecticides the soldiers were exposed to were also cholinesterase inhibitors (not DEET).

Tardive Dysautonomia in GWI (cont.)

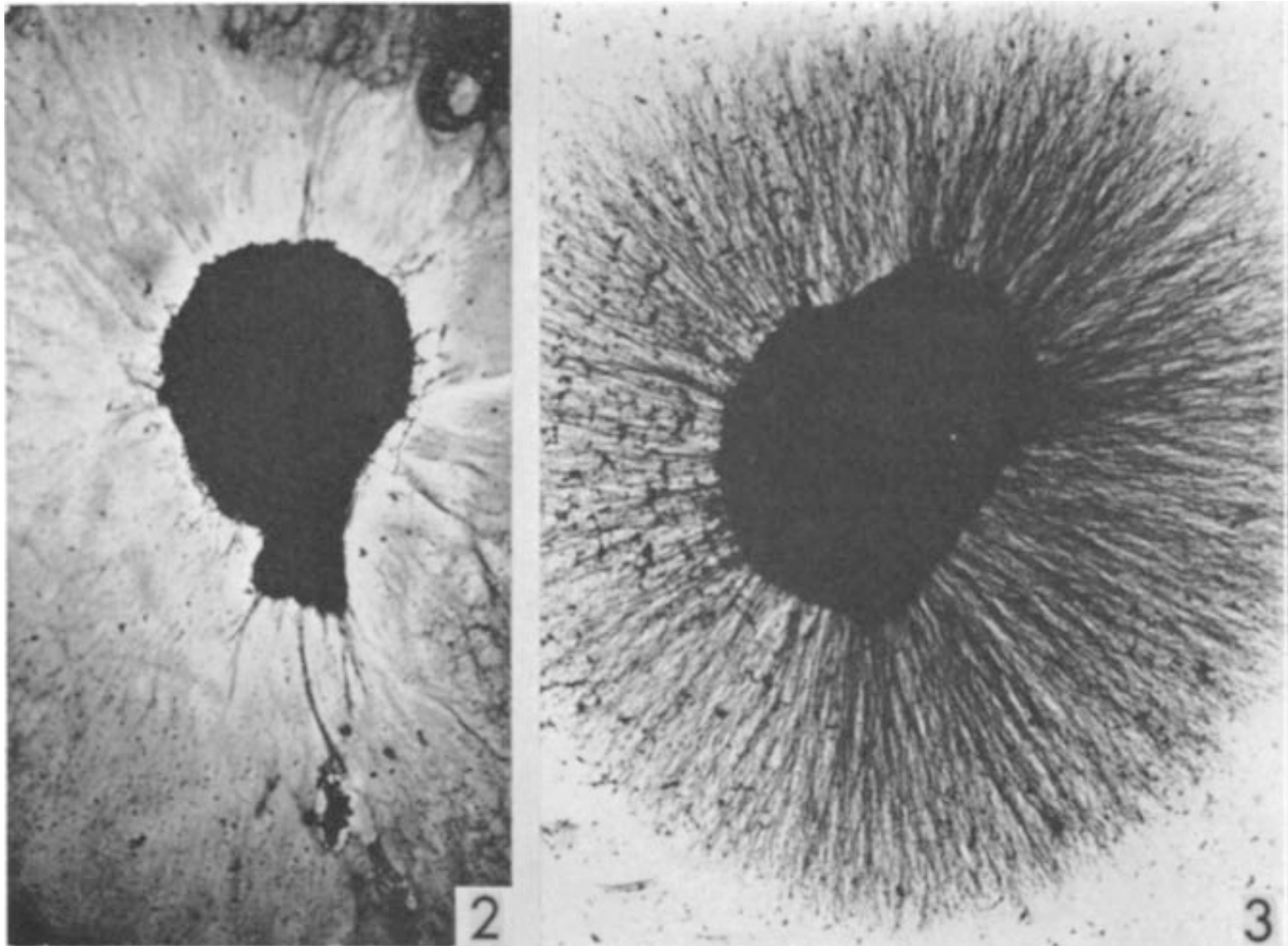
Acetyl-cholinesterase inhibitor withdrawal hypothesis:

- While exposed to cholinesterase inhibitors, the cholinergic synapses will have an excess of acetylcholine
- PB tablets (pyridostigmine is a cholinesterase inhibitor which is a “polar compound” that tends not to enter the brain) will increase the acetylcholine at peripheral synapses. PB effects include increase bowel motility, slowing of the heart rate, and many other changes
- In response to excess acetylcholine, neurons will down-regulate the neurotransmitter receptors (muscarinic in the case of the autonomic nervous system) and increase production of acetyl-cholinesterase molecules
- When the cholinesterase inhibitor is removed (e.g., PB, other), there is an excess of acetyl- cholinesterase and decrease cholinergic activation. So, target neurons responsively produce **“nerve growth factor” (NGF)**, which is retrogradely transported to the neuronal cell bodies (in the brain stem) to stimulate the acetylcholine neurons to grow more connections
- The excess sprouting of autonomic nervous system axons (nerve fibers) can explain the excess pains, the chronic fatigue (constant efforts to conserve energy), and the irritable bowel syndrome (Vagus Nerve) as well as neurocognitive and dermatologic conditions (skin blood flow is managed by the autonomic nervous stem)

NGF (nerve growth factor)

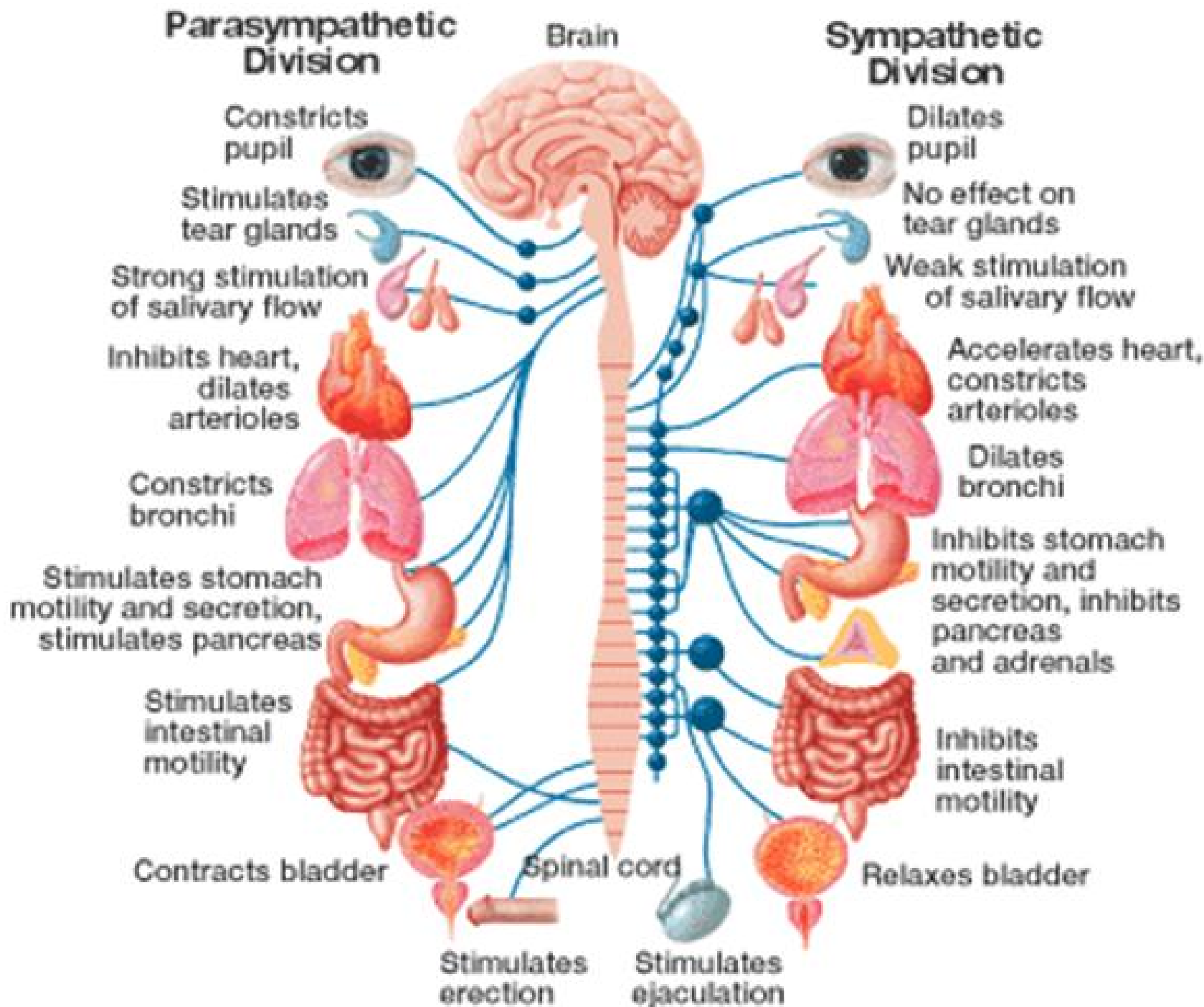
- Autonomic neurons leaving the brain and spinal cord are all cholinergic, as are post-ganglionic parasympathetic neurons, but sympathetic post-ganglionic neurons are noradrenergic
- NGF stimulates the outgrowth of sympathetic (norepinephrine) post-ganglion fibers
- NGF is required by acetylcholine neurons of the brain for survival
- **NGF injections cause chronic pain syndromes**
 - (seen in Alzheimer's disease subjects in a clinical trial)
- NGF genetic abnormalities are associated with a lack of pain sensation (Carvalho et al., 2014)
- Sympathetic neurons also moderate gut motility and blood flow everywhere, including the brain, and pathways to the pineal gland moderate sleep and energy levels

Nerve Growth Factor (NGF) effect (Right) on sympathetic ganglion



Levi-Montalcini, Booker, PNAS, 1960

Levi-Montalcini won the Nobel prize for this image in 1986

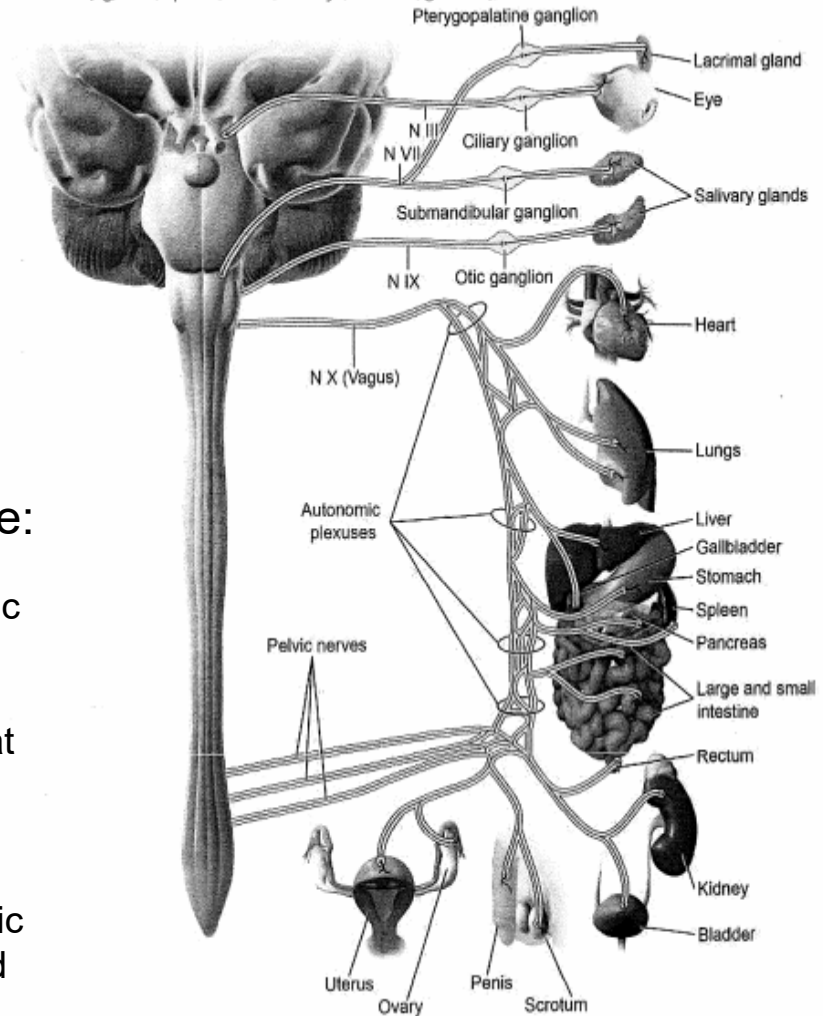


Divisions of the Autonomic Nervous System

Division	Effects
Sympathetic	<p>Increases the following:</p> <ul style="list-style-type: none"> • Heart rate and contractility • Bronchodilation • Hepatic glycogenolysis and glucose release • BMR • Muscular strength <p>Causes sweaty palms</p> <p>Decreases less immediately life-preserving functions (eg, digestion)</p> <p>Controls ejaculation</p>
Parasympathetic	<p>Stimulates GI secretions and motility (including evacuation)</p> <p>Slows heart rate</p> <p>Reduces BP</p> <p>Controls erection</p>

Parasympathetic

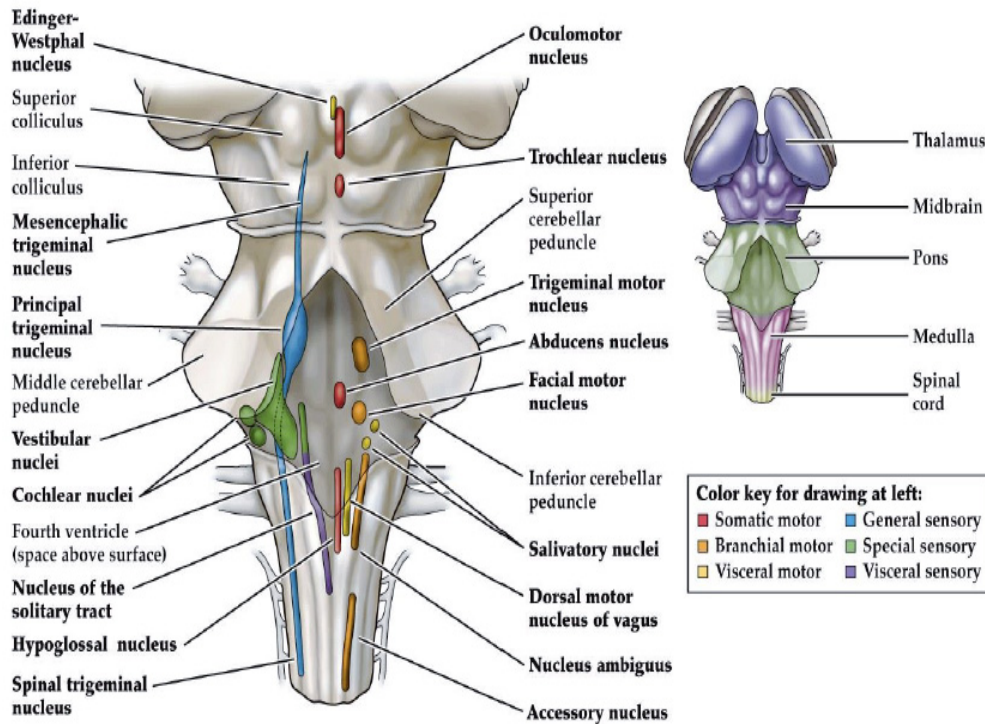
The preganglionic cell bodies of the parasympathetic system are located in the brain stem and sacral portion of the spinal cord. Preganglionic fibers exit the brain stem with the 3rd, 7th, 9th, and 10th (vagus) cranial nerves and exit the spinal cord at S2 and S3; the vagus nerve contains about 75% of all parasympathetic fibers. Parasympathetic ganglia (eg, ciliary, sphenopalatine, otic, pelvic, and vagal ganglia) are located within the effector organs, and postganglionic fibers are only 1 or 2 mm long. Thus, the parasympathetic system can produce specific, localized responses in effector organs, such as blood vessels of the head, neck, and thoracoabdominal viscera; lacrimal and salivary glands; smooth muscle of glands and viscera (eg, liver, spleen, colon, kidneys, bladder, genitals); and ocular muscles.



The two major neurotransmitters in the ANS are:

- Acetylcholine: Fibers that secrete acetylcholine (cholinergic fibers) include all preganglionic fibers, all postganglionic parasympathetic fibers, and some postganglionic sympathetic fibers (those that innervate piloerectors, sweat glands, and blood vessels).
- Norepinephrine: Fibers that secrete norepinephrine (adrenergic fibers) include most postganglionic sympathetic fibers. Sweat glands on the palms and soles also respond to adrenergic stimulation to some degree.

Cranial Nerve and Neuromodulatory Nuclei of the Brainstem



NEUROSCIENCE 5e, Figure A8
© 2012 Sinauer Associates, Inc.

Figure 3.2. At left, a “phantom” view of the dorsal surface of the brainstem shows the locations of the brainstem cranial nerve nuclei that are either the target or the source of the cranial nerves. (See Table A2 for the relationship between each cranial nerve and cranial nerve nuclei and Table A3 for a functional scheme that localizes cranial nerve nuclei with respect to brainstem subdivision and sensory or motor function.) With the exception of the cranial nerve nuclei associated with the trigeminal nerve, there is fairly close correspondence between the location of the cranial nerve nuclei in the midbrain, pons, and medulla and the location of the associated cranial nerves. At right, the territories of the major brainstem subdivisions are indicated (viewed from the dorsal surface).

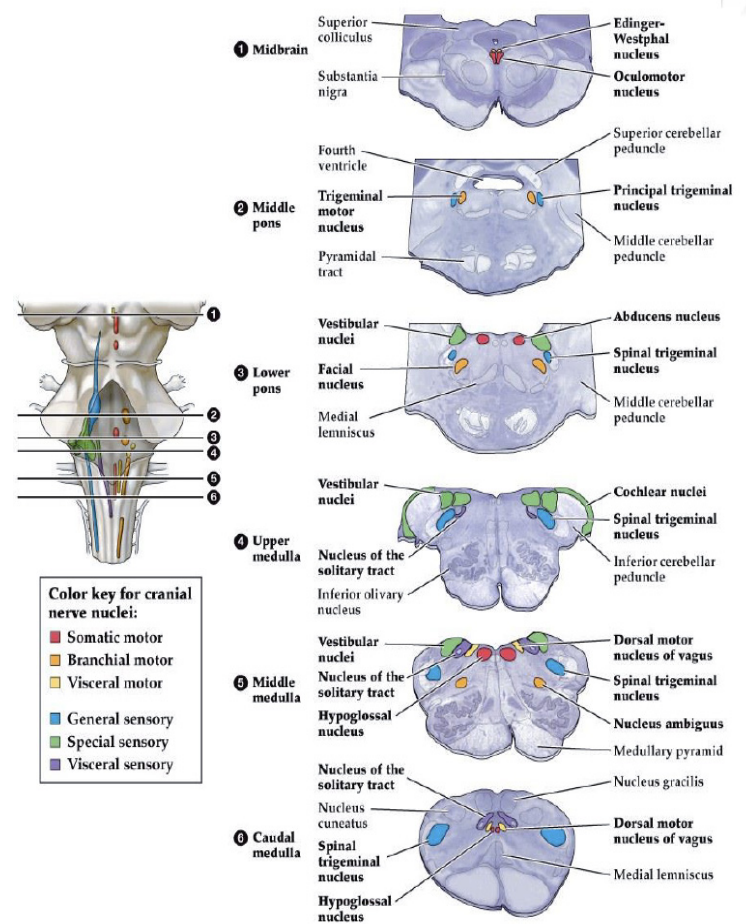


Figure 3.3. Transverse sections through the brainstem along the rostral-caudal axis show the locations of the cranial nerve nuclei; ascending and descending tracts are indicated in each representative section. The identity of the nuclei (somatic sensory or motor; visceral sensory or motor; branchial sensory or motor) is indicated using the color key. Each motor group forms an interrupted column of cells that lie in the same relative location (relative to the midline and ventricle) along the length of the brainstem (the nucleus ambiguus is also the source of cardio-inhibitory outflow and should also be co-listed under visceral motor.) Note: the sections are NOT drawn to scale; you should be sure to appreciate the relative proportions of the different subdivisions when you examine slabs of the human brainstem in the lab.

Chronic Pain Syndromes

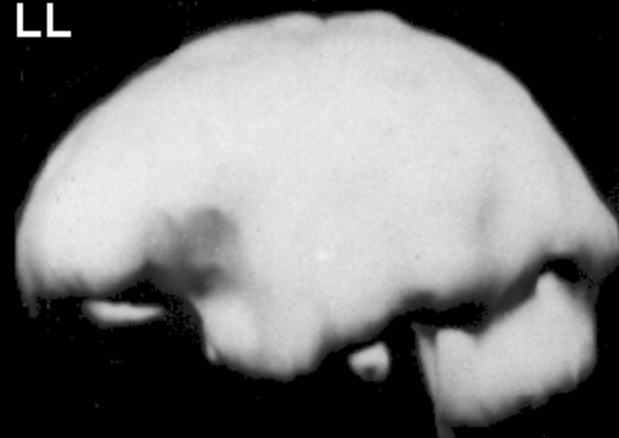
- **Chronic Regional Pain Syndrome (CRPS)**
 - (described as the most painful long-term condition)
 - **Type 1: Reflex Sympathetic Dystrophy (RSD)**
 - No demonstrable nerve lesions
 - **Type 2: Causalgia**
 - Related to specific nerve injury – presumably sympathetic nerve pathways
- **Chronic Pervasive Pain Syndrome (CPPS)**
 - **Tardive Sympathetic Dysautonomia (TSD)**
 - possibly NGF related – excess connections
 - Difficult to determine histopathologically

SPECT Brain Scans

- SPECT (single photon emission computed tomography) shows cerebral blood flow, which is controlled by the autonomic nervous system and local neural activity.
- Comparisons of normal, PTSD, Alzheimer patients with
- 10 Veterans (1-10) of ODS/S/S with GWI symptoms including memory complaints.

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

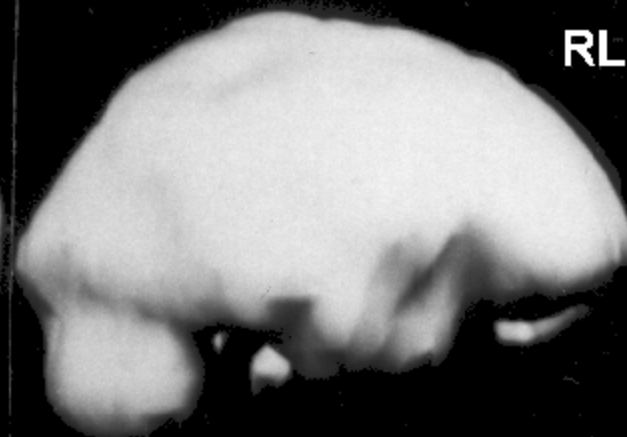
LL



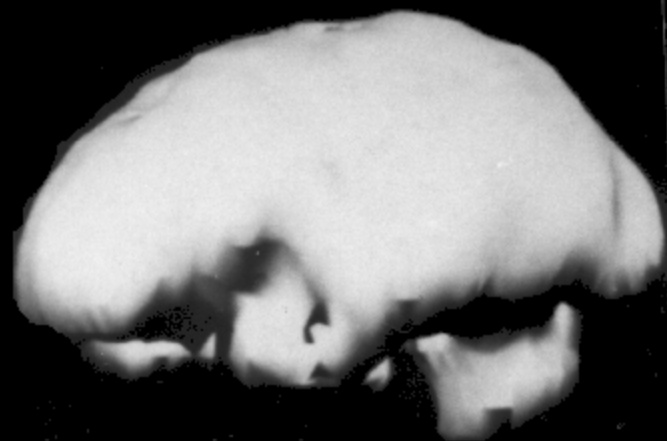
VX



RL

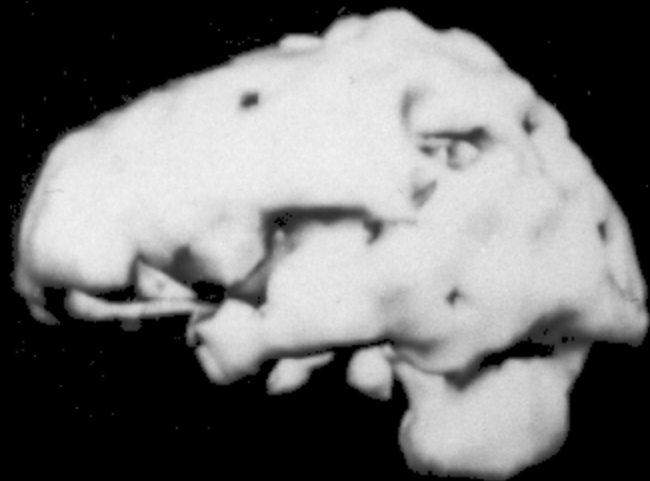


46 y/o male, post-traumatic stress disorder

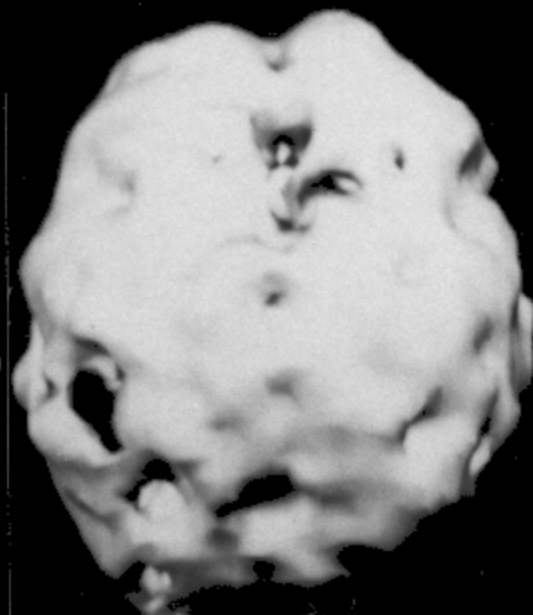


74 y/o male with autopsy confirmed Alzheimer's disease

LL



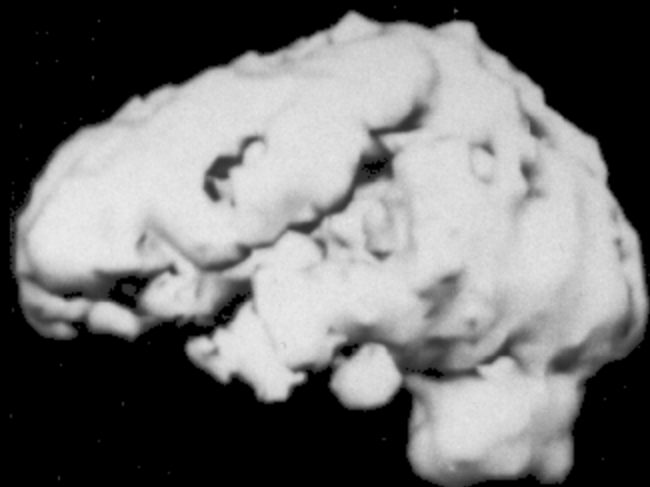
mild to moderate = 3



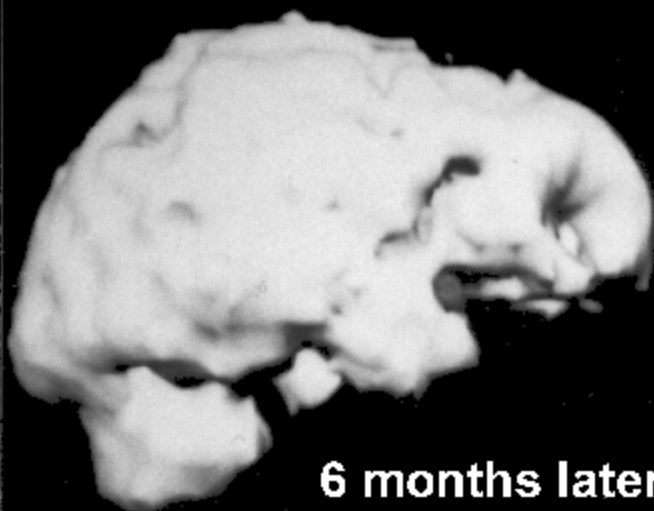
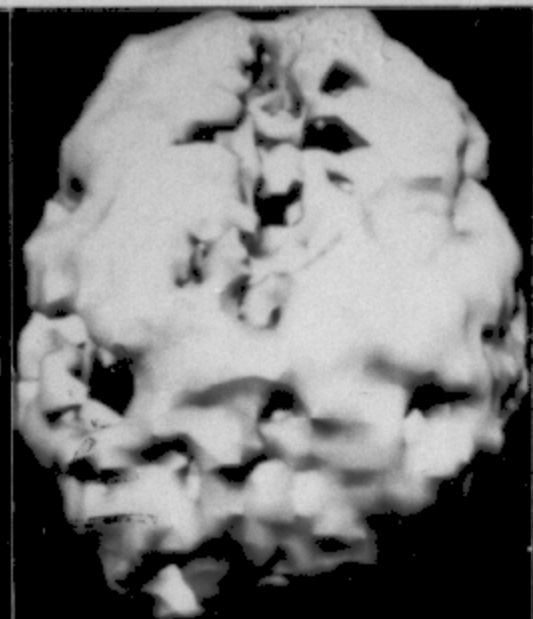
RL



MMSE = 13



moderate = 4



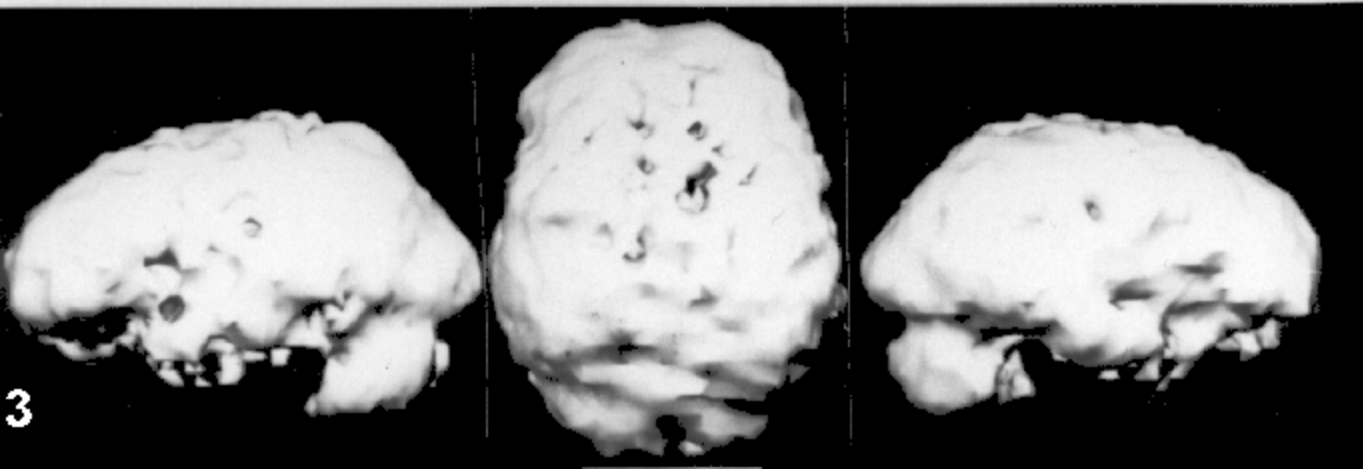
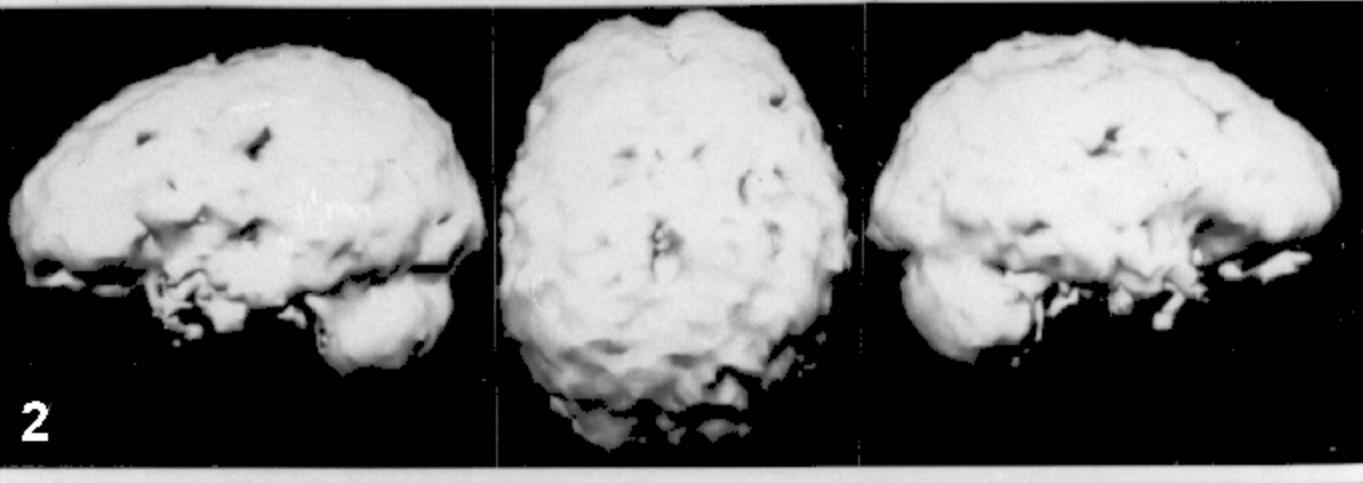
**6 months later
MMSE = 2**

LL

VX

RL

1

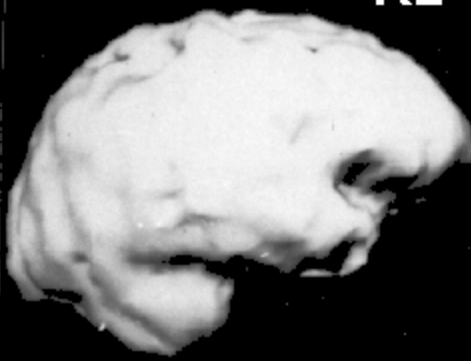
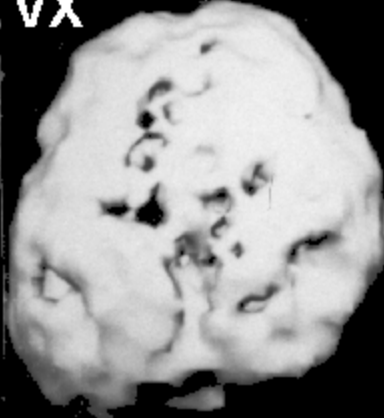
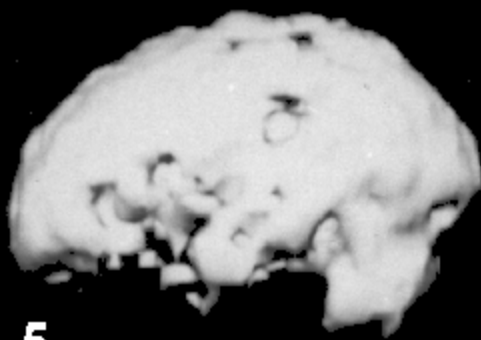


LL

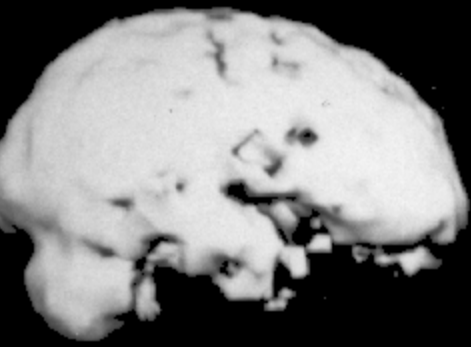
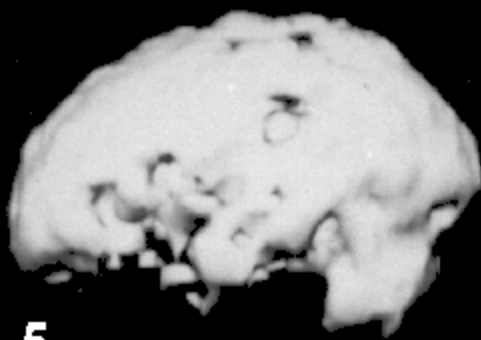
VX

RL

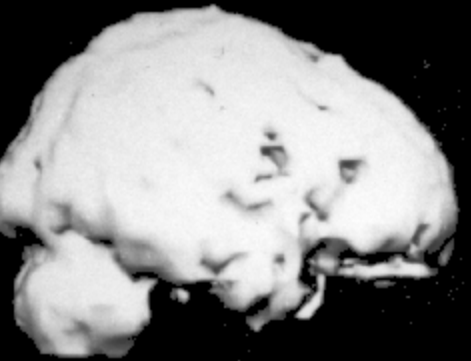
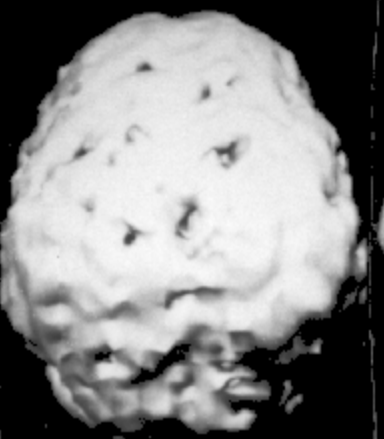
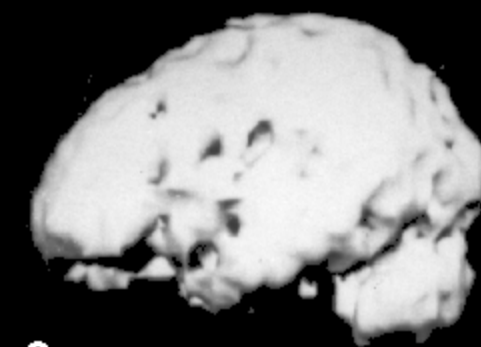
4



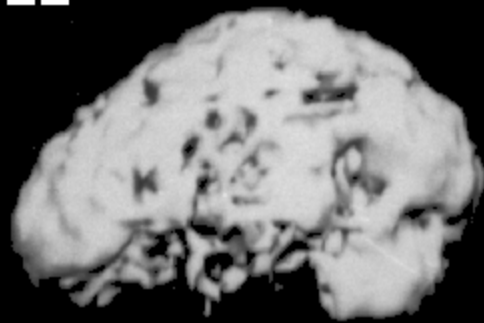
5



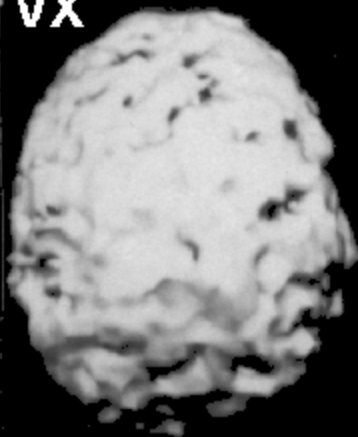
6



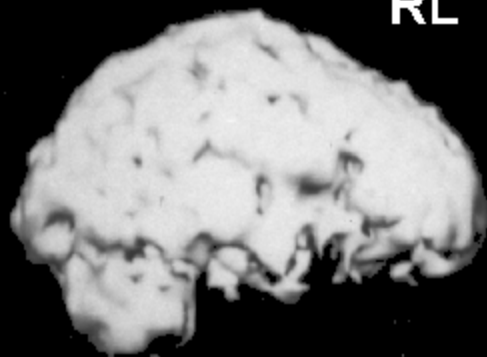
LL



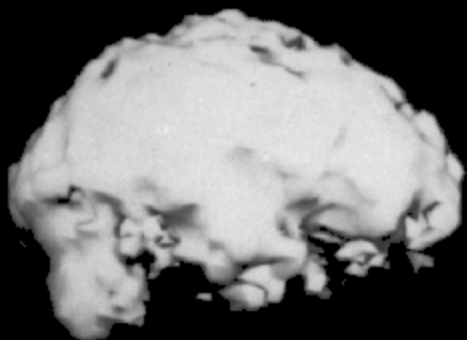
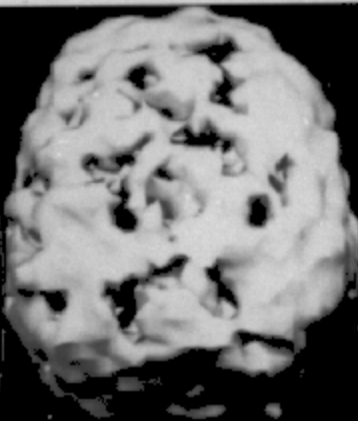
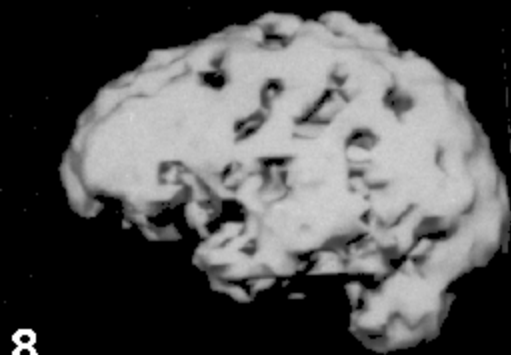
VX



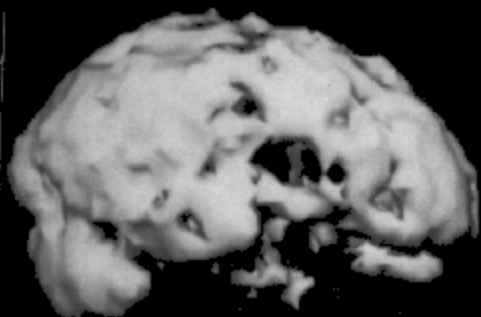
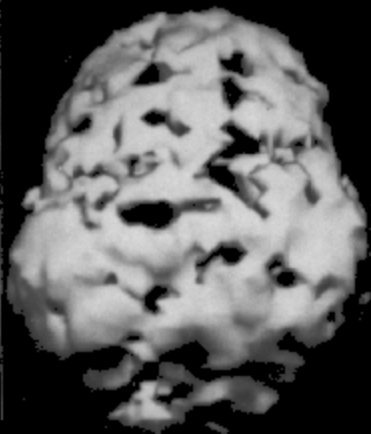
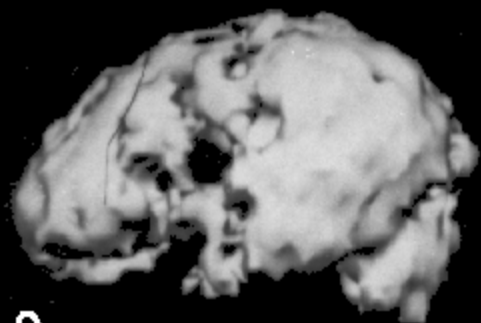
RL



7

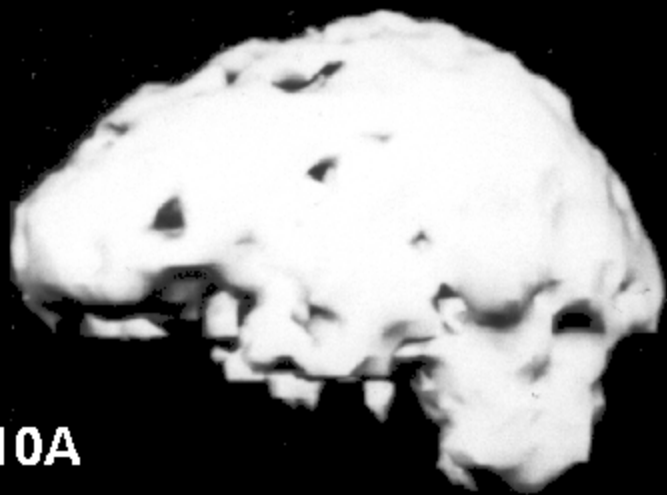


8

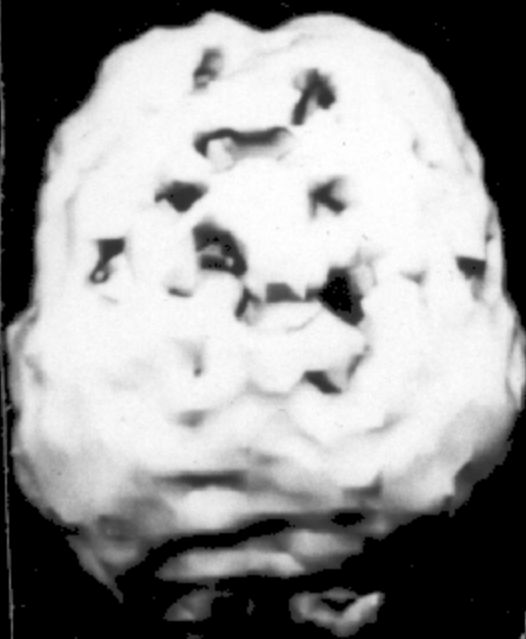


9

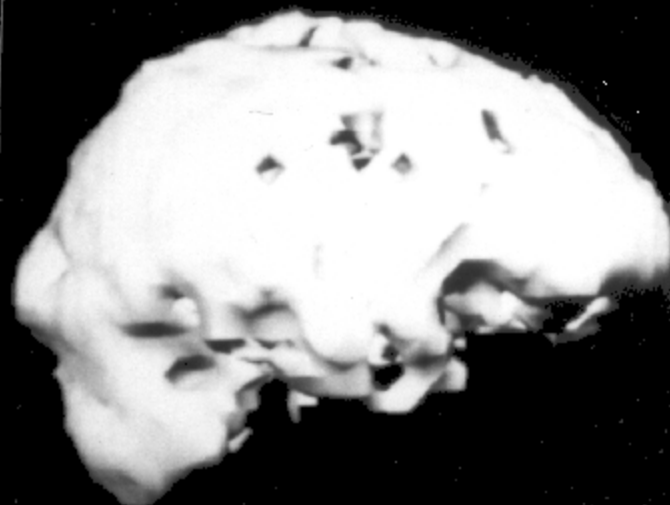
LL



VX



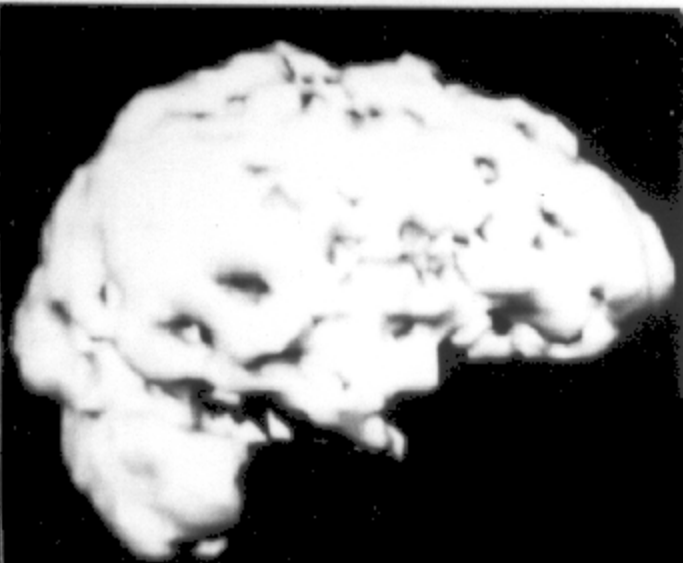
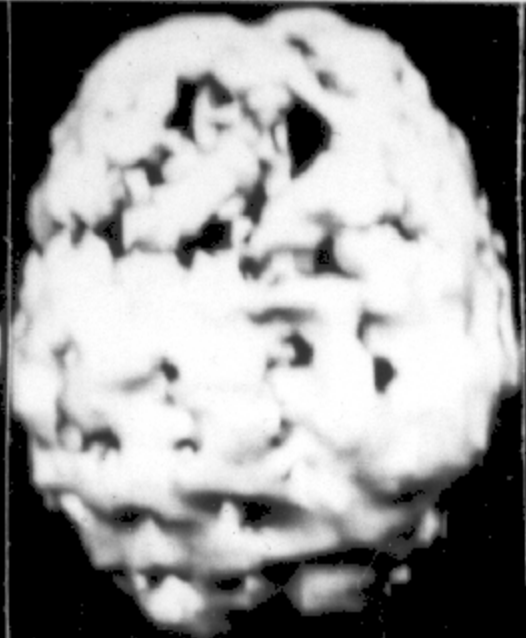
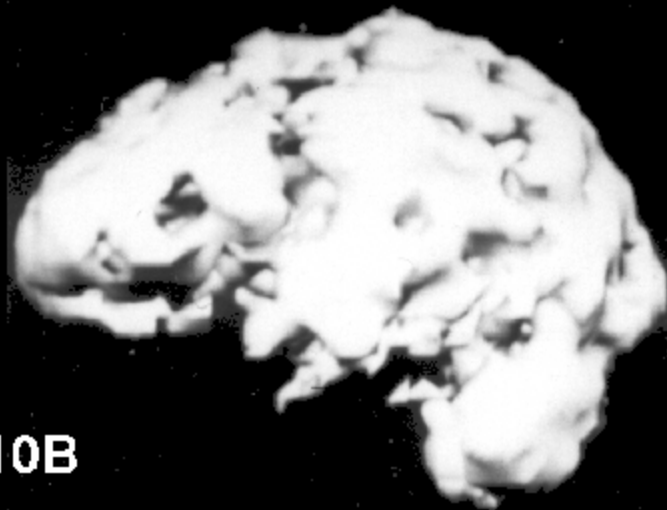
RL



10A



10B



Brain Function Changes in Veterans of ODS/S/S Referred for Memory Complaints

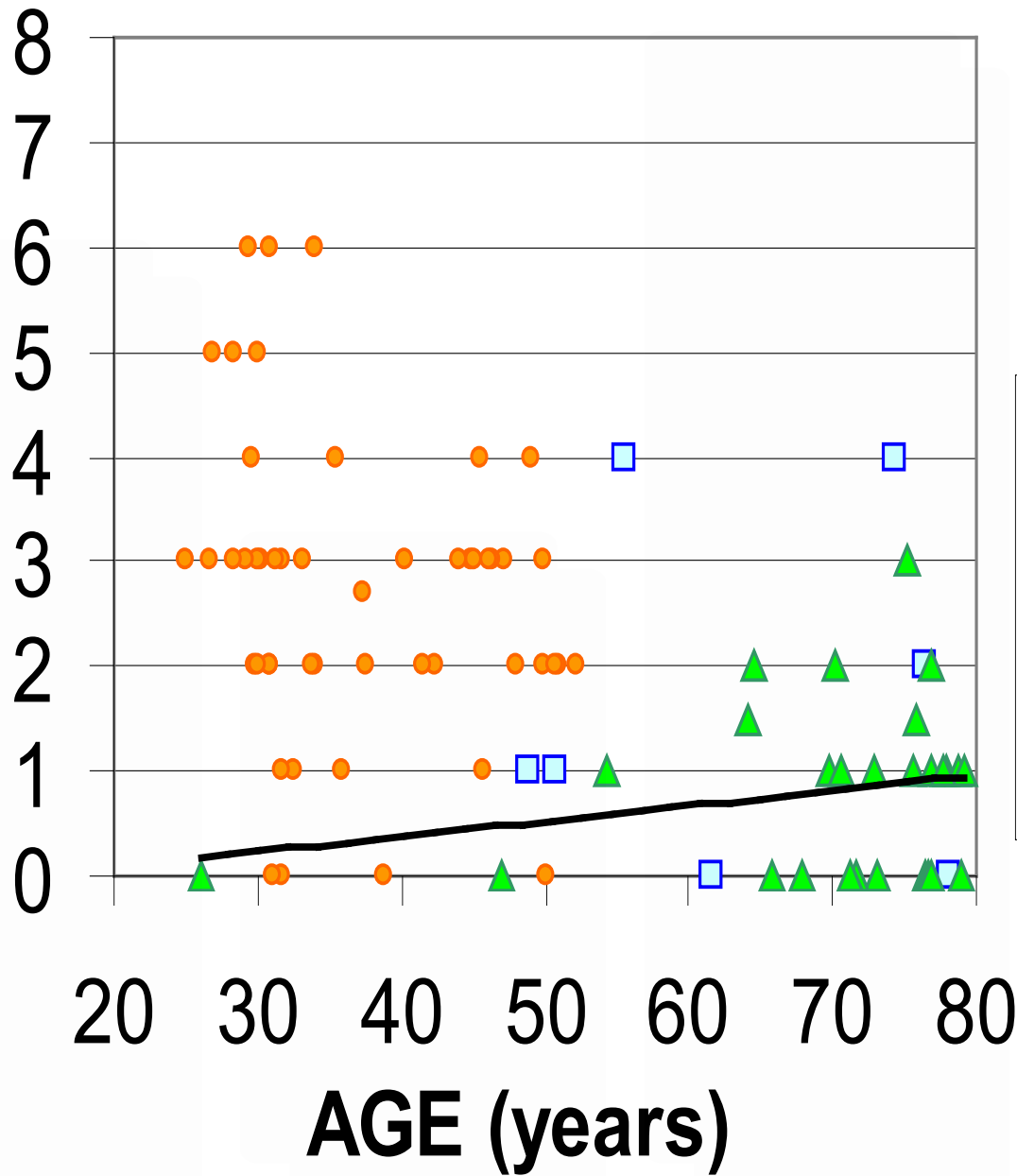
SPECT gradations (n=49)

<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

(All Veterans had normal MRI brain scans)

Ashford & Shih, VA Lexington, 2002, unpublished

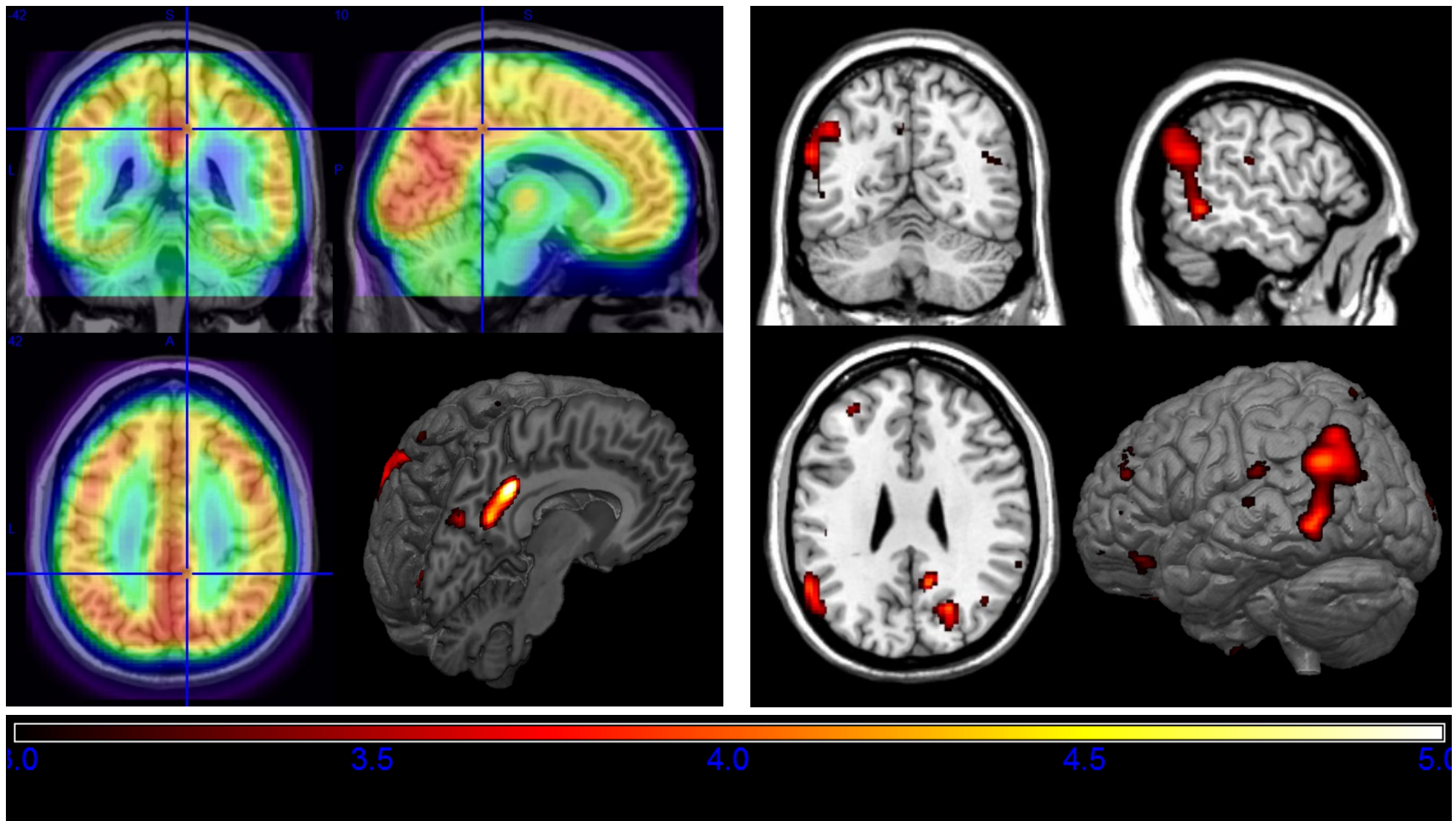
SPECT cortical severity score



$y = 0.0145x - 0.2043$
 $R^2 = 0.0422$

- Gulf War Vets
- Memory Disordered Patients
- ▲ Non-demented Elderly
- Linear (Non-demented Elderly)

PET scan in WRIISC Veterans with TBI



Evaluation of WRIISC Veterans (n=50, mean age 46), with history of varying degrees of TBI (mild=27, moderate=5; GW1=15) or not (18; GW1=11) demonstrating areas of hypometabolism in precuneus and angular gyrus when controlling for age, CAPS score.

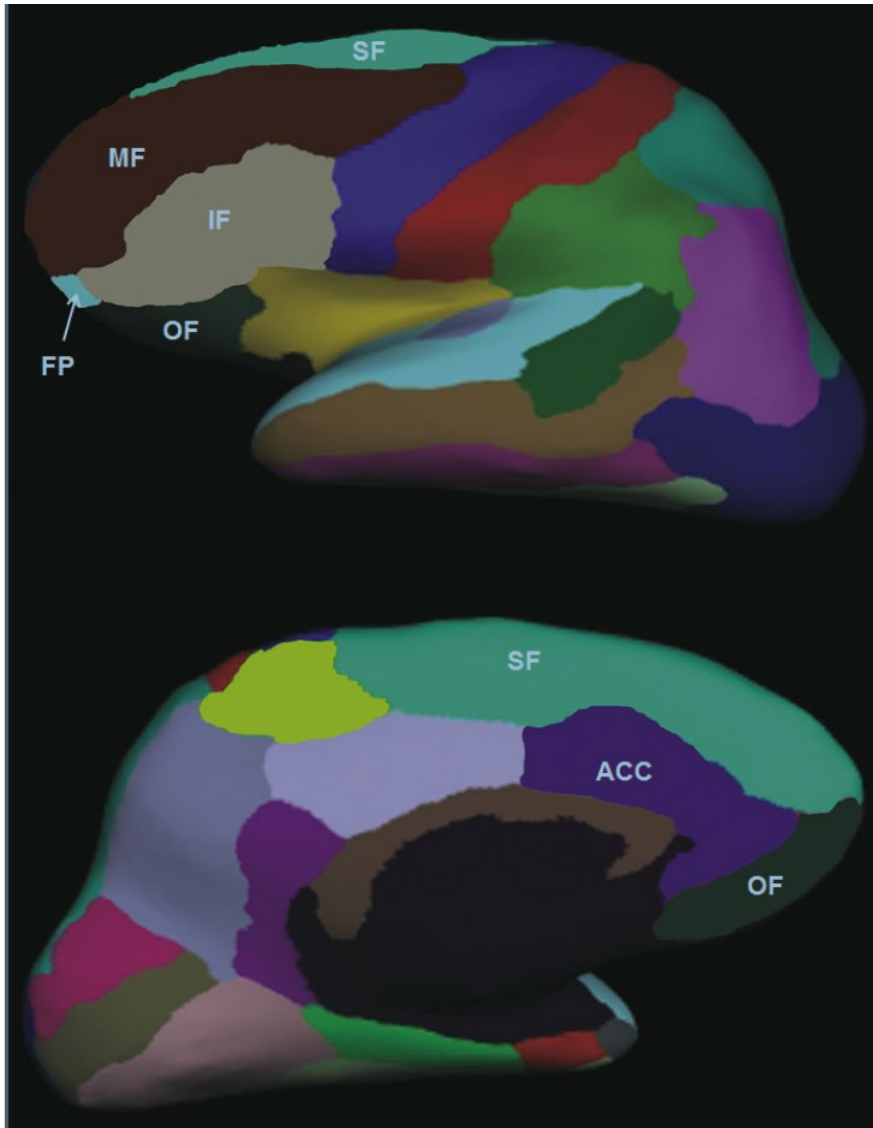
Significance of SPECT changes in Gulf Vets with memory complaints

- Cortical gradations relative to normal elderly:
 - significance of abnormality: $p < 10^{-9}$
- The pattern of changes on the cortex involve all, including primary, cortical regions, unlike Alzheimer's disease.
- Decreased perfusion in thalamus, basal ganglia
- Smaller changes on PET scans
 - (PET scans may reflect metabolism, which is less affected)
- Difference suggests that problems are due to cerebral blood flow dysregulation, symptom of brainstem dysfunction and dysautonomia, not a metabolic problem

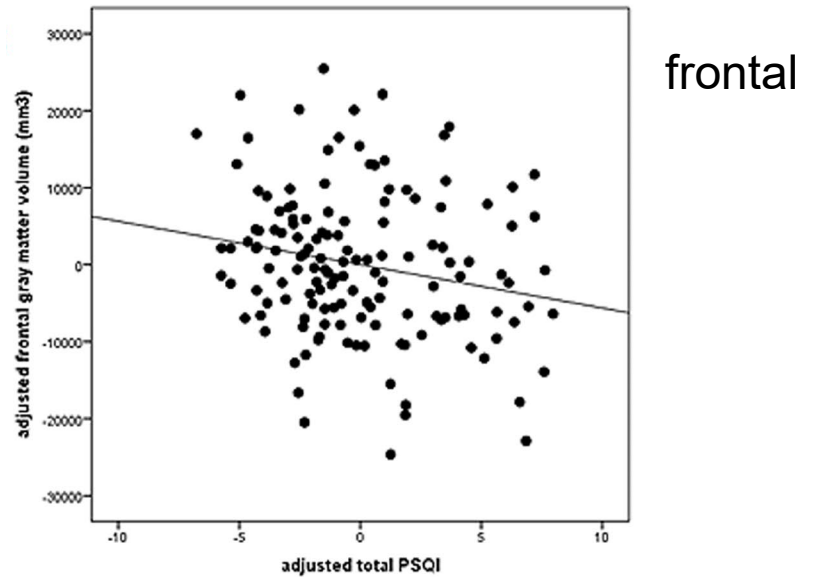
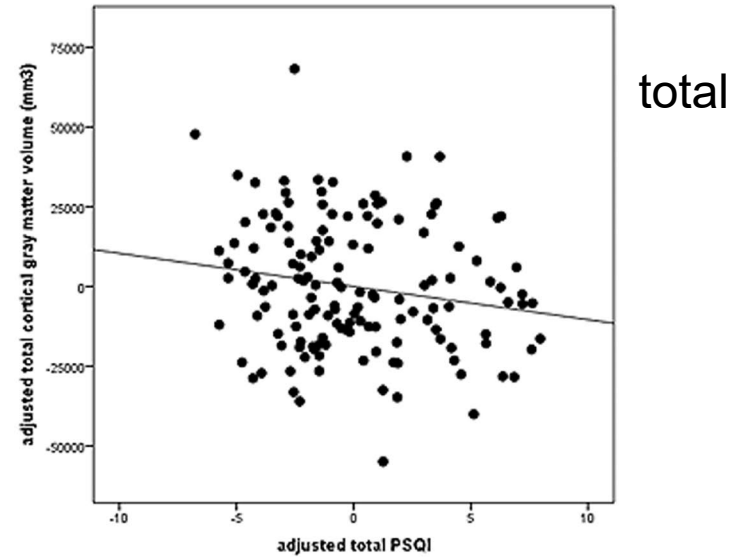
Brain Volume Changes in GWI

- Two Subgroups with Altered Brain Structure and Function
 - Post-exertional malaise with orthostatic tachycardia correlates with brainstem atrophy
 - Post-exertional malaise with exercise induced hyperalgesia correlates with cortical atrophy
 - Rakib U. Rayhan, Benson W. Stevens, Megna P. Raksit, Joshua A. Ripple, Christian R. Timbol, Oluwatoyin Adewuyi, John W. VanMeter, James N. Baraniuk. PlosOne (2013)
- Subcortical brain atrophy in Gulf War Illness
 - Highest atrophy was observed in the brainstem
 - Graded atrophy of regions anatomically connected through the brainstem via the crossed superior cerebellar peduncle (left cerebellum → right thalamus, right cerebellum → left thalamus)
 - Distribution of atrophy and systematic reduction in volume of other subcortical areas (basal ganglia, amygdala and diencephalon), resembles the distribution of atrophy seen in toxic encephalopathy
 - Peka Christova, Lisa M. James, Brian E. Engdahl, Scott M. Lewis, Adam F. Carpenter & Apostolos P. Georgopoulos. Experimental Brain Research (2017)
- Brainstem atrophy in Gulf War Illness
 - Significant subcortical atrophy, but no cortical differences, in the GWI group relative to controls
 - Largest effect in the brainstem, followed by ventral diencephalon, the thalamus
 - Smaller brainstem volumes were significantly correlated with increased severities of fatigue and pain symptoms.
 - Yu Zhang, Timothy Avery, Andrei A. Vakhtina, Danielle C. Mathersul, Eric Tranvinh, Max Wintermark, Payam Massaband, J. Wesson. Ashford, Peter J. Bayley, Ansgar J. Furst. NeuroToxicology (2020)

Gulf War Veterans' Pittsburgh Sleep Quality Index declines with gray matter loss



Freesurfer analysis



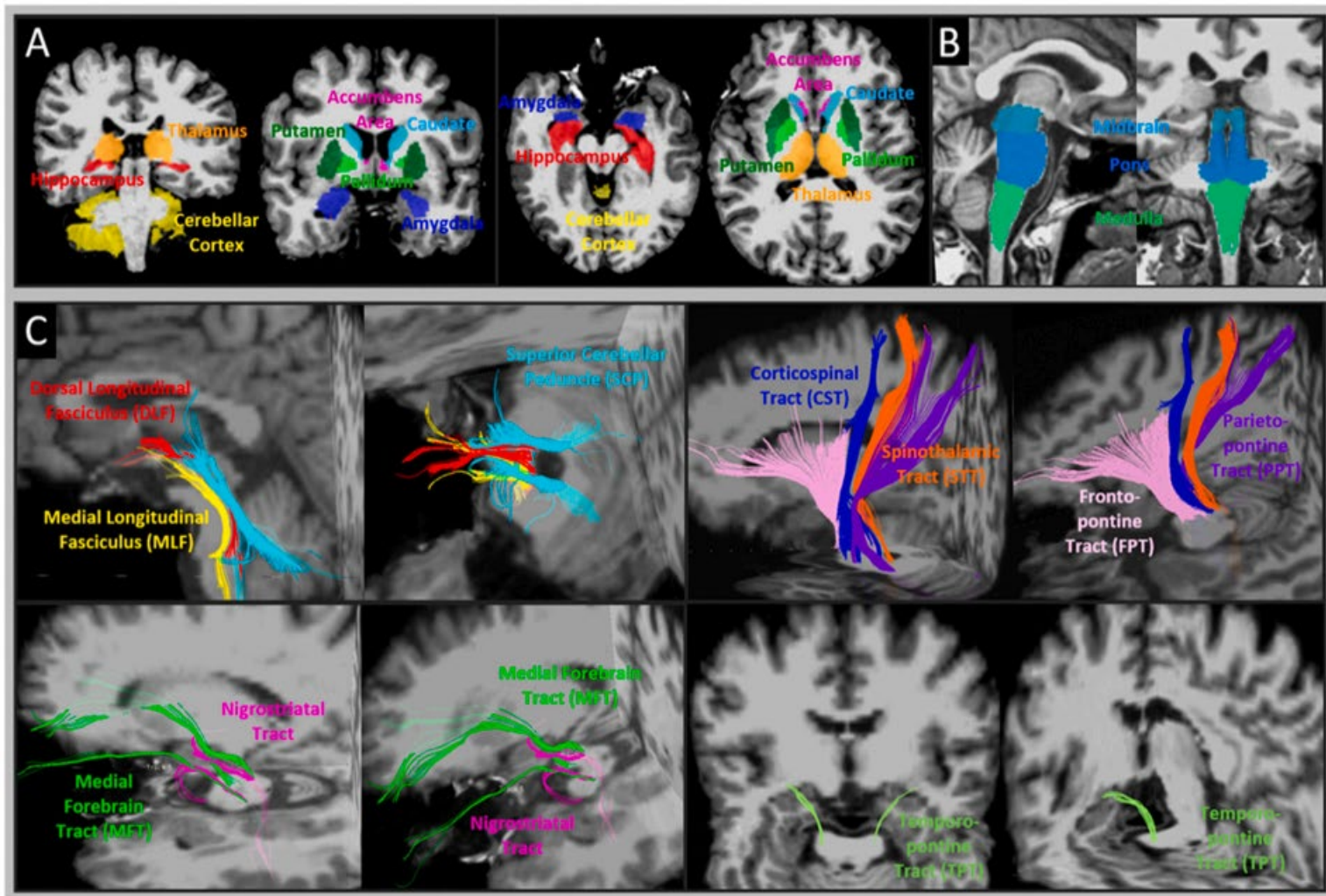


Fig. 1. Illustration of ROI where the volumes of the brainstem nuclei and diffusion metrics were measured. A: example of 8 subcortical ROIs (hippocampus, amygdala, accumbens area, thalamus, caudate, putamen, pallidum, cerebellar cortex) and B: 3 brainstem ROIs (medulla, pons and midbrain) that volumetric measures were taken. C: example of 10 bilateral pairs of brainstem tract-of-interest, including dorsal longitudinal fasciculus (DLF), medial longitudinal fasciculus (MLF), superior cerebellar peduncle (SCP), nigrostriatal tract (NST), medial forebrain tract (MFT), corticospinal tract (CST), spinothalamic tract (STT), frontopontine tract (FPT), parietopontine tract (PPT), and temporopontine tract (TPT).

Brainstem damage is associated with poorer sleep quality and increased pain in gulf war illness veterans

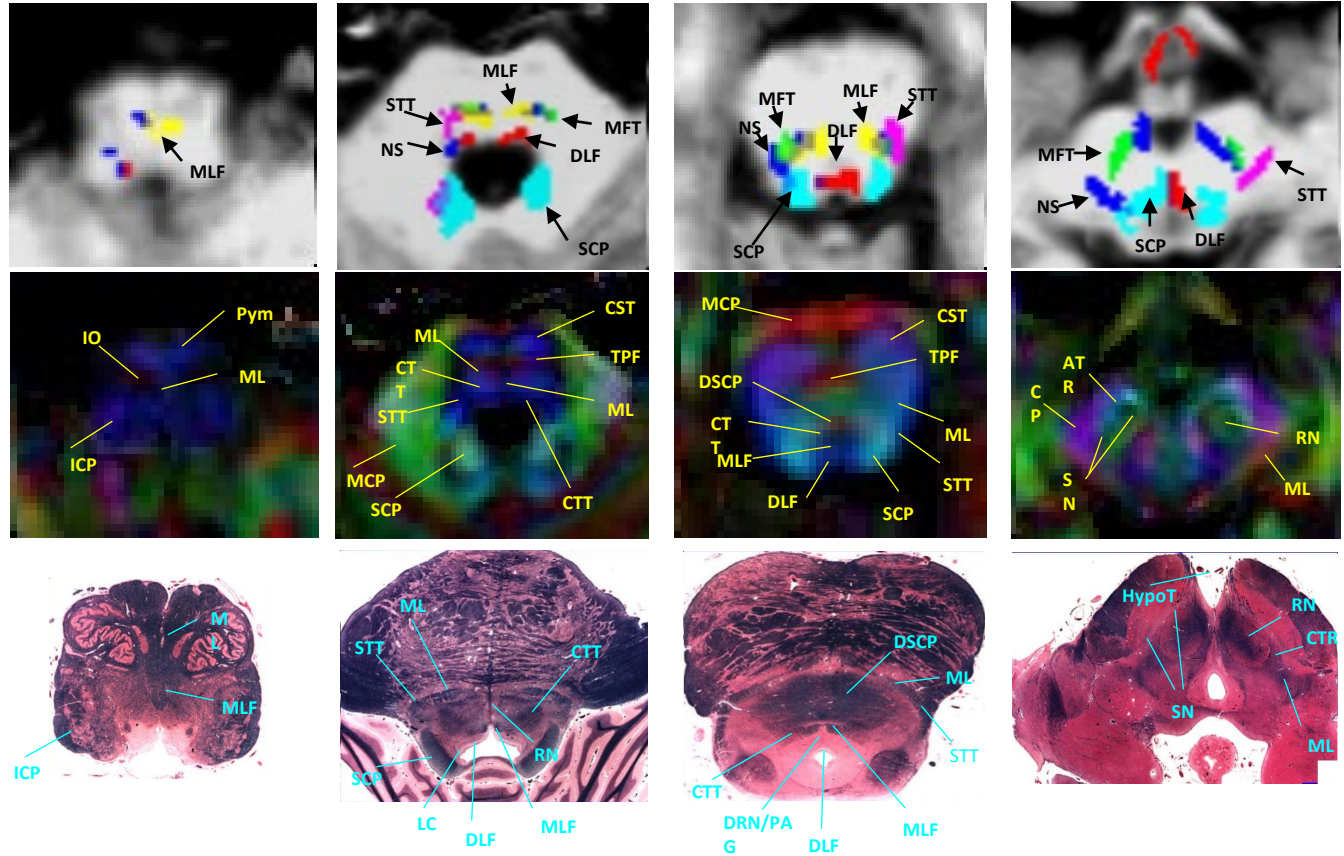
Yu Zhang a,* , Andrei A. Vakhtin c , Jessica Dietch a,b , Jennifer S. Jennings a , Jerome A. Yesavage a,b , J. David Clark a,b , Peter J. Bayley a,b , J. Wesson Ashford a,b , Ansgar J. Furst a,b,a - War Related Illness & Injury Study Center (WRIISC), VA Palo Alto Health Care System, Palo Alto, CA, United States b Stanford University, Stanford, CA, United States c The Mind Research Network, Albuquerque, NM, United States. Life Sciences 280 (2021) 119724.

Axial sections of anatomic structures on reticular fiber maps, color-FA and atlas

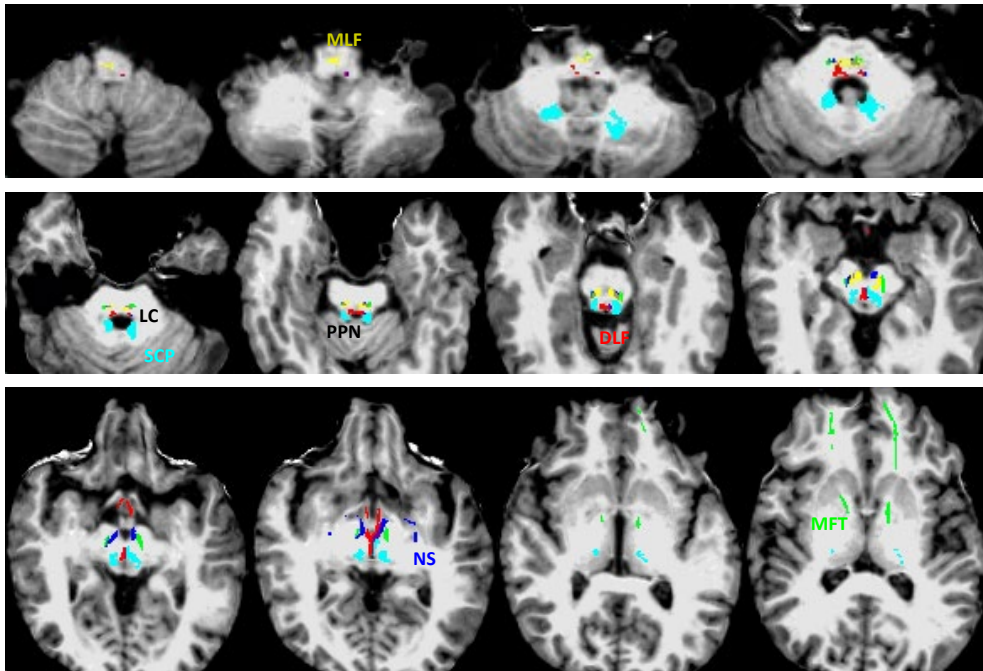
MFT- medial forebrain tract
 STT- spinothalamic tract
 NS- nigrostriatal tract
 SCP- superior cerebellar peduncle
 DLF- dorsal longitudinal fasciculus
 MLF- medial longitudinal fasciculus

CST- corticospinal tracts
 TPF- transverse pontine fibers
 ML- medial lemniscus
 STT- spinothalamic tract
 CTT- central tegmental tract
 MCP- middle cerebellar peduncle
 SCP- superior cerebellar peduncle
 ICP- inferior cerebellar peduncle
 DSCP- Decussation of superior cerebellar peduncle
 Pym- Pyramid tract
 CP- cerebral peduncle
 IO- inferior olivary nucleus
 ATR- anterior thalamic radiation

RaN- raphe nucleus
 DRN- dorsal raphe nucleus
 PAG- periaqueductal gray
 Tegn- tegmental nuclei
 LC- locus coeruleus
 HypoT- hypothalamus
 RN- red nucleus
 LG- lateral geniculate nucleus
 CTR- cerebellotthalmic tract

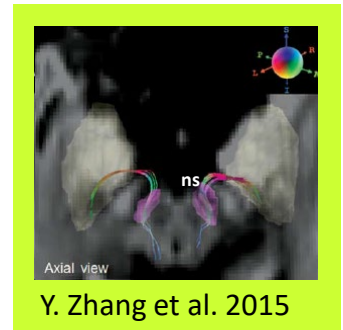
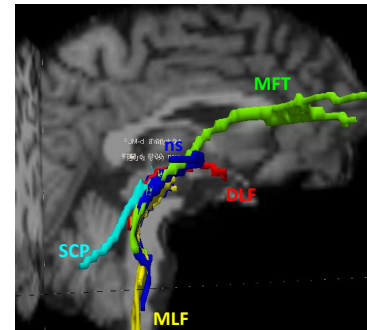


Consistency with literature

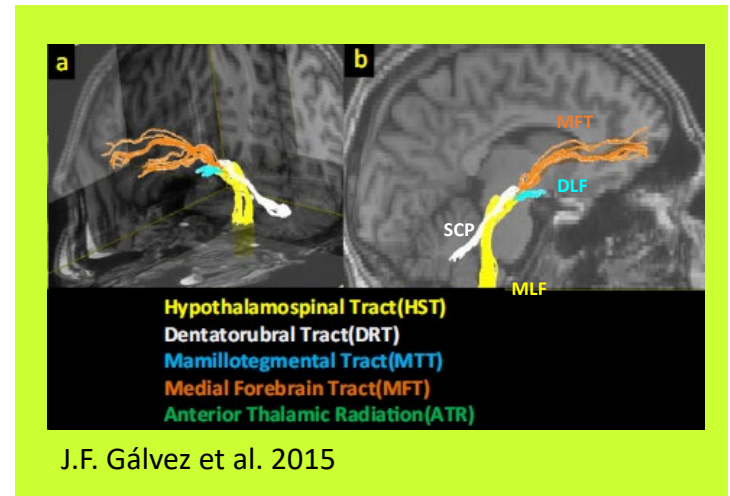


MFT = medial forebrain tract
 SCP = superior cerebellar peduncle
 NS = nigrostriatal tract
 DLF = dorsal longitudinal fasciculus
 MLF = medial longitudinal fasciculus
 Pedunclopontine

PPN = Pedunclopontine nuclei
 LC = locus coeruleus



Y. Zhang et al. 2015



J.F. Gálvez et al. 2015

Brainstem atrophy and loss of FA in brainstem tracts

Such damage could cause dysautonomia

Y. Zhang et al.

Life Sciences 280 (2021) 119724

Table 6

Correlations between sleep/pain severities and MRI measures with and without controlling for confounding factors.

ROI	Measure	Sleep (PSQI-GLOB)			Pain (BPI-sum)		
		Control for none	Control for 3-factors ^a	Control for 6-factors ^b	Control for none	Control for 3-factors ^a	Control for 6-factors ^b
Total subcortices	Volume	-0.226*	-0.262*	-0.172	-0.137	-0.144	-0.109
Hippocampus	Volume	-0.211*	-0.192	-0.114	-0.080	-0.049	-0.026
Amygdala	Volume	-0.213*	-0.181	-0.159	-0.019	0.017	0.060
Pallidum	Volume	-0.316**	-0.312**	-0.233*	-0.156	-0.146	-0.083
Total Brainstem	Volume	-0.298**	-0.325**	-0.191	-0.147	-0.149	-0.106
Midbrain	Volume	-0.294**	-0.330**	-0.202	-0.190	-0.232*	-0.201
Pons	Volume	-0.280**	-0.285**	-0.176	-0.114	-0.093	-0.070
Medulla	Volume	-0.260*	-0.245*	-0.142	-0.154	-0.151	-0.133
DLF	FA	-0.267*	-0.268*	-0.194	-0.302**	-0.290**	-0.252*
SCP	FA	-0.230*	-0.198	-0.116	-0.236*	-0.236*	-0.204
NST	FA	-0.390**	-0.400***	-0.303**	-0.242*	-0.224*	-0.194
MFT	FA	-0.317**	-0.304**	-0.298**	-0.169	-0.154	-0.155

Bold: significant after adjusting with False Discovery Rate (FDR).

Abbreviations: MLF = medial longitudinal fasciculus, DLF = dorsal longitudinal fasciculus, SCP=superior cerebellar peduncle, NST = Nigrostriatal tracts, MFT = medial forebrain tract.

Significant correlations:

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

^a Partial correlation controlling for 3-factors: age, sex and eTIV.

^b Partial correlation tests between sleep and each MRI measures after controlling for 6-factors: age, sex, eTIV, years of education, severities of neurological and depressive symptoms.

Explanation of DTI (diffusion tensor imaging) tractography And relationship to brainstem functions affected in GWI

Reticular tracts – fibers project to deep nuclei and subcortical gm regions

	Fiber name	Also includes or other names	Pathing (projecting) key regions	Functional pathway	Possible functions
MFT	Medial forebrain tract	anterior thalamic radiation;	Lateral tegmentum – hypothalamus and NAc – ATR – VMPFC, VLPFC	Cholinergic	Major depression, reward and pleasure
SCP	Superior cerebellar peduncle	Pedunculopontine projection	Cerebellar DN – PPN – SCP – Thalamus	cholinergic	sleep, cognition, mood, attention, arousal
NS	Nigrostriatal tract	VTA projections; mesocortical pathway	VTA and SNc – STN – Amygdala,HP – putamen	Dopamine, Serotonin	Motor function, mood, pleasure and reinforcement
DLF	dorsal longitudinal fasciculus	Mamillotegmental Tract, hypothalamospinal Tract, Rostral Raphe,	LC – PAG – hypothalamus – mamillary body	Serotonin, Noradrenaline, Histamine	sleep-waking cycle; consciousness, stress and reward;
MLF	medial longitudinal fasciculus	central tegmental tract, rubrospinal tract, medullary Raphe,	dorsal spinal cord – anterior to DLF – inferior to red nuclear	Serotonin, Noradrenaline	pain threshold; cardiovascular control

VMPFC = ventral medial prefrontal cortex
 VLPFC = ventral lateral prefrontal cortex
 ATR = anterior thalamic radiation
 VTA = ventral tegmental area;

DN = dentate nucleus (cerebellum);
 PAG = periaqueductal area
 LC = locus coeruleus

SNc = substantia nigra compacta
 STN = subthalamic nuclei
 RN = red nuclei

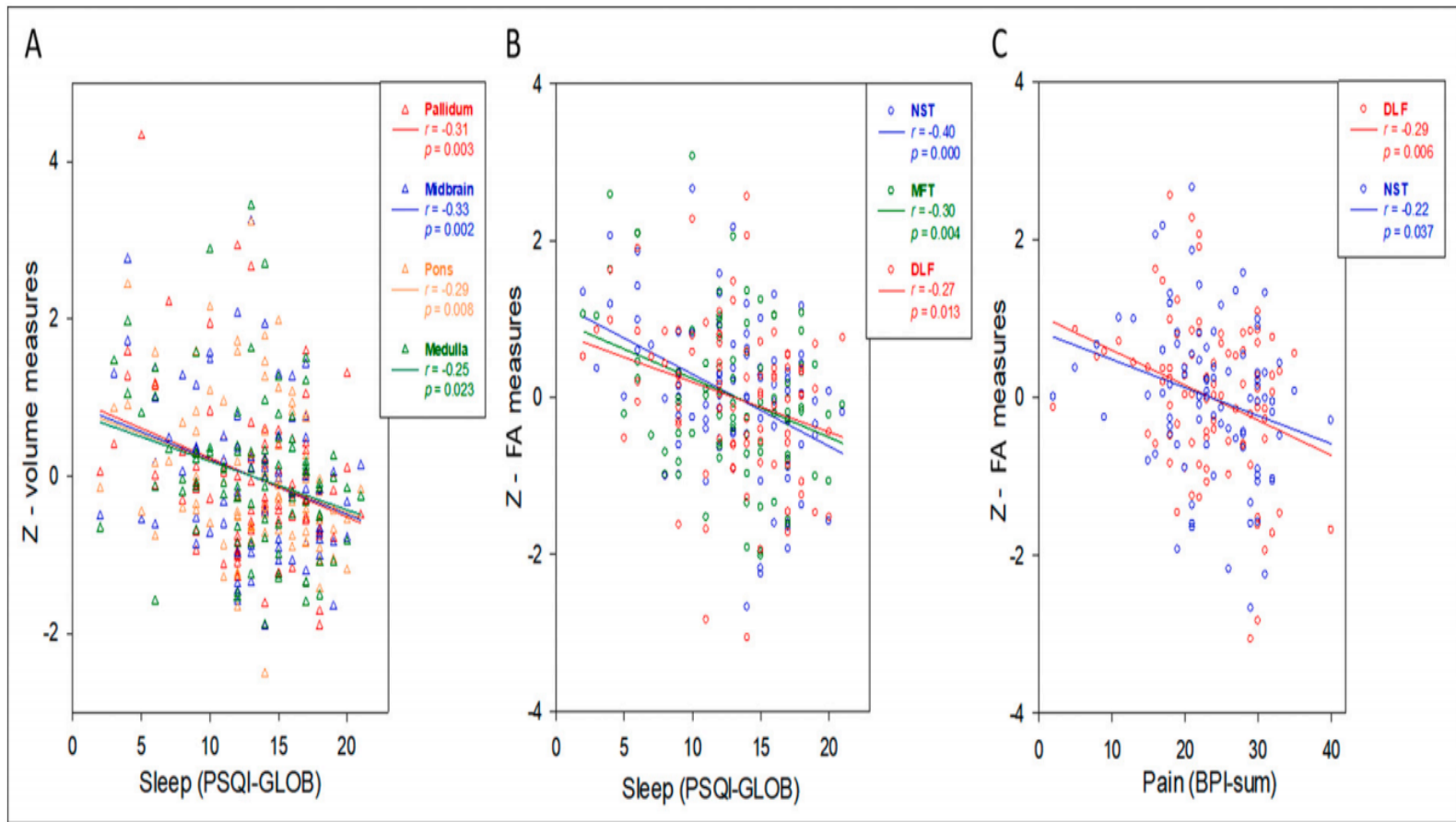


Fig. 2. Scatter plots of relationships between standardized Z score of MRI measures and sleep/pain severities that were statistically significant. A) Significant correlations between PSQI-GLOB and volumes of the pallidum and 3 brainstem ROIs (midbrain, pons and medulla). B) Significant correlations between PSQI-GLOB and FA of the nigrostriatal tract (NST), medial forebrain tract (MFT) and the dorsal longitudinal fasciculus (DLF). C) Significant correlations between BPI-sum and FA of the DLF and NST. Each neuroimaging measure is presented as standardized Z score to be comparable with different measurement scalars. The r and p values indicate the significance of partial correlation after controlling for age, sex and eTIV.

Acetyl-Cholinesterase Inhibitor Withdrawal Hypothesis: Conclusions

- Acetylcholinesterase inhibitor exposure is the factor most closely associated with “Gulf War Illness”
 - Golomb, 2008 – (though disputed by Blazer et al., 2008)
- Anti-cholinesterase agent exposure was widespread, including:
 - Insecticides (organophosphates, flea collar stories)
 - Pyridostigmine Bromide (PB) – widely administered for months
 - Sarin exposure (unlikely significant since no deaths)
 - Combinations
- The excess sprouting of autonomic nervous system axons (nerve fibers) can explain the excess pains, the chronic fatigue (constant efforts to conserve energy), and the irritable bowel syndrome (Vagus Nerve) as well as neurocognitive and dermatologic conditions (skin blood flow is managed by the autonomic nervous stem).
- The reported symptoms are not typical of anti-cholinesterase effects, and PB is commonly used long term with myasthenia gravis. However, a potential explanation is that withdrawal from the anti-cholinesterase agents, particularly PB, could have induced a diffuse anti-cholinergic state, with post-synaptic production of **nerve-growth factor**, leading to aberrant cholinergic sprouting and all of the symptoms typically reported in First Gulf War Veterans, particularly chronic pain, chronic fatigue, and GI irritability. (Like tardive dyskinesia in schizophrenia treated with anti-dopamine drugs.)

Dysautonomia and Other Possible Causes

- See: Gean et al., 2021 – Life Sciences
 - Title: “Biological measures and diagnostic tools for Gulf War Illness – A systematic review”
 - Areas of focus – 56 included studies in field: mostly central nervous system, immune system
 - Described 5 studies of the autonomic nervous system
 - Central nervous system is controlled by brainstem and autonomic nervous system
 - Immune system can affect brain and could be explanatory
- Recent paper: Martinez-Lavin & Tegada-Ruiz, 2020, Autoimmunity Review, 19(9) 102603
 - Title: “Gulf war illness, post-HPV vaccination syndrome, and Macrophagic Myofasciitis. Similar disabling conditions possibly linked to vaccine-induced **autoimmune dysautonomia**”
 - This paper states, “Several large independent epidemiological studies suggest that multiple vaccinations at the time of the military operation played a role on the illness development (see their discussion). There are two other vaccine-related chronic syndromes: Macrophagic Myofasciitis originally associated to hepatitis B vaccine, and a syndrome occurring after HPV vaccination.”

Possible Treatments for Symptoms of GWI

In all cases, treatments must address the symptoms of the Veterans, minimize their discomfort, and maximize their function, emphasize strong healthy behaviors

- Pharmacologic
 - Avoid narcotics, tranquilizers, central anti-cholinergics
 - Consider anti-depressants with anti-pain effects
 - With anti-cholinergic effects: Nortriptyline, doxepin (stabilize GI symptoms)
 - Without anti-cholinergic effects: duloxetine
 - Anti-convulsant agents: gabapentin, pregabalin
 - Consider cholinergic agents (galantamine – short acting), lecithin
- Non-pharmacologic Approaches
 - Diet – management of Irritable Bowel Syndrome (low FODMAP)
 - Exercise – low-impact, non-exhausting, > 150 minutes/week:
 - Swimming (higher water temperature – need more Masters Swimming Programs)
 - Aerobic exercises - elliptical exercise machines
 - Stretching and resistance routines (carefully graded to minimize fatigue)
- New approaches needed for pain control
 - CAM: Yoga, Acupuncture, meditation, mindfulness, etc.
 - Noninvasive brain stimulation (TMS) – may help cognition, reorganize brainstem

Care for the Symptoms of Gulf War Veterans

Focus on Brainstem Treatments

- **Pain – MSK**: Rehab/PT/exercise/CAM/acupuncture to help with pain management (?rTMS)
- **Cognition**: Neurocognitive assessment and directed interventions
- **Fatigue**: medical, endocrine evaluation, management, consider metabolic disorders, 24/7 routine, graded increase of exercise
- **GI**: referral to GI Clinic, Dietician for management of Irritable Bowel Syndrome (IBS) (low-FODMAP diet) (? Glycopyrrolate)
- **Respiratory**: Pulmonary or Cardiology for shortness of breath, autonomic dysfunction
- **Headache/migraine/Neurologic**: Neurology assessment for TBI, migraine, balance
- **Sleep**: Sleep clinic evaluation, sleep hygiene, 24/7 routine, exercise, CPAP as needed, ENT referral
- **Dermatologic**: Dermatology for management of skin problems
- **Mood/PTSD**: Evaluation, f/u by Mental Health, monitor for PTSD, depression, substance/opiate dependence and suicide risk

Trial of Yoga as a Treatment for GWI

Gulf War illness (GWI) is characterized by autonomic nervous system dysfunction (higher heart rate [HR], lower heart rate variability [HRV])

In a sample of Veterans randomized to CBT (cognitive behavioral therapy) or yoga, HR increases with CBT yet remains stable with yoga

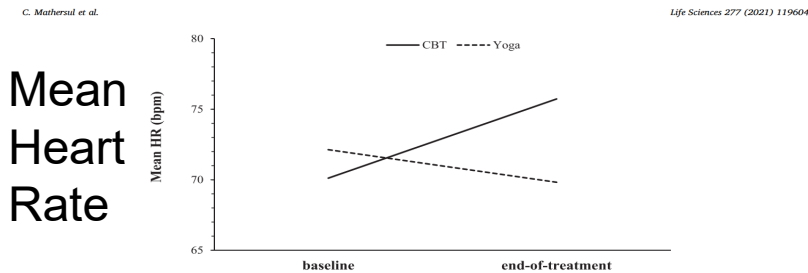


Fig. 2. Mean HR at baseline (week 0) and end-of-treatment (week 10) for Veterans with GWI who received either yoga or CBT for pain.

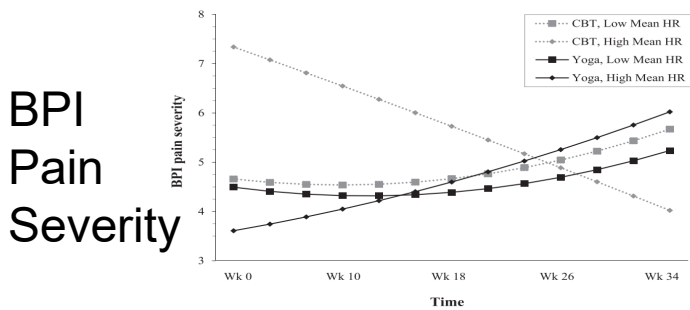


Fig. 3. Baseline mean HR (where “low”/“high” refer to $\pm 1SD$ from the mean) predicting standardised BPI pain severity over time (baseline [week 0], end-of-treatment [week 10], 2-month follow-up [week 18], 4-month follow-up [week 26], 6-month follow-up [week 34]) depending on treatment group (CBT vs. yoga). Note that points are used to differentiate lines rather than to represent data plotting (<http://www.jeremydawson.co.uk/slopes.htm>; [55,57]).

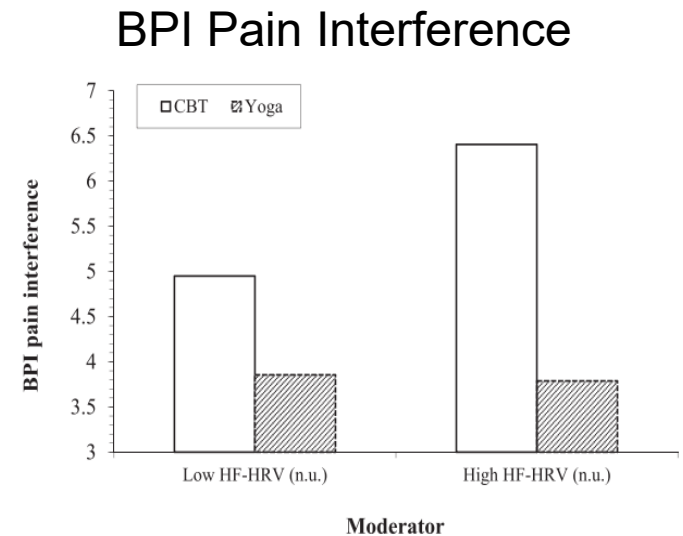
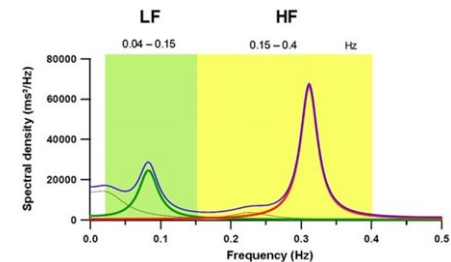
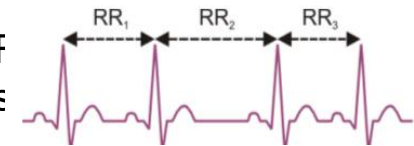


Fig. 7. Baseline HF-HRV (n.u.; where “low”/“high” refer to $\pm 1SD$ from the mean) predicting standardised BPI pain interference by treatment group (CBT vs. yoga). HF-HRV = high frequency – heart rate variability

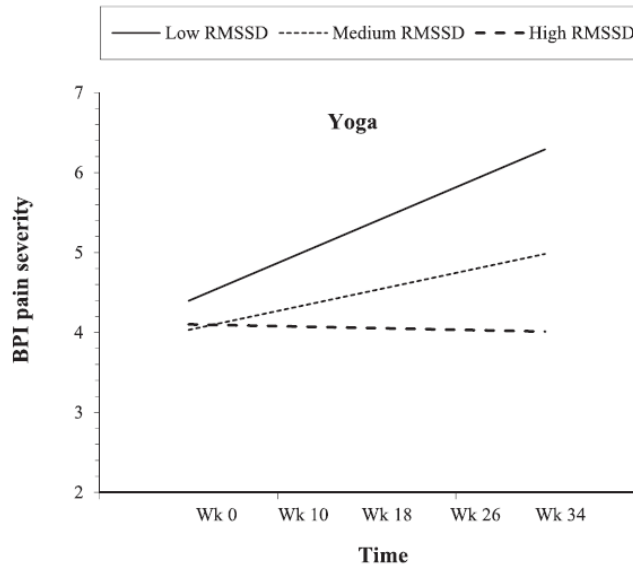
Heart Rate Variability predicted pain outcome following yoga treatment

- Autonomic nervous system dysfunction may be a characteristic of GWI
- ANS function can be measured using heart rate variability (HRV)
- Baseline HRV calculated from beat-to-beat intervals (RR_1 , RR_2 , RR_3) in a 5 min time window in RCT of yoga vs CBT for Gulf War Illness (Bayley et al, 2020)
- Power spectral ranges computed to yield low, medium and high frequency bands



Mathersul, Dixit, Avery, Schulz-Heik, Zeitzer, Mahoney, Cho, & Bayley (2021) Heart rate and heart rate variability as outcomes and longitudinal moderators of treatment for pain across follow-up in Veterans with Gulf War illness. *Life Sciences*

Heart Rate Variability predicted pain outcome following yoga treatment



RMSSD = $\sqrt{\text{mean squared differences in beat-to-beat intervals}}$

- HRV used as a predictor of treatment response
- Low baseline HRV (Low RMSSD) associated with an increase in pain following yoga treatment
- High baseline HRV (High RMSSD) associated with reduction in pain following yoga treatment
- In conclusion, ANS function in Veterans with GWI moderated treatment outcome

ACKNOWLEDGEMENTS

- Lexington VA Memory Disorders Clinic (SPECT):
 - Cathie Cool
 - Linda Godfrey
 - Joel Stephens
 - Jonathan Sickman
 - Wei-Jen Shih
 - Vickie Stipp
- The WRIISC-CA program (VA PaloAlto -HCS)
 - Sandy Bell
 - Maheen Adamson
 - Louise Mahoney
 - Stacy Moeder
 - Ansgar Furst
 - Valerie Darcy
 - Janet Baldwin
 - Jennifer Kong
 - Mohsen Jahani
 - Allyson Rosen
 - Peter Bayley
 - Ahmad Salehi
 - Jerome Yesavage
 - Jennifer Jennings
 - Ronit Katz
 - Leah Eizadi
 - Angela Malenfant
 - Jauhtai Joseph Cheng
 - Yu Zhang
 - Vince Torres
 - Tamera Guess
 - Rachel Cooper
 - Marina Vetkamp
 - Lindsey Proctor
 - Miguel Robinson
 - Andre Vahktin

HOME-WRIISC HISTORY

- Health Outcomes of Military Exposures
 - (until recently Post-Deployment Health Services -PDHS)
- War Related Illness & Injury Study Center
- WRIISC is a National VA Post-Deployment Health Program, established by **Public Law 105-368, 105th Congress, 1998**)
- There are three WRIISC sites: Washington, DC (VISN 5), East Orange, NJ (VISN 2); Palo Alto, CA (VISN 21, since July, 2007)
- The WRIISC develops and provides post-deployment health expertise to Veterans and their health care providers through clinical programs, education and risk communication, and research

WRIISC CLINICAL SERVICES

Multi-disciplinary team approach to address complex symptoms related to deployment.

WRIISC E-Consults

- Thorough medical record review
- Diagnostic impressions
- Tailored recommendations for next steps
- Engages Provider(s) and Veteran

Comprehensive Multidisciplinary Evaluations

- 3-5 day visit with WRIISC clinical team; Some diagnostic testing
- Provides diagnostic impressions and a “road map” of tailored recommendations to improve function and quality of life

Environmental Exposure Assessments

- Assesses potential contribution of exposures to Veteran health concerns as a component of comprehensive evaluation
- Stand-alone service with telephone consults available



Choose **VA**

VA



U.S. Department
of Veterans Affairs

WRIISC REFERRALS – WHO IS ELIGIBLE

Any deployed Veteran with a complex health condition and no known cause (medically unexplained symptoms (MUS))

Veteran has been already been thoroughly evaluated by their Primary care provider, but specific questions remain unanswered

Any Veteran that has had many tests and/or treatments with little to no symptom improvement

Any Veteran with possible deployment-related environmental exposure problems or concerns possibly related to their health symptoms



REFERRAL PROCESS

Who Makes the Referral

- Veteran's VA Primary Care Provider
- Patient Aligned Care Team
- Post-deployment Health Champion
- Environmental Health Provider

Referral Process

- Uses the Inter Facility Consult process in the VA Computerized Patient Record System (CPRS)
- Refer to War Related Illness & Injury Center (WRIISC)
- Referrals are automatically triaged to regional WRIISC based on VISN location

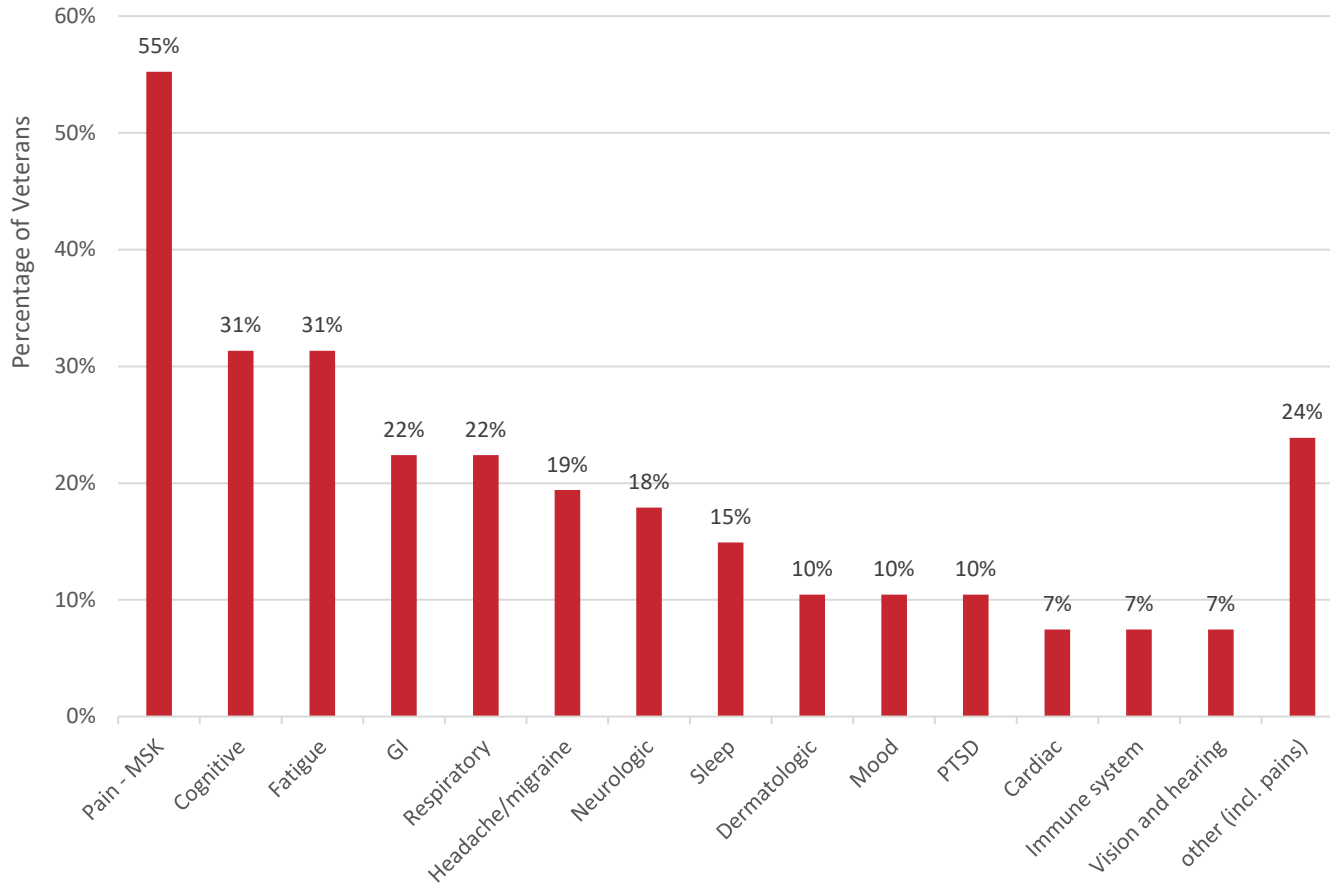
Who Can I Contact for More Information

- CA WRIISC
888-482-4376.
- DC WRIISC
202-745-8249.
- NJ WRIISC
973-676-1000 ext. 2500



Veterans' Top 3 Reported Symptoms

ODS/S Veterans seen at CA-WRIISC 7/2016 – 6/2018;
N=67 (20 were later in Somalia, OEF/OIF/OND)



Choose VA

VA



U.S. Department of Veterans Affairs

Measurement of Pain

Digital Pain Matrix - 2021

(to be completed by a trained clinician)

ID: DATE: TIME (24hr):

INSTRUCTIONS: On a scale of 0 to 10 with 0 being no pain and 10 being the worst pain imaginable, please rate your pain (may use half numbers):

Overall pain:	None	mild			moderate			severe		extreme	
	0	1	2	3	4	5	6	7	8	9	10
Pain RIGHT NOW	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Worst in last 24 hours	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Worst in last month	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

INSTRUCTIONS: Please rate your pain by checking the one number that best describes your pain at its worst in the past month, for each region in which you have had pain:

Regions affected by pain:	None	mild			moderate			severe		extreme	
	0	1	2	3	4	5	6	7	8	9	10
1. LEFT - Shoulder	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. LEFT - Upper arm/elbow	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. LEFT - Lower arm/wrist/hand	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. RIGHT - Shoulder	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. RIGHT - Upper arm/elbow	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. RIGHT - Lower arm/wrist/hand	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. LEFT - Hip	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8. LEFT - Upper leg/knee	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
9. LEFT - Lower leg/ankle/foot	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
10. RIGHT - Hip	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
11. RIGHT - Upper leg/knee	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
12. RIGHT - Lower leg/ankle/foot	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
13. Neck/cervical spine	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
14. Upper back/thoracic spine	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
15. Lower back/lumbo-sacral spine	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
16. Head /headache	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
17. LEFT - Jaw	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
18. RIGHT - Jaw	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
19. Chest	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
20. Stomach ache / Abdominal pain	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

TEXT FOR YOUR RECORDS

<http://www.medafile.com/PainMatrix-2021.htm>

WRIISC RESEARCH ADDRESSES VETERAN TOP SYMPTOMS

Top WRIISC Veteran Complaints	WRIISC Research	Sample of WRIISC Protocol
1. Pain	★	A Multimodal Evaluation of the Comparative Efficacy of Yoga versus a Patient-Centered Support Group for Treating Chronic Pain in Gulf War Illness
2. Fatigue	★	Post-Exertion Malaise in Gulf War Illness: Brain, Autonomic and Behavioral Interactions
3. Cognition	★	Cognitive Rehabilitation for Gulf War Veterans
4. GI	★	Development of Dietary Polyphenol Preparations for Treating Veterans with GWI
7. Neurological	★	Diagnosis of Late-stage, Early-onset, Small-fiber Polyneuropathy
8. Sleep	★	CAM for Sleep, Health Functioning and Quality of Life in Veterans with GWVI
10. PTSD	★	Breathing Meditation Intervention for PTSD



WRIISC Service Area



How to make a referral to the WRIISC program:

For details, refer to:
www.warrelatedillness.va.gov

Primary Care Clinician should make the referral because that clinician will be the one to whom recommendations are directed.

The referring clinician can open the Veteran's record in CPRS, Consult Tab, then type "WRIISC" and fill out the questionnaire.