

**VA**



U.S. Department  
of Veterans Affairs

Office of Patient Care Services  
Health Outcomes Military Exposures  
War Related Illness and Injury Study Center

# Gulf War Illness (GWI)

## Causation Considerations

Research Advisory Committee on Gulf War  
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[www.warrelatedillness.va.gov](http://www.warrelatedillness.va.gov)

Sides at:

[\*\*http://www.medafile.com/GWI/GulfWar-  
WRIISC-JWA-2022-09-21.pptx\*\*](http://www.medafile.com/GWI/GulfWar-WRIISC-JWA-2022-09-21.pptx)

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# Disclaimer

Dr. Ashford is an employee of the VA

Material presented here does not represent the  
official position of the VA

Dr. Ashford has developed a memory test:

[www.memtrax.com](http://www.memtrax.com)

for assessing memory changes



# WHAT IS GULF WAR ILLNESS (GWI)?

- A condition that affects 30-40% of nearly 700,000 Veterans who were deployed to Operations Desert Shield/Storm/Sabre (ODS/S/S)
- GWI is considered to exist (Institute of Medicine, 2009)
- There have been at least 40 theories that have been considered for GWI, but none has yielded an acceptable pathophysiological explanation
  - Is GWI a nervous system disorder?
    - Brainstem, autonomic nervous system (ANS)
  - Is GWI caused by sarin or related agents?
  - Is GWI related to long-COVID (coronavirus, other virus)?



# CLINICAL FINDINGS OF GWI

Results of Iowa Study – 3,695 Veterans:  
Symptoms, % Prevalence, **Ratio**

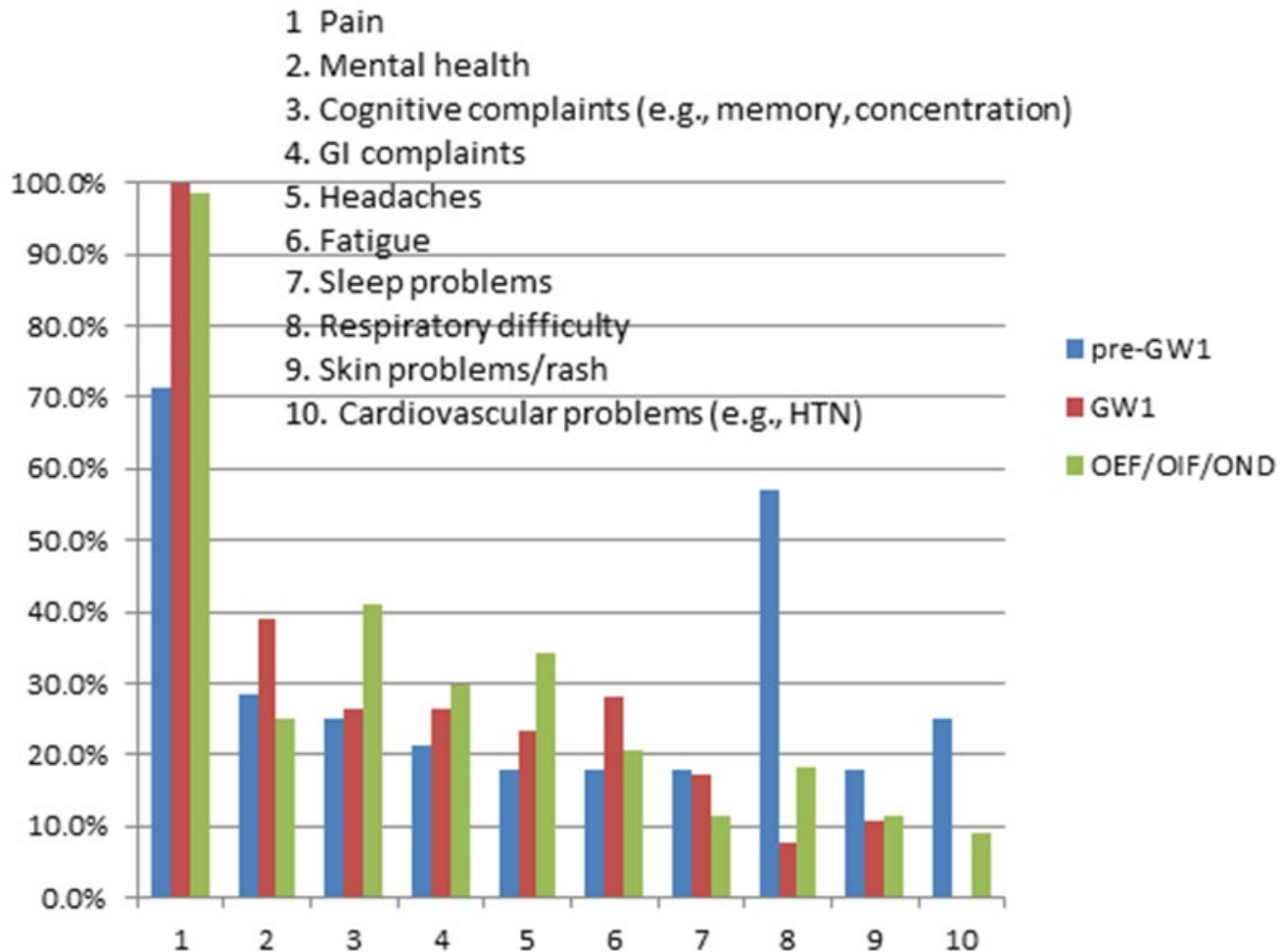
	GW Veterans	Non-GW Veterans	Ratio
Chronic fatigue	1.5	0.3	5.00
Cognitive Dysfunction	18.7	7.6	2.46
PTSD	1.9	0.8	2.38
Fibromyalgia	19.2	9.6	2.00
Asthma	7.2	4.1	1.76
Depression	17	10.9	1.56
Alcohol Abuse	17.4	12.6	1.38
Sexual Discomfort	1.5	1.1	1.36

Iowa Persian Gulf Study Group, 1997



# WRIISC EXPERIENCE

Top 3 Symptoms of Veterans Presenting to the WRIISC program - FY 2013





# COURSE OF GWI

- 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

2012-2013 VA Follow-up Study 30,000 Gulf War/Era Veterans.  
Dursa EK, Barth SK, Schneiderman AI, Bossarte RM, 2016.  
JOEM 58:41-46

There was no increased risk of disease mortality  
among Veterans of the 1990-1991 Gulf War.

Cause-specific mortality risks among U.S. Veterans:  
25 years after their service in the 1990-1991 gulf war.  
Bullman, Schneiderman, Dursa. Ann Epidemiol. 2021 May;57:1-6.



# GWI – DIAGNOSTIC CRITERIA (RESEARCH)

CDC	KANSAS	MODIFIED KANSAS
<p>One symptom required in at least two of the following domains:</p> <ol style="list-style-type: none"> <li>1) fatigue</li> <li>2) mood and cognition (feeling depressed, difficulty remembering/concentrating, feeling moody, anxious, trouble finding words, difficulty sleeping)</li> <li>3) musculoskeletal (joint pain, joint stiffness, muscle pain)</li> </ol> <p>No exclusions.</p> <p>Severity not included in determining case.</p>	<p>Multiple moderately severe symptoms (&gt;=6 months) in at least 3 of the 6 symptom domains:</p> <ol style="list-style-type: none"> <li>1) fatigue and sleep problems</li> <li>2) somatic pain symptoms</li> <li>3) neurologic/cognitive/mood symptoms</li> <li>4) gastrointestinal symptoms</li> <li>5) respiratory symptoms</li> <li>6) skin symptoms</li> </ol> <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 Some medical conditions will resolve or are adequately managed with treatment and should therefore be considered temporary exclusions (Reeves et al., 2003).



# NERVOUS SYSTEM – Related GWI Disorders

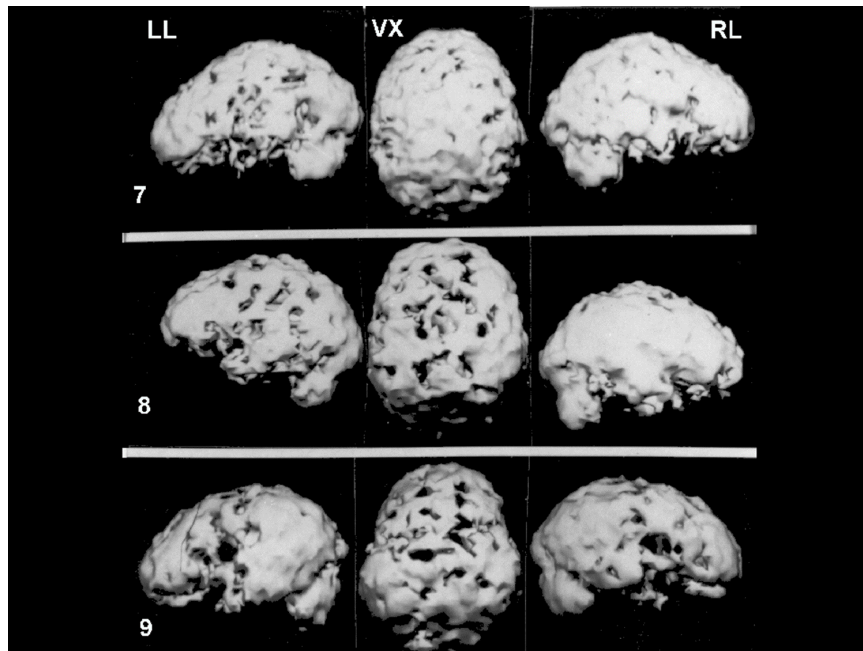
- Peripheral nerves – sensory, small fiber neuropathy, chronic pain
- Autonomic Nervous System (ANS) - dysautonomia
  - Parasympathetic: brainstem (esp: vagus nerve), base of spinal cord (acetylcholine)
  - Sympathetic – spinal cord (norepinephrine)
- Brainstem - Central control of body energy: behavior, ANS
  - Energy feelings/motivation/chronic fatigue/sleep
  - Respiration control, respiration during sleep (OSA), lung management
  - Cardiac, blood pressure control, blood flow control including brain (SPECT changes)
  - Bowel activity (affect by cholinergic, anti-cholinergic drugs) - irritable bowel syndrome
  - Temperature control, skin dilation, blood flow to skin, sweating
  - Pain management, control (peri-aqueductal gray)
  - Management of anxiety (locus coeruleus), mood (raphe, locus coeruleus, depression)
  - Vigilance, awareness of the environment, consciousness (dorsal, RAS, PTSD??)
  - Management of cerebral cortex: memory (complaints)
- Cortex, basal ganglia - Direct injury versus compromise of blood flow



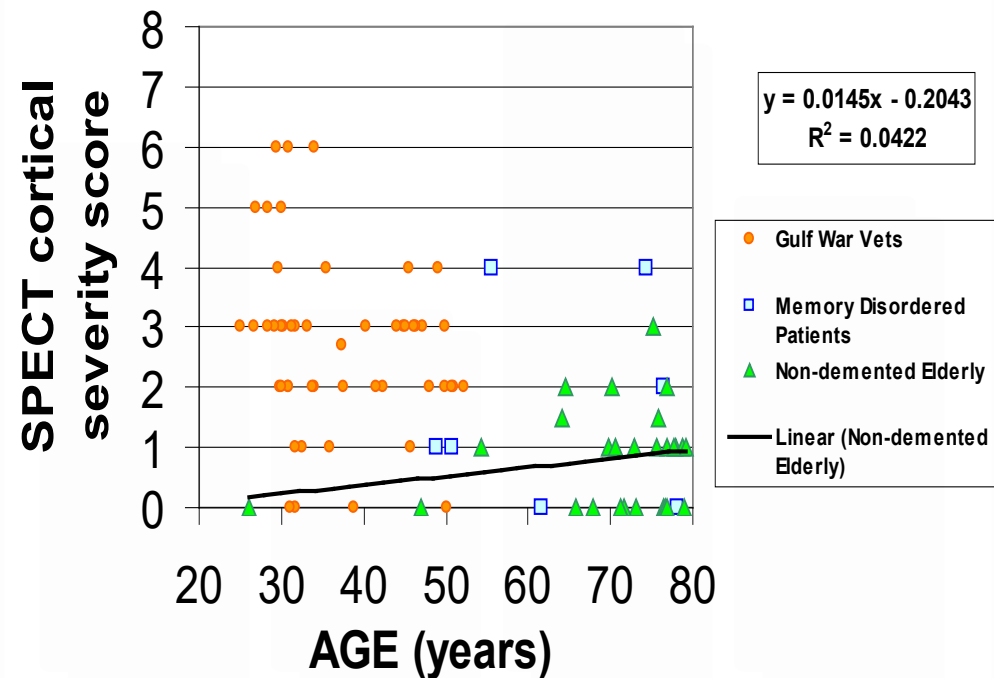


# SPECT Brain Changes in GWI

SPECT (single photon emission computed tomography) shows cerebral blood flow, which is controlled by the autonomic nervous system and local neural activity.



(All Veterans had normal MRI brain scans)



Ashford & Shih, VA Lexington, 2002, unpublished

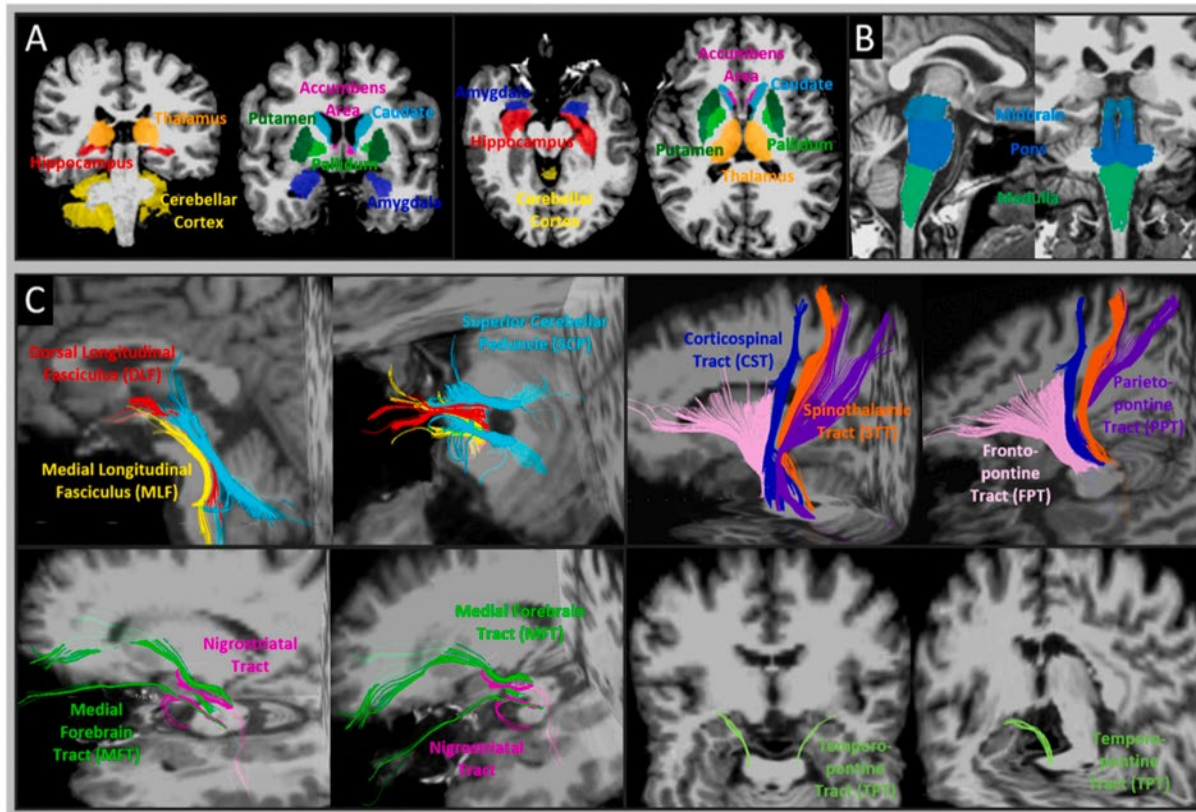


# Brain Stem Changes in GWI

- 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)



# BRAINSTEM DAMAGE IN GWI



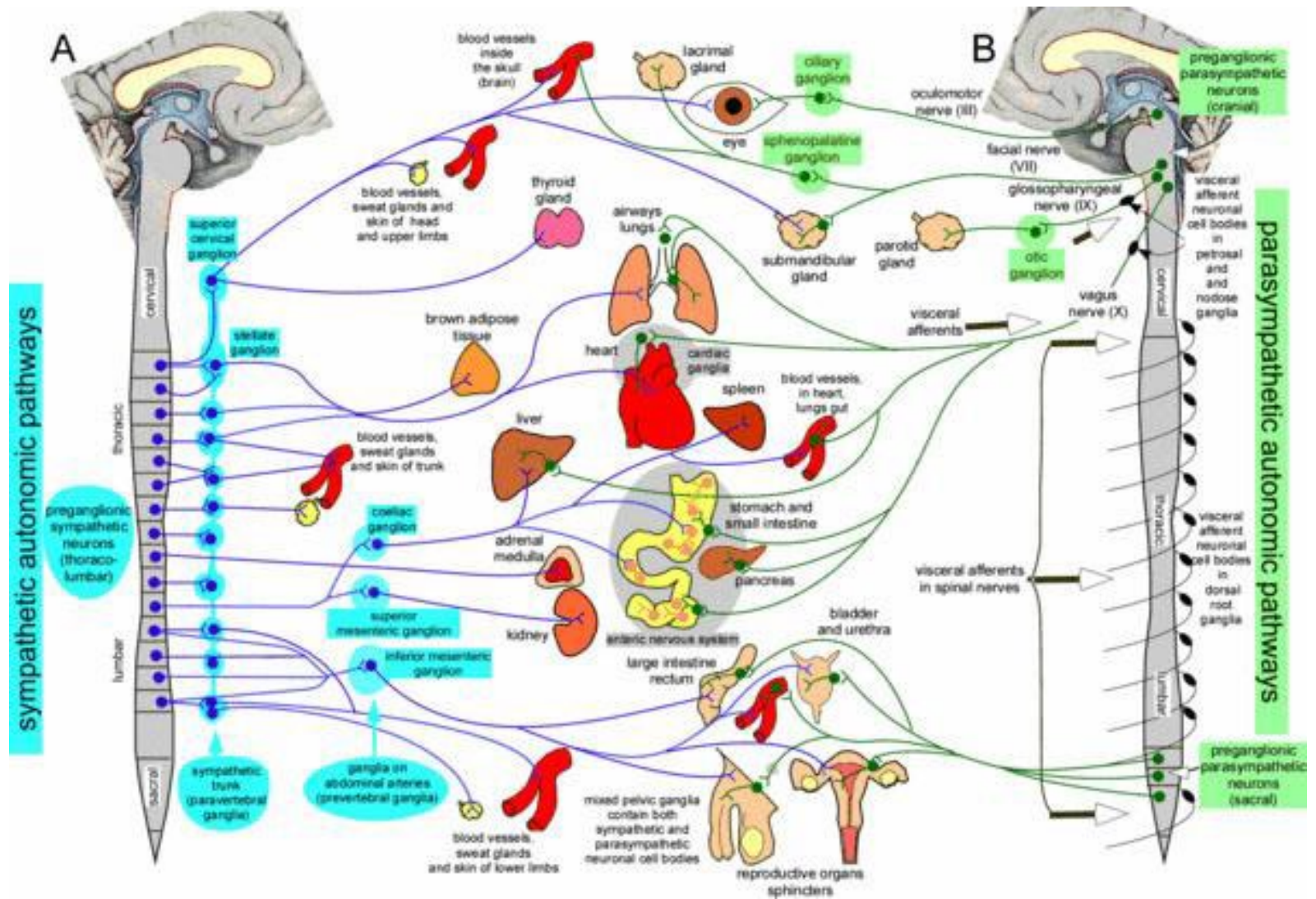
**Fig. 1.** Illustration of ROI where the volumes of the brainstem nuclei and diffusion metrics were measured. A: example of 8 subcortical ROIs (hippocampus, amygdala, accumbens area, thalamus, caudate, putamen, pallidum, cerebellar cortex) and B: 3 brainstem ROIs (medulla, pons and midbrain) that volumetric 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 temporo-pontine 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.



# BRAINSTEM, Autonomic Nervous System





# DYSAUTONOMIA AND THE BRAINSTEM

- Dysautonomia is common in fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome, raising the possibility that such dysautonomia could be their common clustering underlying GWI pathogenesis.
- BUT, GWI occurs late in Gulf War Veterans, usually after return
  - no evidence of an acute condition (e.g., nerve agent poison)
  - suggests long-term response to unknown factor
    - ? Like long-COVID, related to SARS-CoV-2 infection
    - ? MERS ancestor (from camels, which frequented the theatre)
  - numerous environmental factors/stress – disturb immune system
- The Gulf War Veterans have many symptoms
  - usually “unexplained”, but most have possible autonomic relationships
- The autonomic nervous system is under control of the brain stem, so dysautonomia can be caused by disruption of the brain stem.



# Dysautonomia and Related 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
  - Immune system can affect brain and could be explanatory
- 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.”
- Fox et al., 2019 Mar 1, Military Medicine. 184(3-4):e191-e196
  - Presence of autonomic symptoms in a sample of Veterans with Gulf War Illness (GWI) using the Composite Autonomic Symptom Scale (COMPASS-31)
- Avery...Bayley, 2021 Dec 30 - Military Medicine
  - Title: Self-Reported Autonomic Dysregulation in Gulf War Illness
  - Autonomic nervous system dysregulation is commonly observed in Gulf War illness
- For COMPASS-31 form, see: <http://www.medafile.com/COMPASS.htm>



# POTENTIAL EXPLANATIONS FOR ANS DAMAGE IN GWI

- **Anti-cholinesterase agents** (sarin exposure, combinations, PB predisposal, insecticides, flea collar use, not permethryn).
- **Immunological response** – chronic response to infectious agent
  - Autoimmune attack on neurons (like Guillan-Barre syndrome)
  - May be similar to longCOVID – related to SARS-CoV-2 infection
  - The MERS coronavirus came from camels – many in ODS/S theatre, no support for this specific virus
- **Spider Bites** – biological toxin that could damage small neurons (not infectious agent) (? camel spiders?)
- **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), microbiome?



# Operation Desert Sabre

## Summary of the Offensive Ground Campaign



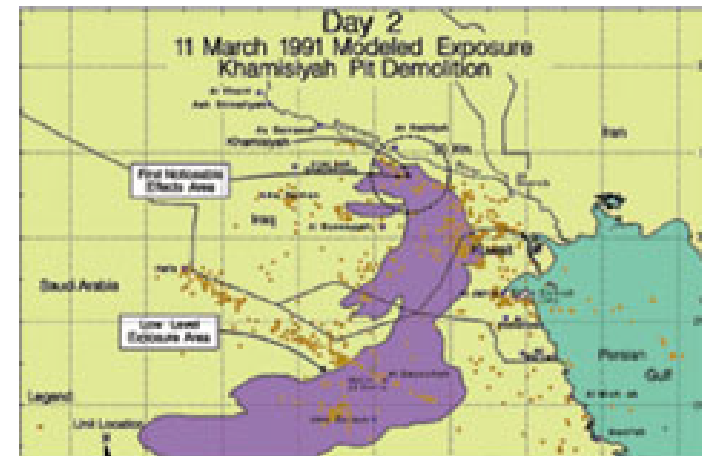




# Possible Chemical Weapon Exposures

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



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.



# LONG-TERM CONSEQUENCES OF SARIN EXPOSURE

Asymptomatic sequelae to acute sarin poisoning in the central and autonomic nervous system 6 months after the Tokyo subway attack

K Murata, S Araki, K Yokoyama, T Okumura, S Ishimatsu, N Takasu, R F White.

J Neurol. 1997 Oct;244(10):601-6.

Six to eight months after the Tokyo subway attack in March 1995, the neurophysiological effects of acute sarin poisoning were investigated in 18 passengers exposed to sarin (sarin cases) in the subways to ascertain the focal or functional brain deficits induced by sarin.

- None of the sarin cases had any obvious clinical abnormalities at testing.
- The P300 and VEP (P100) latencies in the sarin cases were significantly prolonged compared with the matched controls.
- Electrocardiographic R-R interval variability (CVRR) was related to serum cholinesterase (ChE) levels after exposure.
- These findings suggest that asymptomatic sequelae to sarin exposure persist



# COVID-19 “Long Hauler” SYMPTOMS

Survey Report by Dr. Natalie Lambert (U. Indiana) and Survivor Corps, 7/25/2020

60 symptoms occurred more than 10% of the time

Painful symptoms - 26.5%; Painless symptoms - 73.5%		
Of 1,567 respondents - Dr. Natalie Lambert - nalamb@iu.edu		
	#	prop
1 Fatigue	1,567	1.00
2 Muscle or body aches	1,046	0.67
3 Shortness of breath or difficulty breathing	1,020	0.65
4 Difficulty concentrating or focusing	924	0.59
5 Inability to exercise or be active	916	0.58
6 Headache	902	0.58
7 Difficulty sleeping	782	0.50
8 Anxiety	746	0.48
9 Memory problems	714	0.46
10 Dizziness	656	0.42
11 Persistent chest pain or pressure	609	0.39
12 Cough	577	0.37
13 Joint pain	566	0.36
14 Heart palpitations	509	0.32
15 Diarrhea	506	0.32
16 Sore throat	496	0.32
17 Night sweats	475	0.30
18 Partial or complete loss of sense of smell	460	0.29
19 Tachycardia	448	0.29
20 Fever or chills	441	0.28

<https://scholarworks.iupui.edu/handle/1805/25685>



# GWV - Most Frequent Symptoms, Affected Systems

Frequency of Symptoms of 53,835 Participants in Gulf War 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 longCOVID



# Tardive Dysautonomia in GWI

## Late reaction to a MERS coronavirus ancestor - HYPOTHESIS

- **Dysautonomia or brainstem damage can account for all GWI symptoms**
- Since the autonomic nervous system is controlled by the brainstem, 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
- Many of the symptoms of GWI are similar to several of the longCOVID symptoms
- Attack could be a late immunological response to a MERS ancestor coronavirus or another virus
- Local population affected at young age, minimal manifestation of illness
- ODS/S/S soldiers – all over 18 years of age – more susceptible
- Variety of stress factors, chemical exposures (pyridostigmine bromide, insecticides, oil-well fire smoke, possible low-doses of sarin (with PON-1 susceptibility) could have predisposed many soldiers (possibly more northern European descent – more in British than French soldiers, higher proportion in women than men)



# Current WRIISC Research Projects for GWI

- VA-HOME-WRIISC – Clinical Data Collection for Patients Seen in the War Related illness and Injury Study Center
- VA-IN-DEPTH – VA-HOME-WRIISC-DC/Miami VA/NIH – phenotyping
  - Includes WRIISC CA, WRIISC DC
  - Veterans with a history of COVID-19 excluded
- GWICTIC – Gulf War Illness Clinical Trial & Intervention Consortium
  - Includes WRIISC CA, WRIISC NJ, Miami VA
- VA-HOME-WRIISC-CA
  - The role of the brain stem in GWVI pathology – Ansgar Furst
  - Biopredictors of cognitive and behavioral outcomes
    - (sleep in GWI) – Ansgar Furst



# Planning WRIISC Research Projects for GWI

- Gulf War Illness and long-COVID (Veterans ineligible for VA-IN-DEPTH)
  - VA-HOME-WRIISCCA, DC, Miami VA, Boston VA, Charleston VA, NIH
  - Registry, clinical evaluation, longitudinal monitoring program
  - Developing – registry, questionnaires, on-line assessments (under development)
    - General Health Survey (based on Rand SF-36): <http://www.medafile.com/longCOVID/GHS38.htm>
    - Somatic Symptom Scale (PHQ-15): <http://medafile.com/PHQ15.htm>
    - Pain scale: <http://www.medafile.com/PainMatrix-2021.htm>
    - Fatigue scale: <http://www.medafile.com/longCOVID/FatigueSeverityScale.htm>
    - Neuropathy Scale: <http://www.medafile.com/DS21sfn.htm>
    - Autonomic function scale (COMPASS-31): [www.medafile.com/COMPASS.htm](http://www.medafile.com/COMPASS.htm)
    - Depression Scale: <http://medafile.com/cdn/GDS15.htm>
    - Anxiety Scale: <http://medafile.com/longCOVID/BAI.html>
    - Sleep Scale: Pittsburgh Sleep Quality Index Scale: <http://www.medafile.com/WRIISC/PSQI.htm>
    - Memory Impairment – on-line test: [www.memtrax.com](http://www.memtrax.com)
- Possible NIH/CDC data analyses, collaborations for long-COVID:
  - <https://recovercovid.org/>
  - <https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html>



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- Andre Vahktin

Appreciate discussion  
regarding MERS with  
Stanley Perlman,  
University of Iowa





# THANK YOU

Slides at:

[www.medafile.com/GWI/GulfWar-WRIISC-JWA-2022-09-21.pptx](http://www.medafile.com/GWI/GulfWar-WRIISC-JWA-2022-09-21.pptx)

or

[www.medafile.com/GWI](http://www.medafile.com/GWI)

(this slide deck link at lower left)

For WRIISC referral, see: [www.warrelatedillness.va.gov](http://www.warrelatedillness.va.gov)

More of Dr. Ashford's developments at:

[www.medafile.com](http://www.medafile.com)

[www.medafile.com/COVIDstudy](http://www.medafile.com/COVIDstudy)

[www.memtrax.com](http://www.memtrax.com) (memory test)

NIH long-COVID research: <https://recovercovid.org/>

WHO-MERS [https://www.who.int/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-\(mers-cov\)](https://www.who.int/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov))