Two studies in Gulf War Veterans:

I. Effects of low-level sarin exposure

II. Cognitive behavioral therapy for insomnia in Veterans with GWI

Linda Chao, Ph.D.

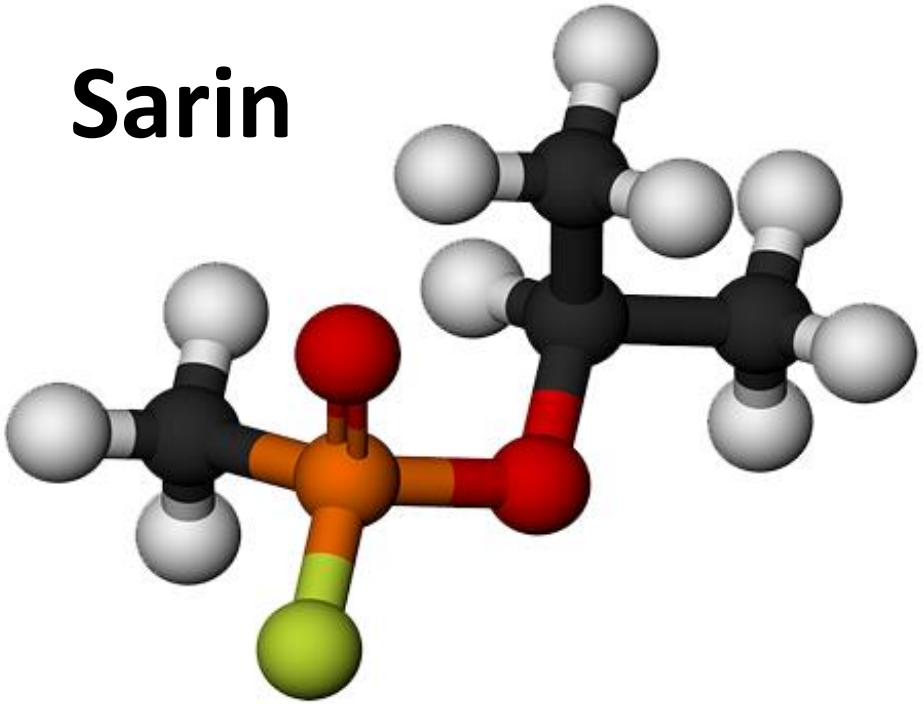
Research Advisory Committee on Gulf War Veterans' Illness
October 4, 2019

Part I. Neuroimaging studies on the effects of low-level sarin exposure in Gulf War Veterans

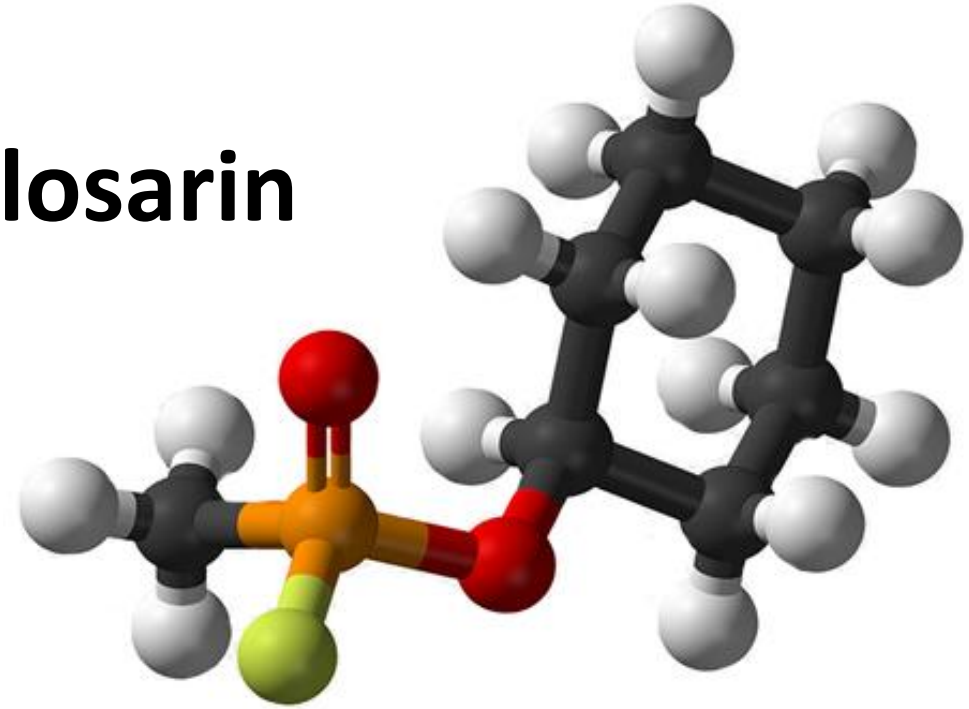
In March 1991, US troops destroyed several ammunition storage complexes at Khamisiyah, Iraq.

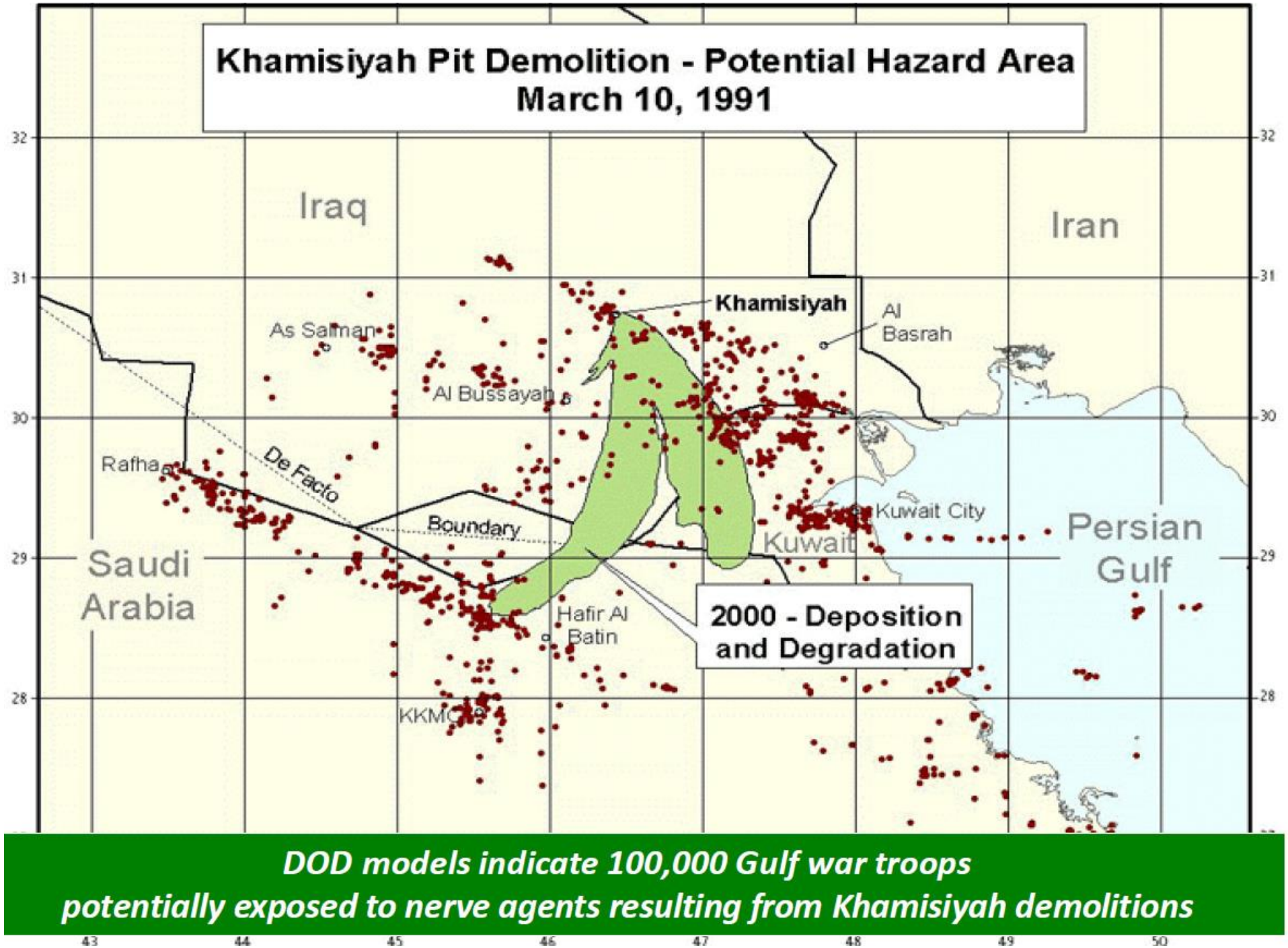
Organophosphate nerve agents

Sarin



Cyclosarin





DOD models indicate 100,000 Gulf war troops potentially exposed to nerve agents resulting from Khamisiyah demolitions

Science 2 February 2001:
Vol. 291 no. 5505 p. 814
DOI: 10.1126/science.291.5505.814

Science

NEWS FOCUS

MEDICINE

Congress Explores the Scientific Fringe

Martin Enserink

United States General Accounting Office

GAO

Testimony

Before the Subcommittee on National Security, Emerging Threats, and International Relations, Committee on Government Reform, House of Representatives

For Release on Delivery
Expected at 1:00 p.m. EDT
Tuesday, June 1, 2004

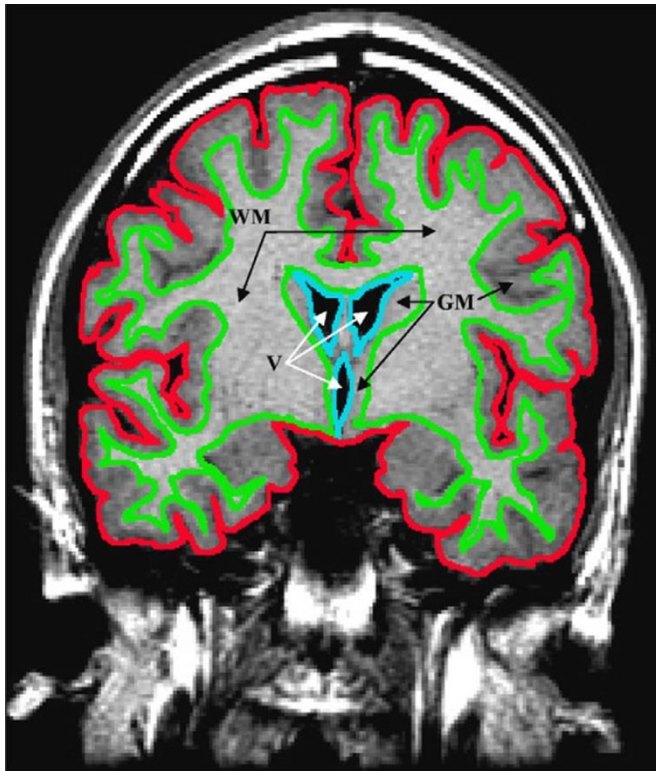
GULF WAR ILLNESSES

DOD's Conclusions About U.S. Troops' Exposure Cannot Be Adequately Supported

Available online at www.sciencedirect.com
ScienceDirect
NeuroToxicology 28 (2007) 761–769
NeuroToxicology

Quantitative magnetic resonance brain imaging in US army veterans of the 1991 Gulf War potentially exposed to sarin and cyclosarin

Kristin J. Heaton [a,b,c,1,*], Carole L. Palumbo [a,d], Susan P. Proctor [a,b,c,1], Ronald J. Killiany [d,e,f], Deborah A. Yurgelun-Todd [f,g], Roberta F. White [a,b,d]



- Significant association between estimated levels of sarin/cyclosarin exposure and volumes of the white matter (reduced) and lateral ventricles (increased).

Demographics of 1.5 T sample

	Exposed	Unexposed
N	40	40
No. Female (%)	7 (18%)	7 (18%)
Age, years	44.0 ± 10.2	42.7 ± 9.3
Education, years	14.9 ± 3.7	14.5 ± 2.0
No. current PTSD diagnosis (%)	5 (13%)	5 (13%)
No. current MDD diagnosis (%)	2 (5%)	3 (7%)
No. CDC CMI cases (%)	21 (54%)	23 (59%)

PTSD: Posttraumatic Stress Disorder
MDD: Major Depressive Disorder
CDC CMI according to Fukuda et al.,1998

NeuroToxicology 31 (2010) 493–501

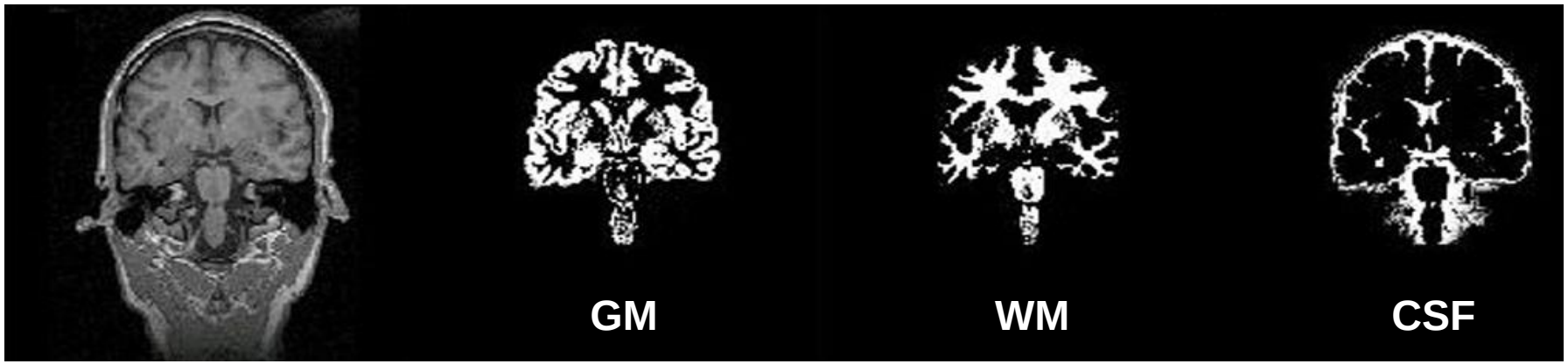
Contents lists available at ScienceDirect

NeuroToxicology

Effects of low-level exposure to sarin and cyclosarin during the 1991 Gulf War on brain function and brain structure in US veterans

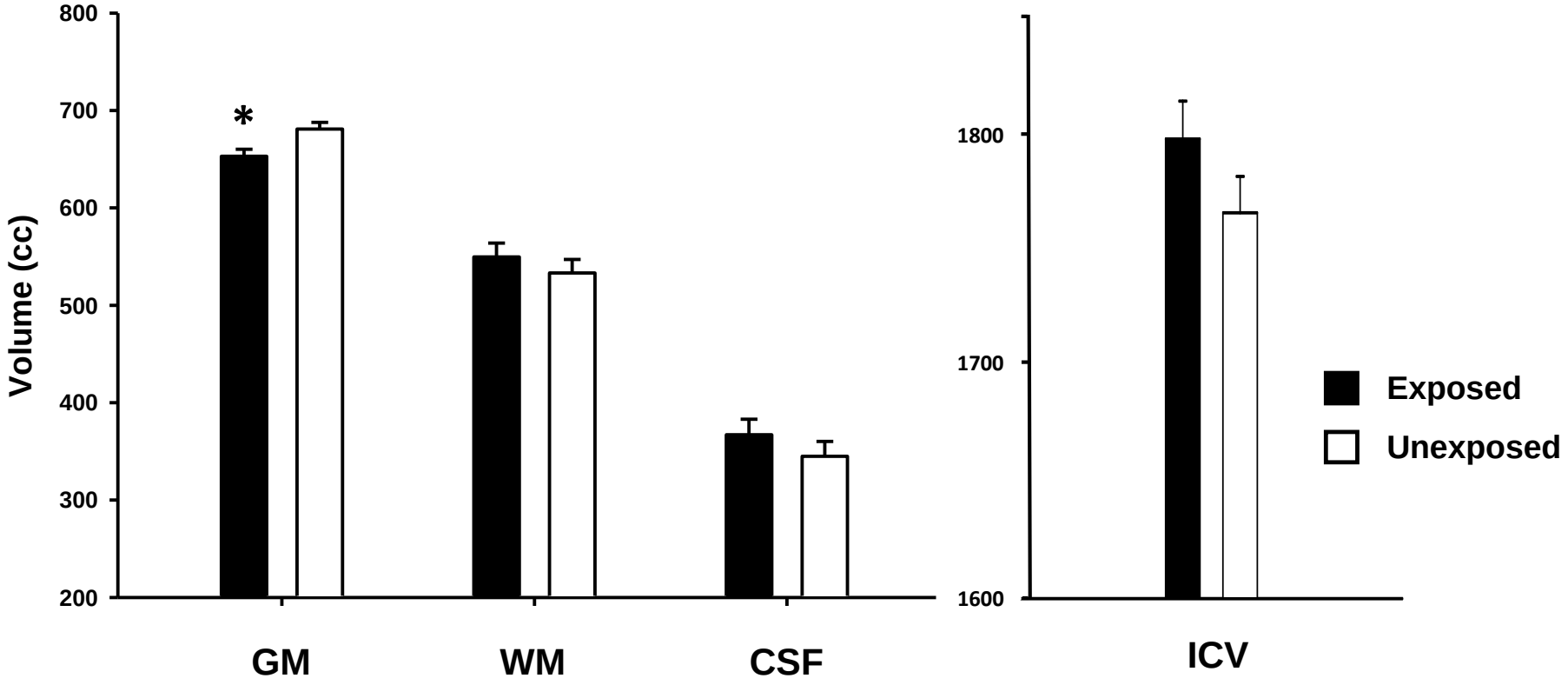
Linda L. Chao [a,b,c,*], Johannes C. Rothlind [b], Valerie A. Cardenas [a,c], Dieter J. Meyerhoff [a,c], Michael W. Weiner [a,b,c]

[a] Center for Imaging of Neurodegenerative Diseases, San Francisco Veterans Affairs Medical Center, 4150 Clement Street, 114 M, San Francisco, CA, 94121, United States
[b] Department of Psychiatry, University of California, San Francisco, San Francisco, CA, United States
[c] Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA, United States



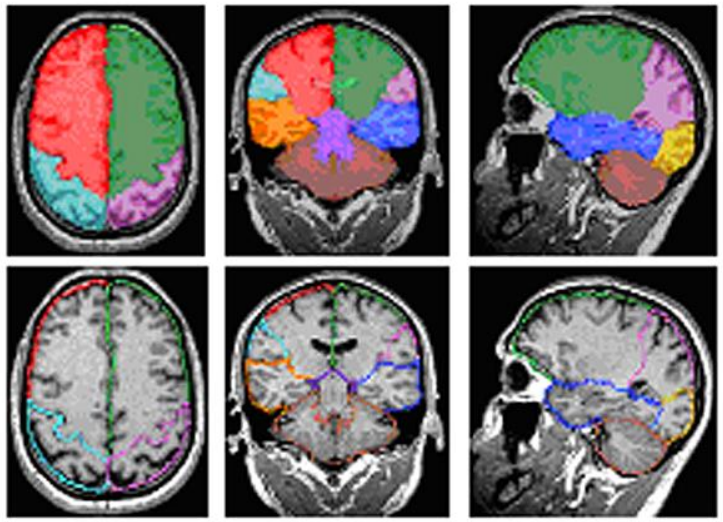
1.5 T MRI Results

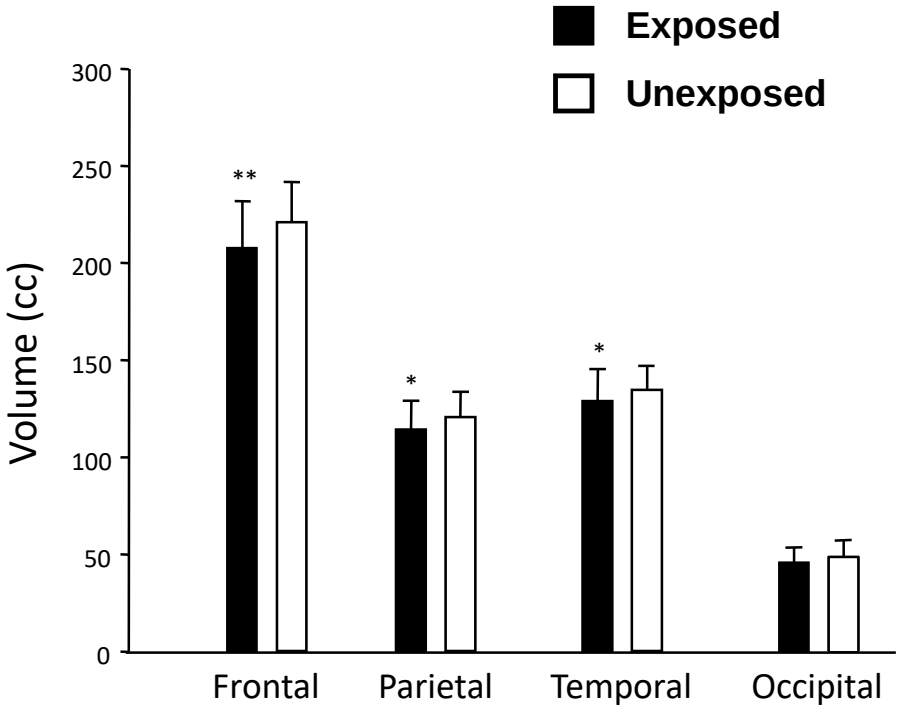
- After accounting for intracranial volume (ICV), age, and gender, veterans with predicted exposure had less total brain GM volume compared to matched, unexposed veterans.



1.5 T MRI Results

- Group differences in regional lobar GM volume were examined in post-hoc analyses.





TOXICOLOGY AND APPLIED PHARMACOLOGY **104,** 440–456 (1990)

The Neurotoxicity of Subchronic Acetylcholinesterase (AChE) Inhibition in Rat Hippocampus

BELLINA VERONESI, KIMBERLY JONES, AND CAREY POPE

Health Effects Research Laboratory, U.S. Environmental Protection Agency, Neurotoxicology Division (MD74B), Research Triangle Park, North Carolina 27711

JOURNAL OF APPLIED TOXICOLOGY
J. Appl. Toxicol. **21**, S87–S94 (2001)
DOI:10.1002/jat.818

Soman-induced Seizures: Limbic Activity, Oxidative Stress and Neuroprotective Proteins†‡

T. L. Pazdernik,* M. R. Emerson, R. Cross, S. R. Nelson and F. E. Samson
Ralph L. Smith Research Center, University of Kansas Medical Center, Kansas City, KS 66160, USA

Pergamon
www.neuroscience-ibro.com
PII: S0306-4522(02)00176-8
Neuroscience Vol. 113, No. 3, pp. 721–741, 2002

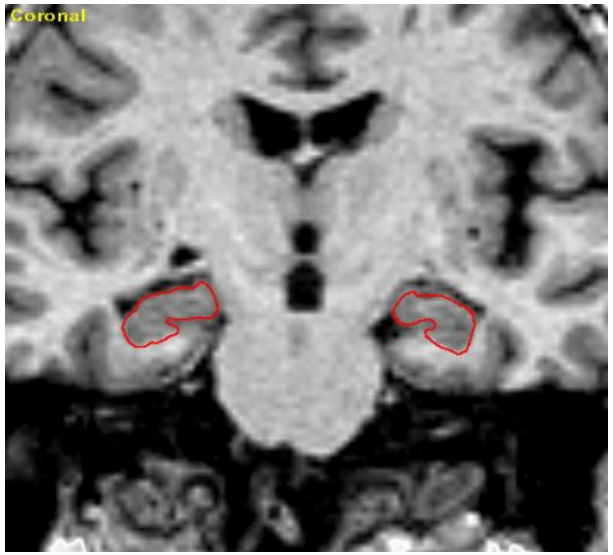
0306-4522/02 $22.00+0.00

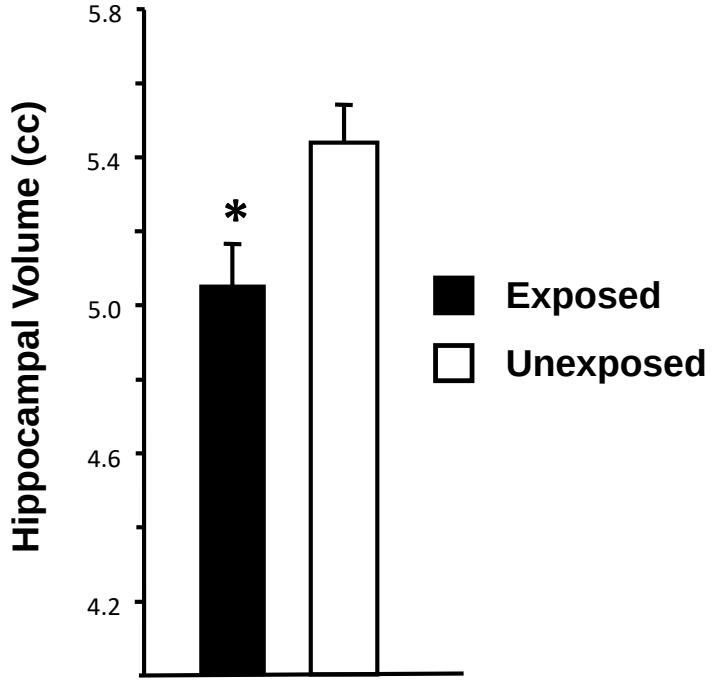
ACUTE EXPOSURE TO SARIN INCREASES BLOOD BRAIN BARRIER PERMEABILITY AND INDUCES NEUROPATHOLOGICAL CHANGES IN THE RAT BRAIN: DOSE–RESPONSE RELATIONSHIPS

A. ABDEL-RAHMAN,[a] A. K. SHETTY[b,c] and M. B. ABOU-DONIA[a,d*]
[a]Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC 27710, USA
[b]Department of Surgery (Neurosurgery), Duke University Medical Center, Durham, NC 27710, USA
[c]Medical Research Service, Veterans Affairs Medical Center, Durham, NC 27705, USA
[d]Department of Neurobiology, Duke University Medical Center, Durham, NC 27710, USA

1.5 T MRI Results

- After accounting for ICV, age, and gender, the veterans with predicted exposure had smaller hippocampal volume compared to matched, unexposed GW veterans.





Demographics of 4 T sample

	Exposed	Unexposed
N	64	64
No. Female (%)	5 (8%)	5 (8%)
Age, years	48.4 ± 7.0	48.5 ± 7.8
Education, years	15.1 ± 2.3	15.1 ± 2.1
No. current PTSD diagnosis (%)	5 (8%)	5 (8%)
No. current MDD diagnosis (%)	6 (9%)	8 (13%)
No. CDC CMI cases (%)	33 (52%)	33 (52%)

PTSD: Posttraumatic Stress Disorder
MDD: Major Depressive Disorder
CDC CMI according to Fukuda et al., 1998

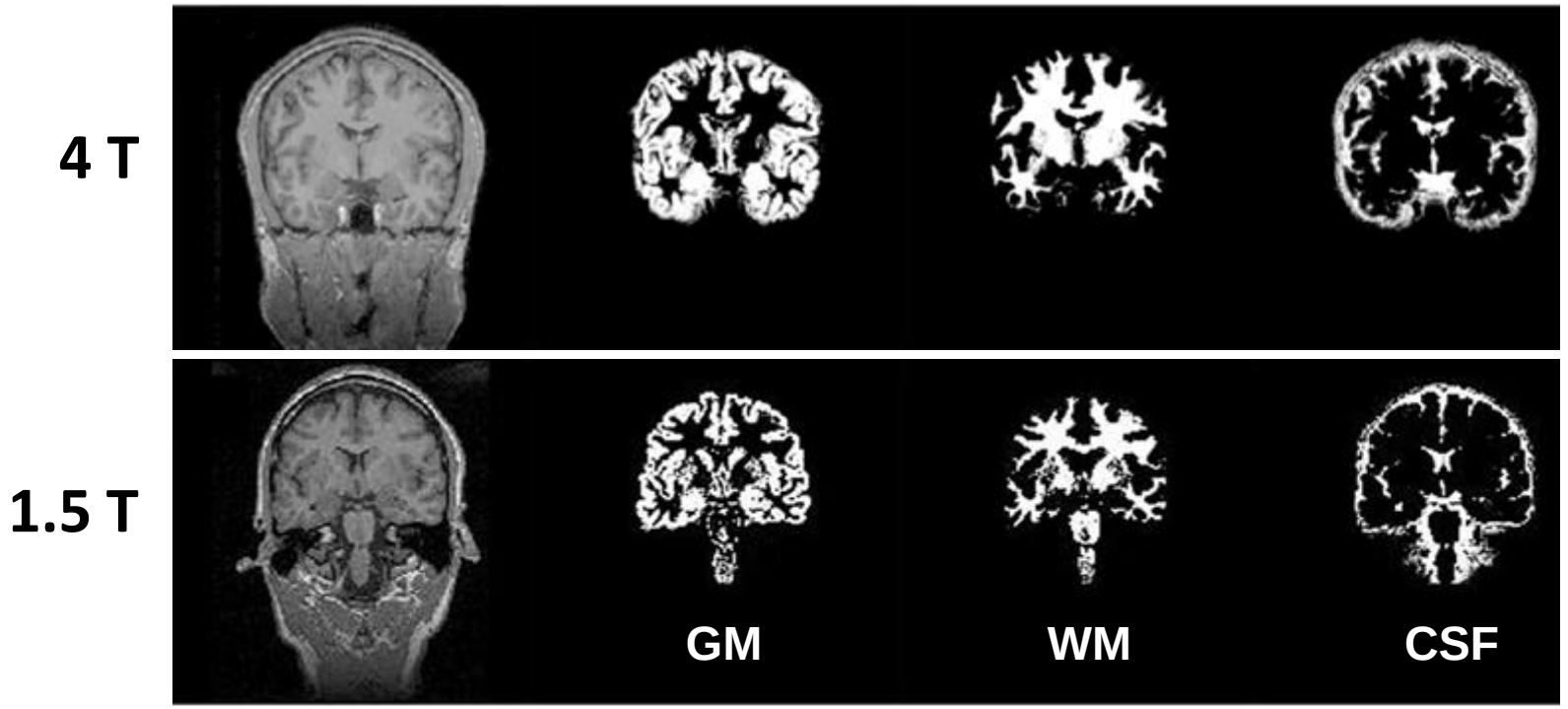
NeuroToxicology 32 (2011) 814–822

Contents lists available at ScienceDirect

NeuroToxicology

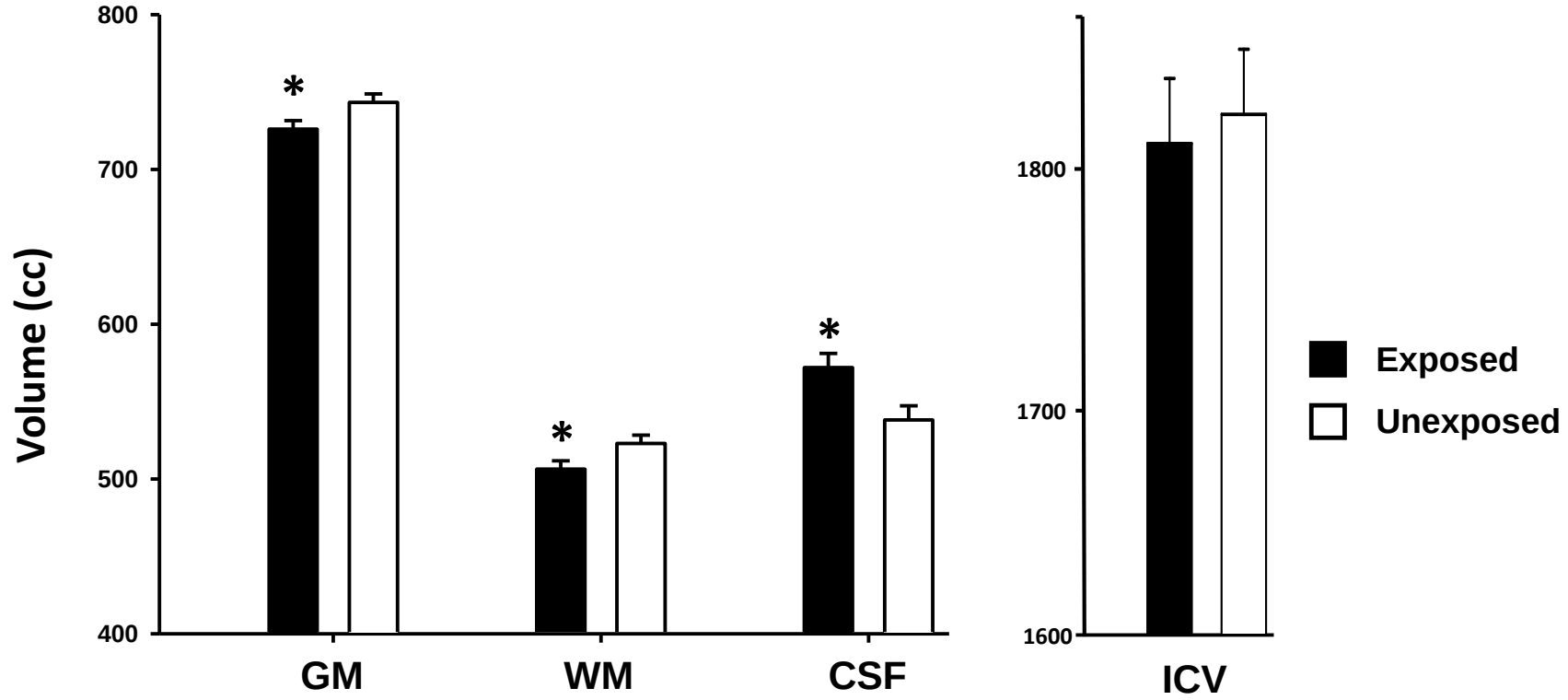
Effects of low-level sarin and cyclosarin exposure and Gulf War Illness on Brain Structure and Function: A study at 4 T

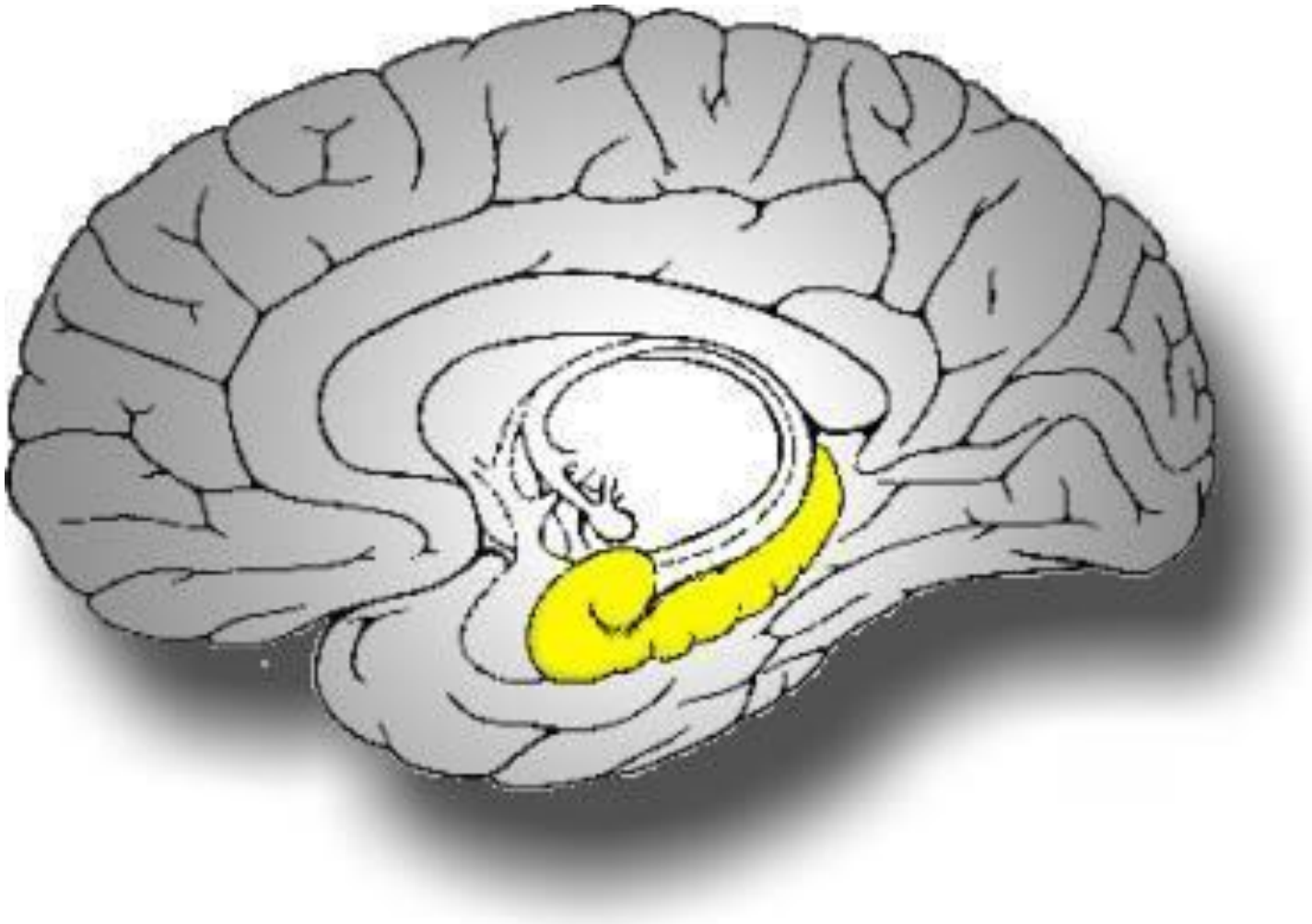
Linda L. Chao [a,b,c,*], Linda Abadjian [a], Jennifer Hlavin [a], Deiter J. Meyerhoff [a,c], Michael W. Weiner [a,b,c]

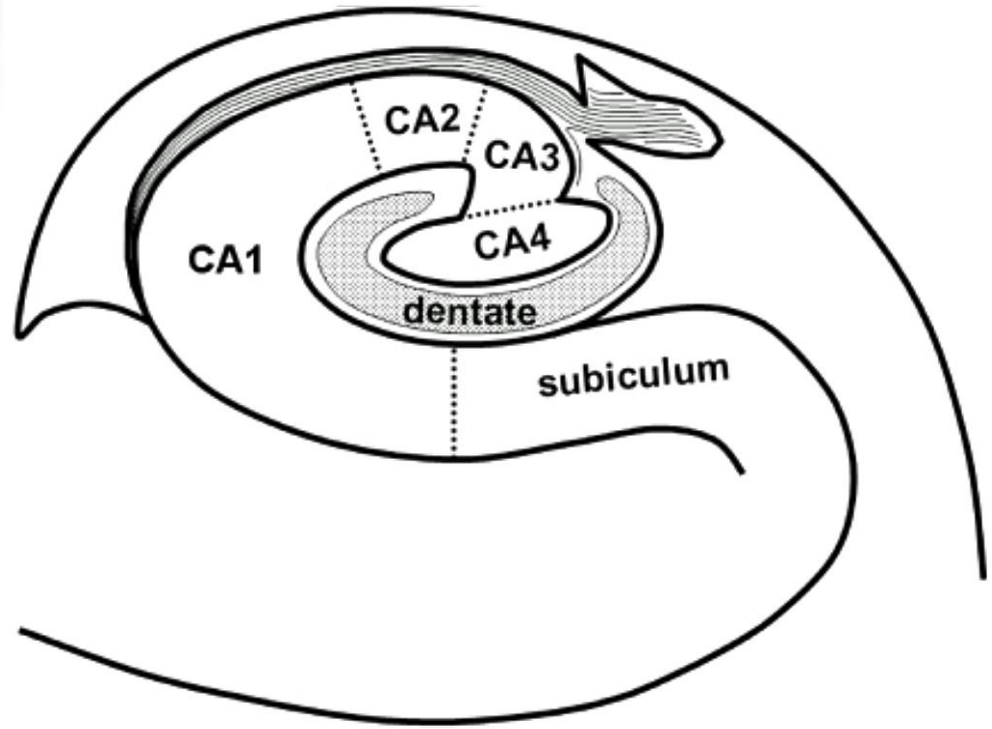


4 T MRI Results

- After accounting for intracranial volume (ICV), age, and gender, veterans with predicted exposure had less total brain GM and WM volume and larger CSF volume compared to matched, unexposed veterans.



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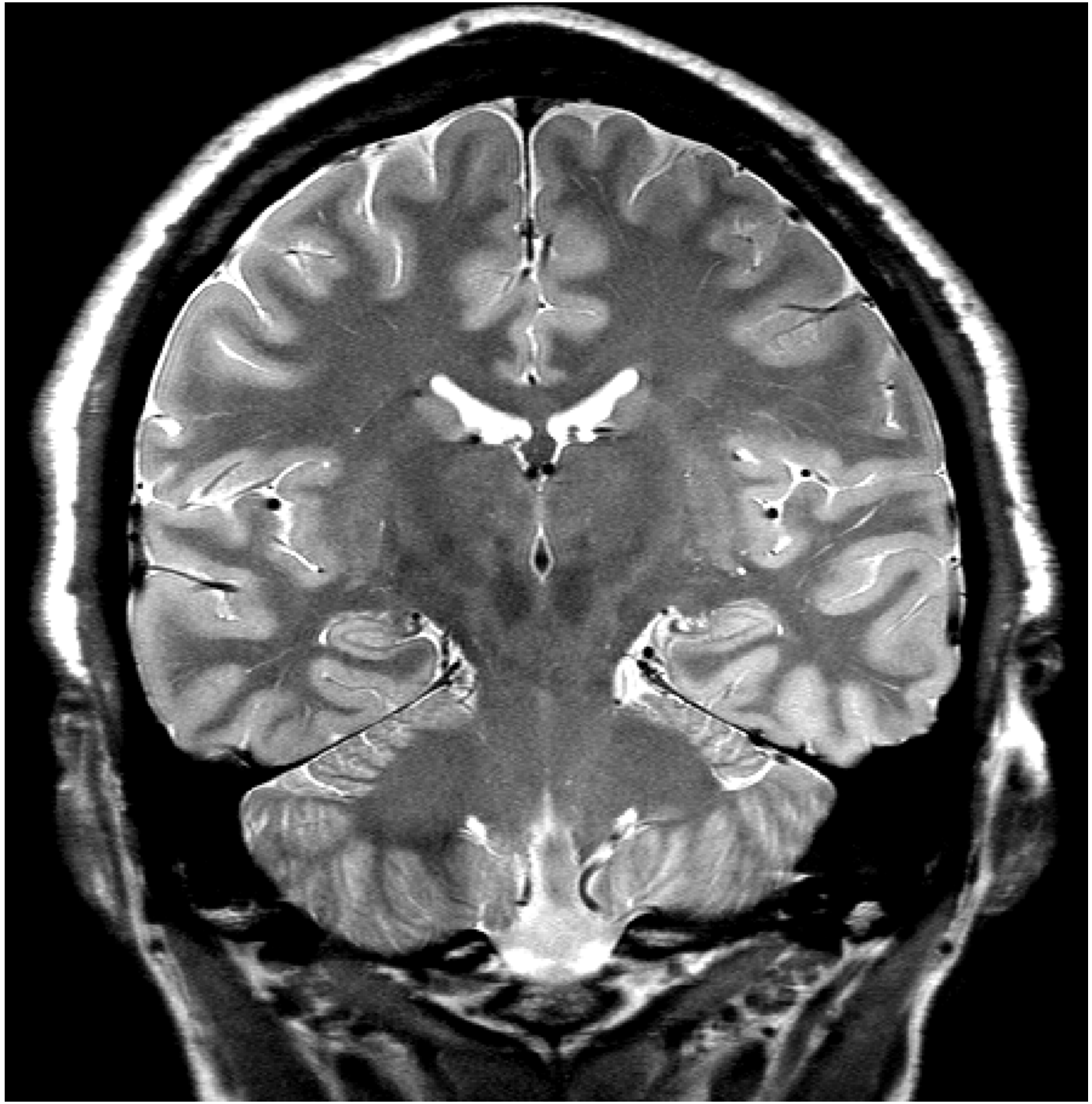
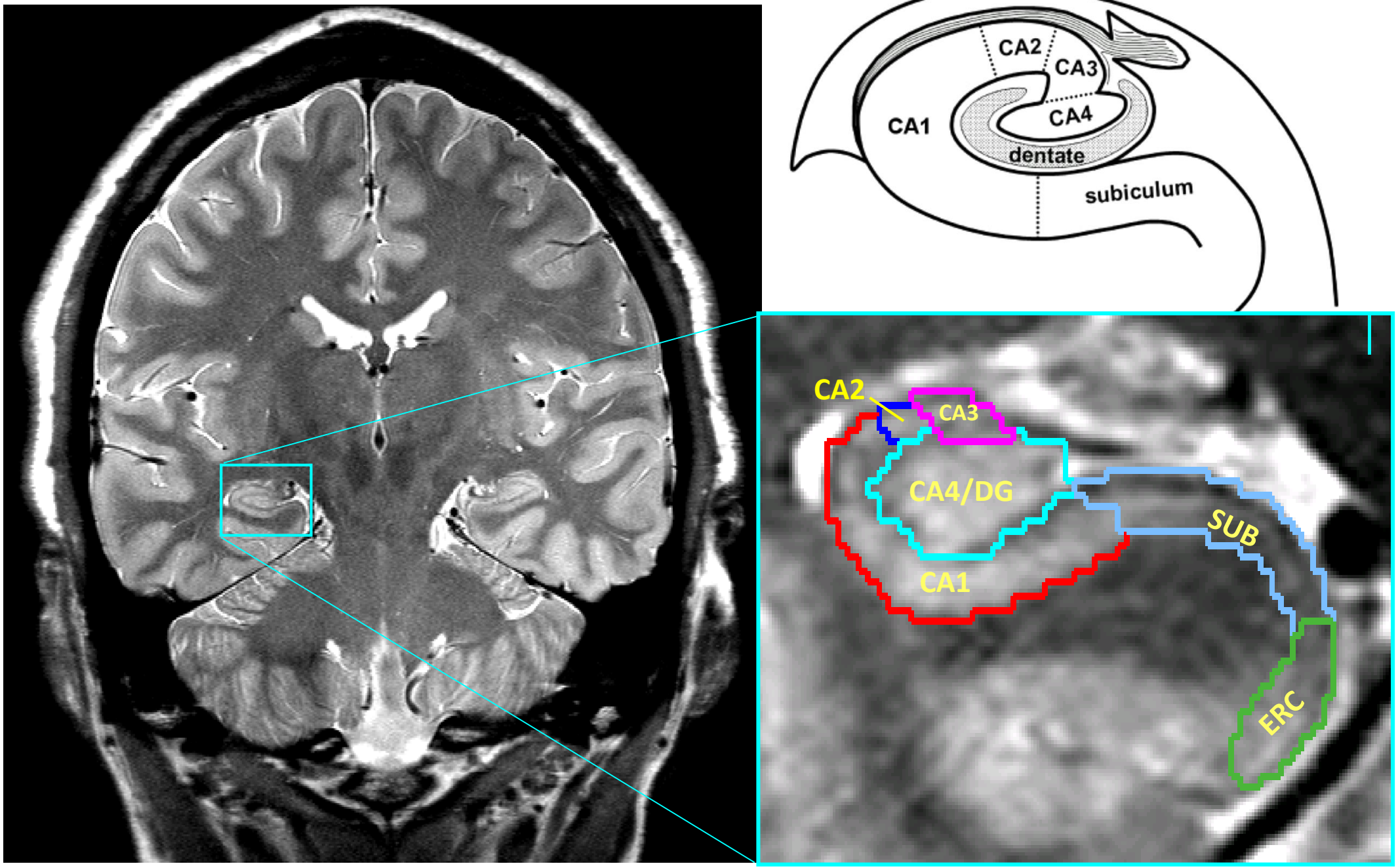


High Resolution T2-weighted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NeuroToxicology 44 (2014) 263–269

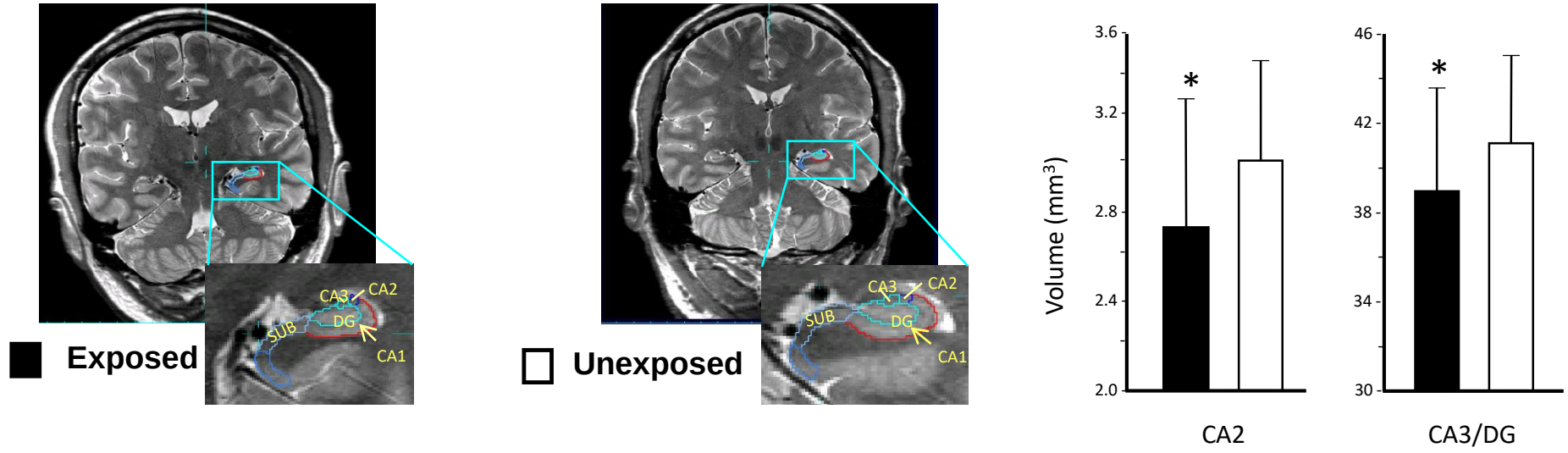
Contents lists available at ScienceDirect

NeuroToxicology

Effects of low-level sarin and cyclosarin exposure on hippocampal subfields in Gulf War Veterans

Linda L. Chao [a,b,c,*], Stephen Kriger [a], Shannon Buckley [a], Peter Ng [a], Susanne G. Mueller [a,b]

[a] Center for Imaging of Neurodegenerative Diseases, San Francisco Veterans Affairs Medical Center, 4150 Clement Street, 114M, San Francisco, CA 94121, United States
[b] Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, United States
[c] Department of Psychiatry, University of California San Francisco, San Francisco, CA, United States



Demographics of 3T sample

	Exposed	Unexposed
N	51	62
No. Female (%)	14 (28%)	12 (19%)
Age, years	52.4 ± 7.7	53.5 ± 8.0
Education, years	14.5 ± 2.5	15.0 ± 2.5
No. current PTSD diagnosis (%)	12 (24%)	8 (13%)
No. current MDD diagnosis (%)	6 (12%)	7 (11%)
No. Kansas GWI cases (%)	25 (49%)	29 (47%)
No. CDC CMI cases (%)	40 (78%)	52 (84%)

PTSD: Posttraumatic Stress Disorder
MDD: Major Depressive Disorder
Kansas GWI, as defined by Steele, 2000
CDC CMI, as defined by Fukuda et al., 1998

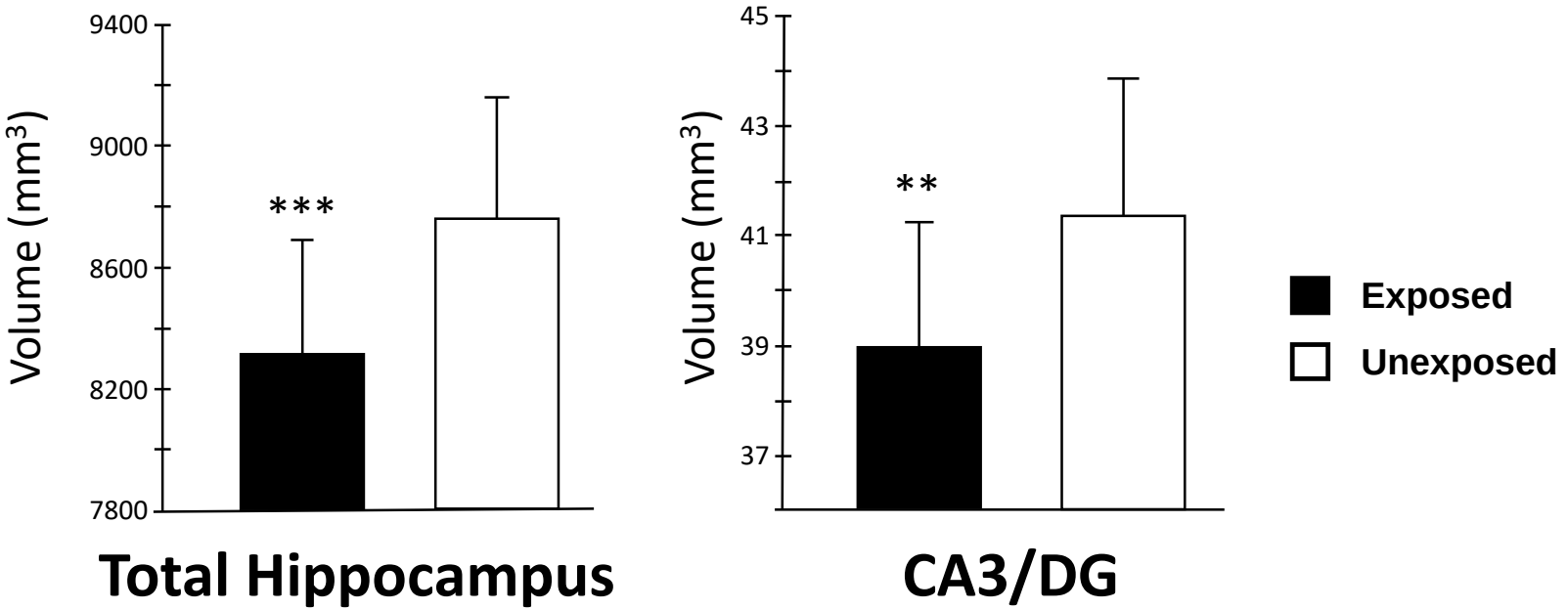
JOEM Journal of Occupational and Environmental Medicine

October 2017 - Volume 59 - Issue 10 - p 923–929

ORIGINAL ARTICLE

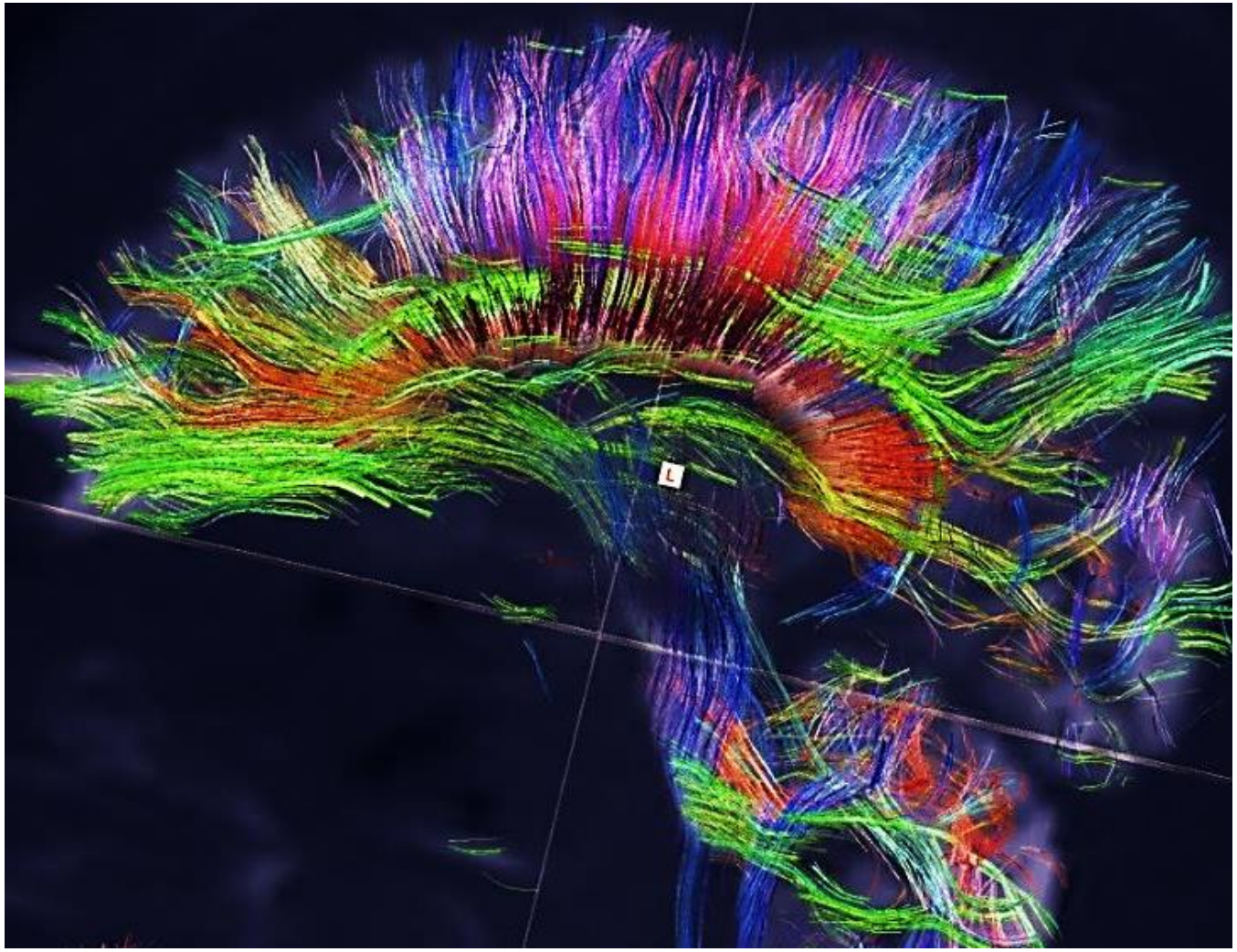
Evidence of Hippocampal Structural Alterations in Gulf War Veterans With Predicted Exposure to the Khamisiyah Plume

Linda L. Chao, PhD, Morgan R. Raymond, BS, Cynthia K. Leo, BA, and Linda R. Abadjian, PhD



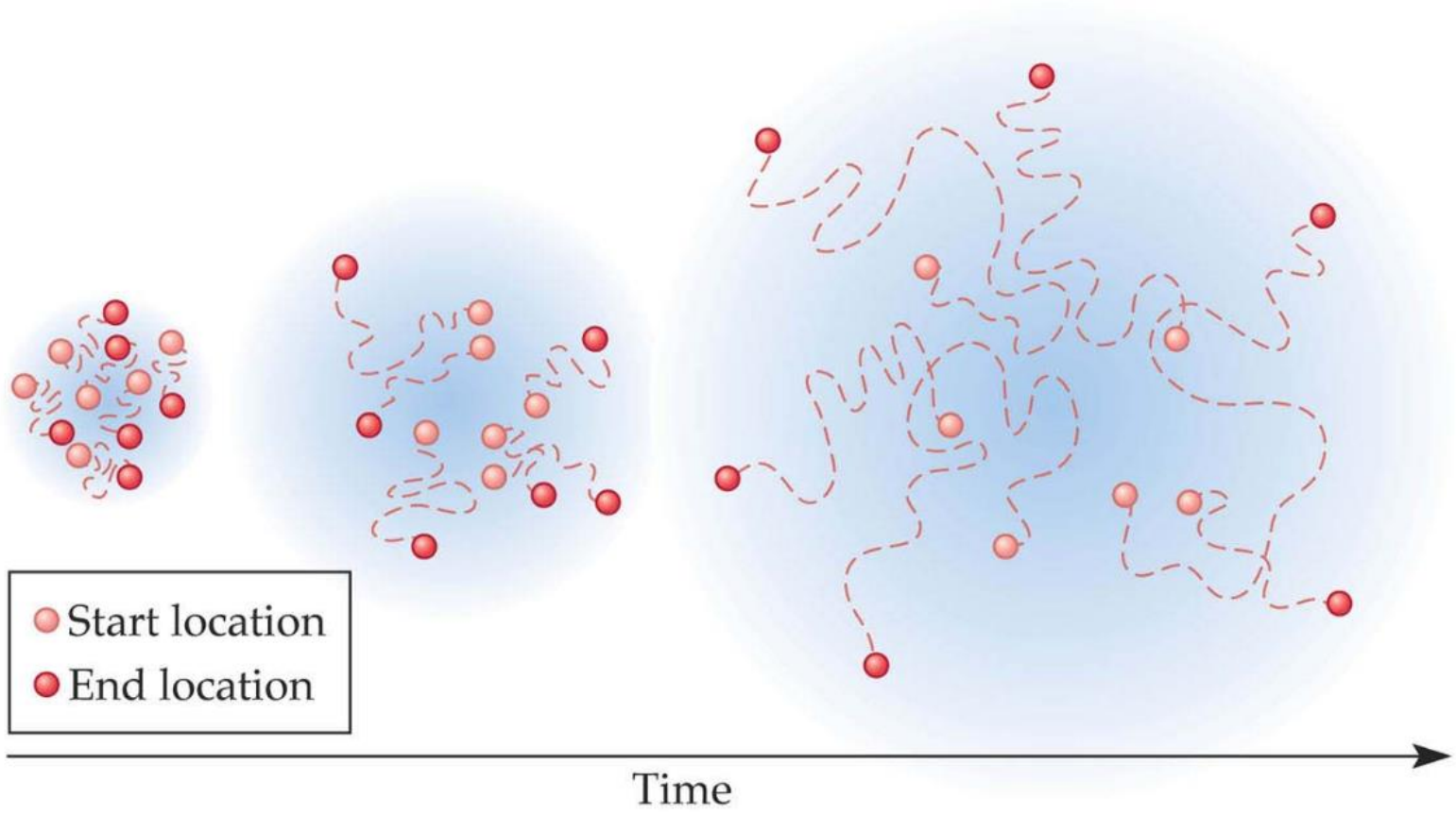
DIFFUSION TENSOR IMAGING

- Non-invasive method of quantifying white matter tracks in the brain.



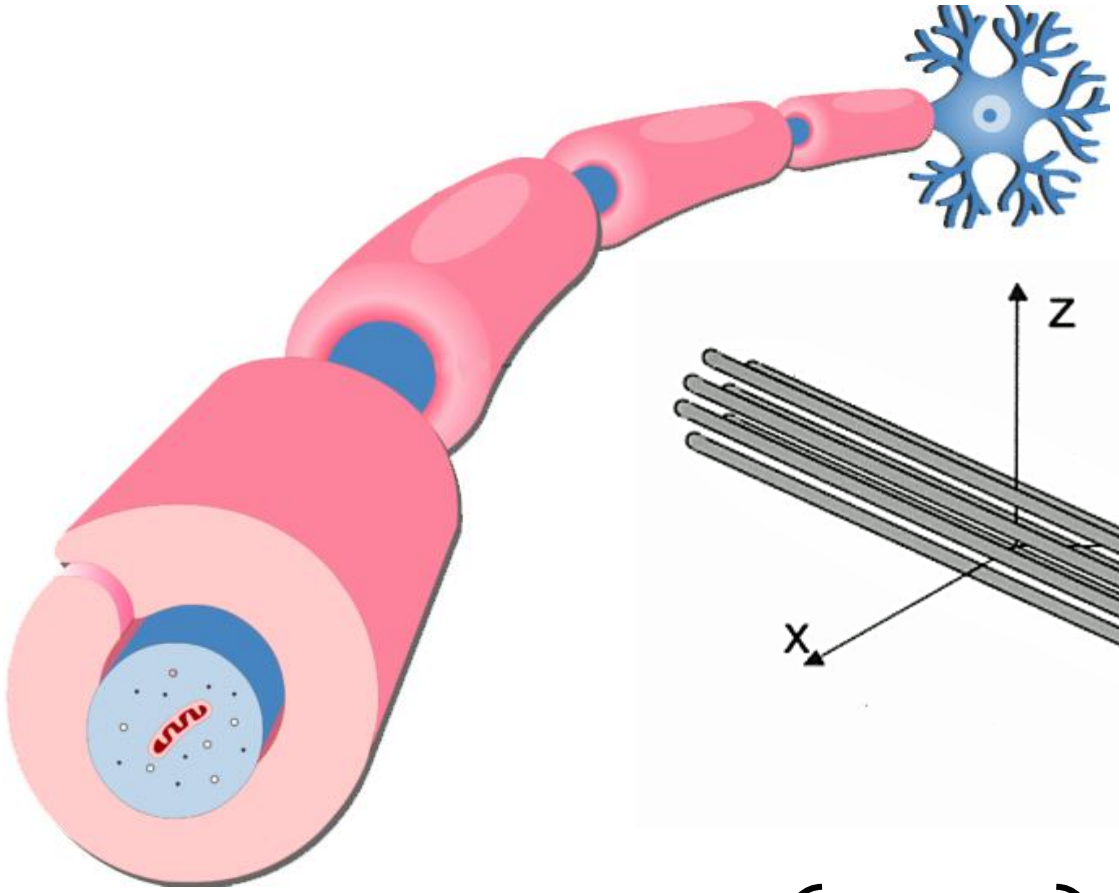
DIFFUSION TENSOR IMAGING

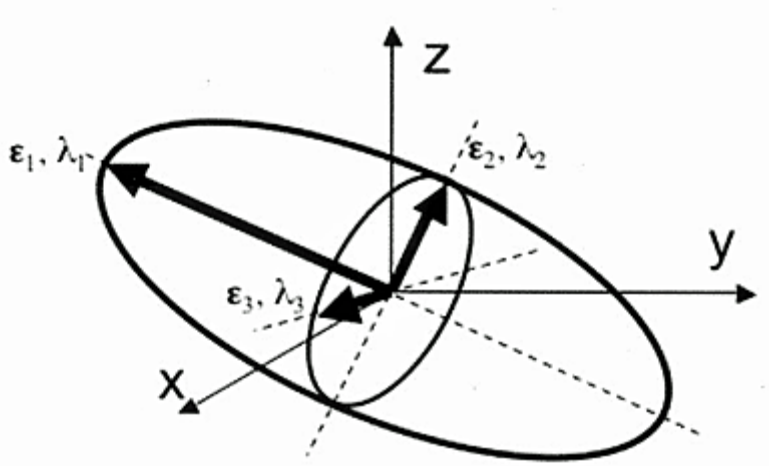
- Measures the random movement of water molecules.



From Functional Magnetic Resonance Imaging, Figure 5.17 © 2004 Sinauer Associates, Inc.

DIFFUSION TENSOR IMAGING





Diffusion Tensor $= \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{pmatrix}$

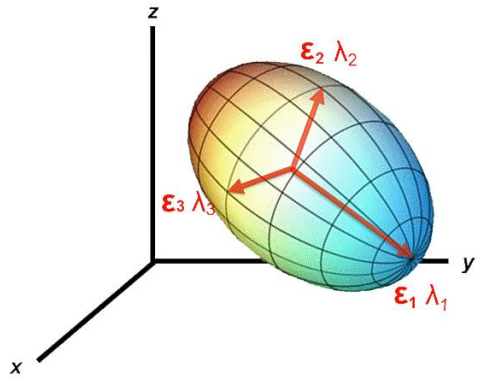
eigenvalues

$\Lambda = \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix}$

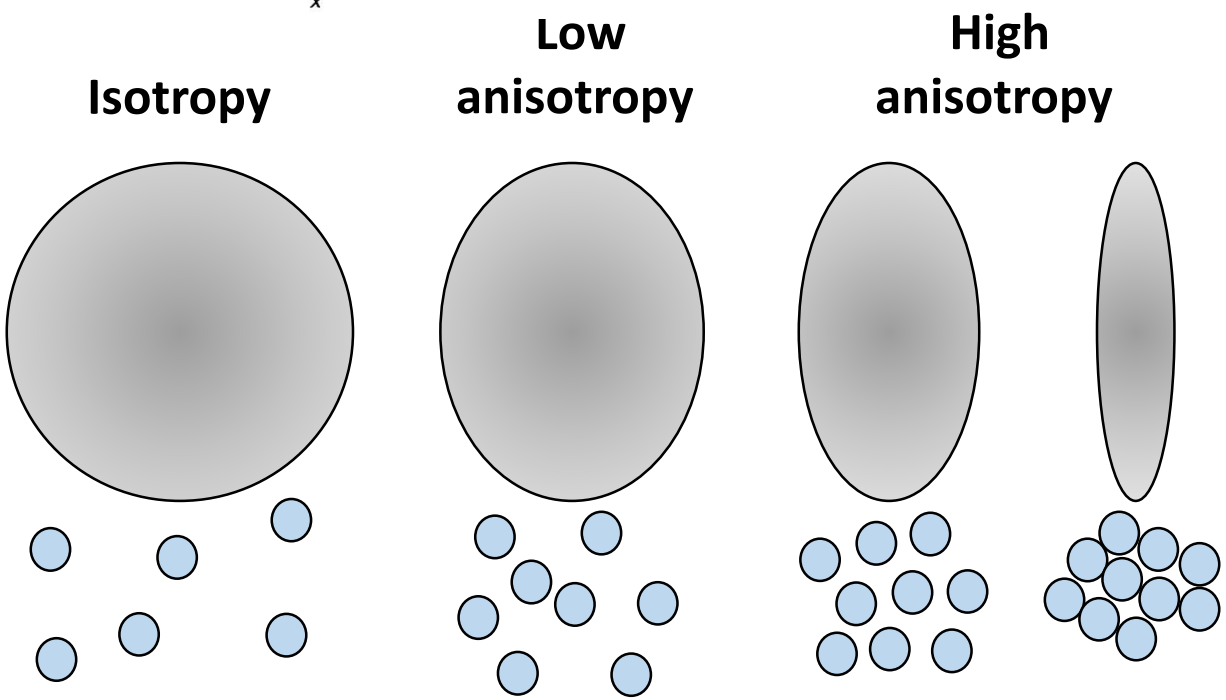
eigenvectors

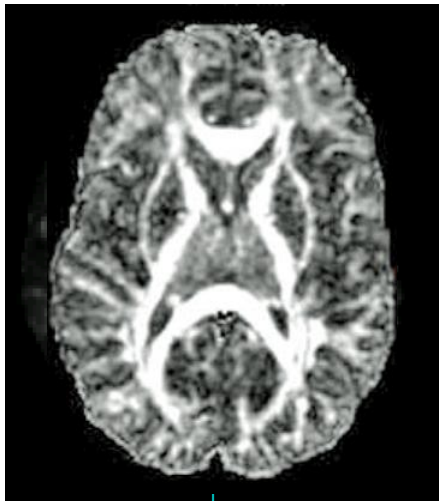
$E = \begin{pmatrix} \varepsilon_{1x} & \varepsilon_{2x} & \varepsilon_{3x} \\ \varepsilon_{1y} & \varepsilon_{2y} & \varepsilon_{3y} \\ \varepsilon_{1z} & \varepsilon_{2z} & \varepsilon_{3z} \end{pmatrix}$

DIFFUSION TENSOR IMAGING



Fractional Anisotropy (FA) = $\sqrt{\frac{3}{2}}\sqrt{\frac{(\lambda_1-\bar{\lambda})^2+(\lambda_2-\bar{\lambda})^2+(\lambda_3-\bar{\lambda})^2}{\lambda_1^2+\lambda_2^2+\lambda_3^2}}$





Lower FA is associated with reduced WM integrity.

Demographics of 4T DTI sample

	Exposed	Unexposed
N	59	59
No. Female (%)	6 (10%)	6 (10%)
Age, years	48.5 ± 7.6	48.4 ± 7.2
Education, years	15.1 ± 2.1	15.6 ± 2.1
No. current PTSD diagnosis (%)	4 (7%)	4 (7%)
No. current MDD diagnosis (%)	5 (8%)	7 (12%)
No. CDC CMI cases (%)	36 (61%)	36 (61%)

PTSD: Posttraumatic Stress Disorder
MDD: Major Depressive Disorder
CDC CMI, as defined by Fukuda et al., 1998

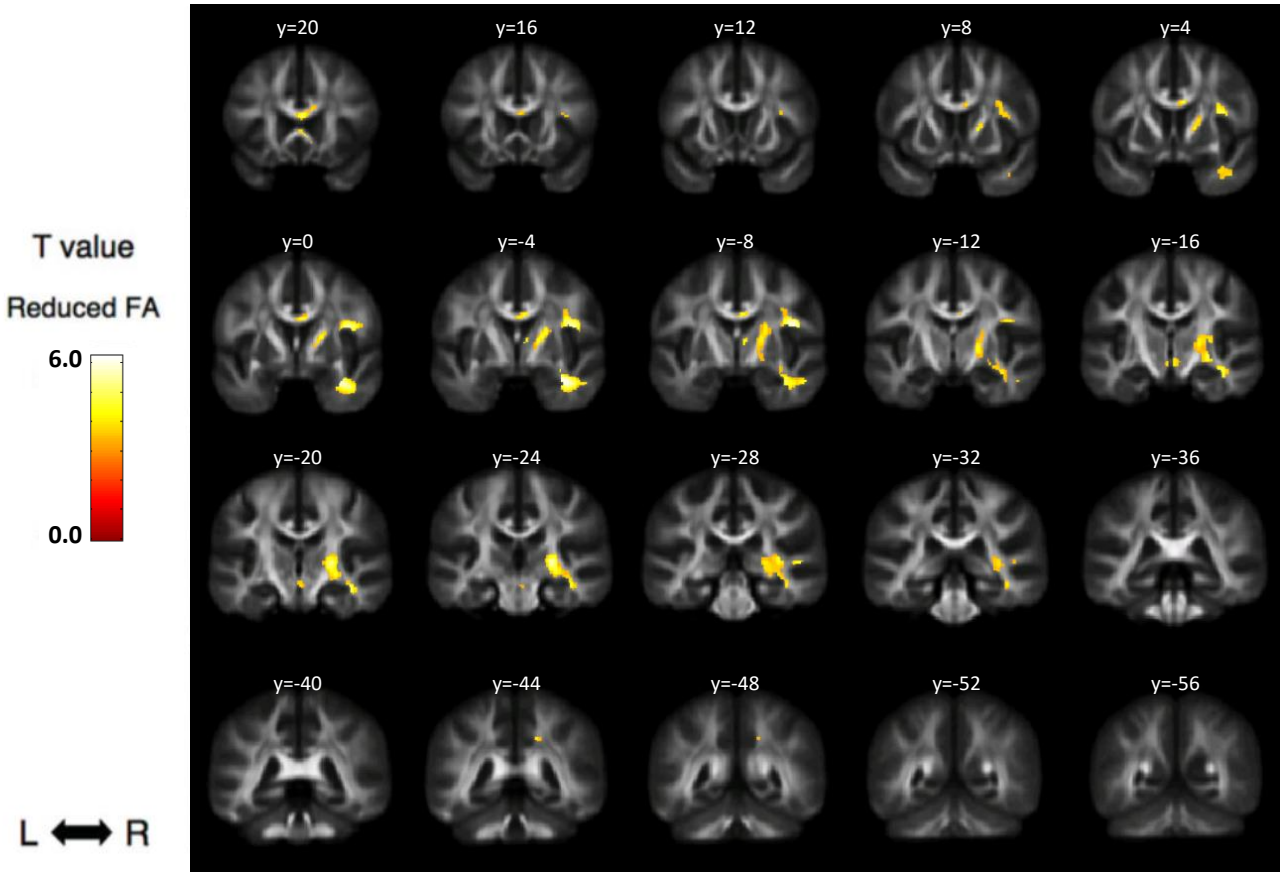
NeuroToxicology 48 (2015) 239–248

Contents lists available at ScienceDirect

NeuroToxicology

Effects of low-level sarin and cyclosarin exposure on white matter integrity in Gulf War Veterans

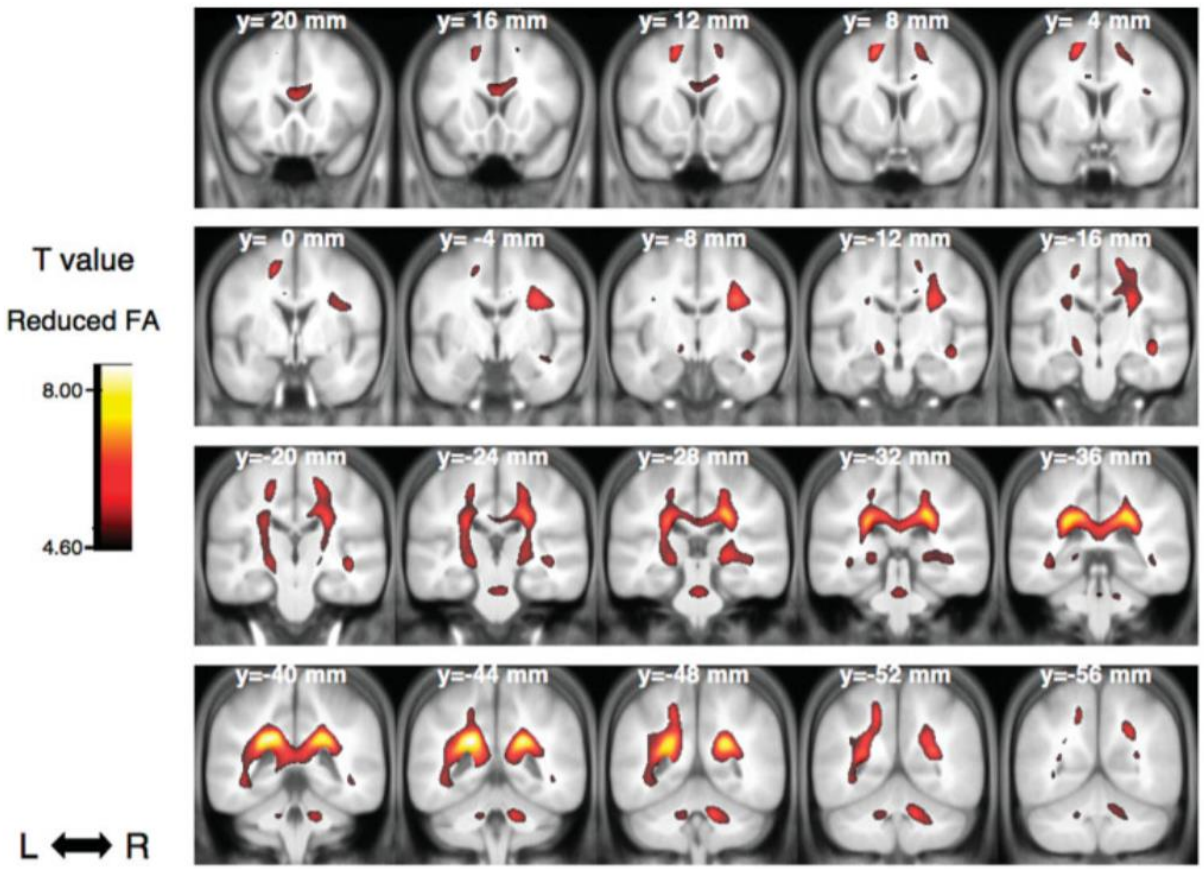
Linda L. Chao [a,b,c,*], Yu Zhang [a,b], Shannon Buckley [a]



In 1995, a Japanese cult released sarin gas in the Tokyo subway.

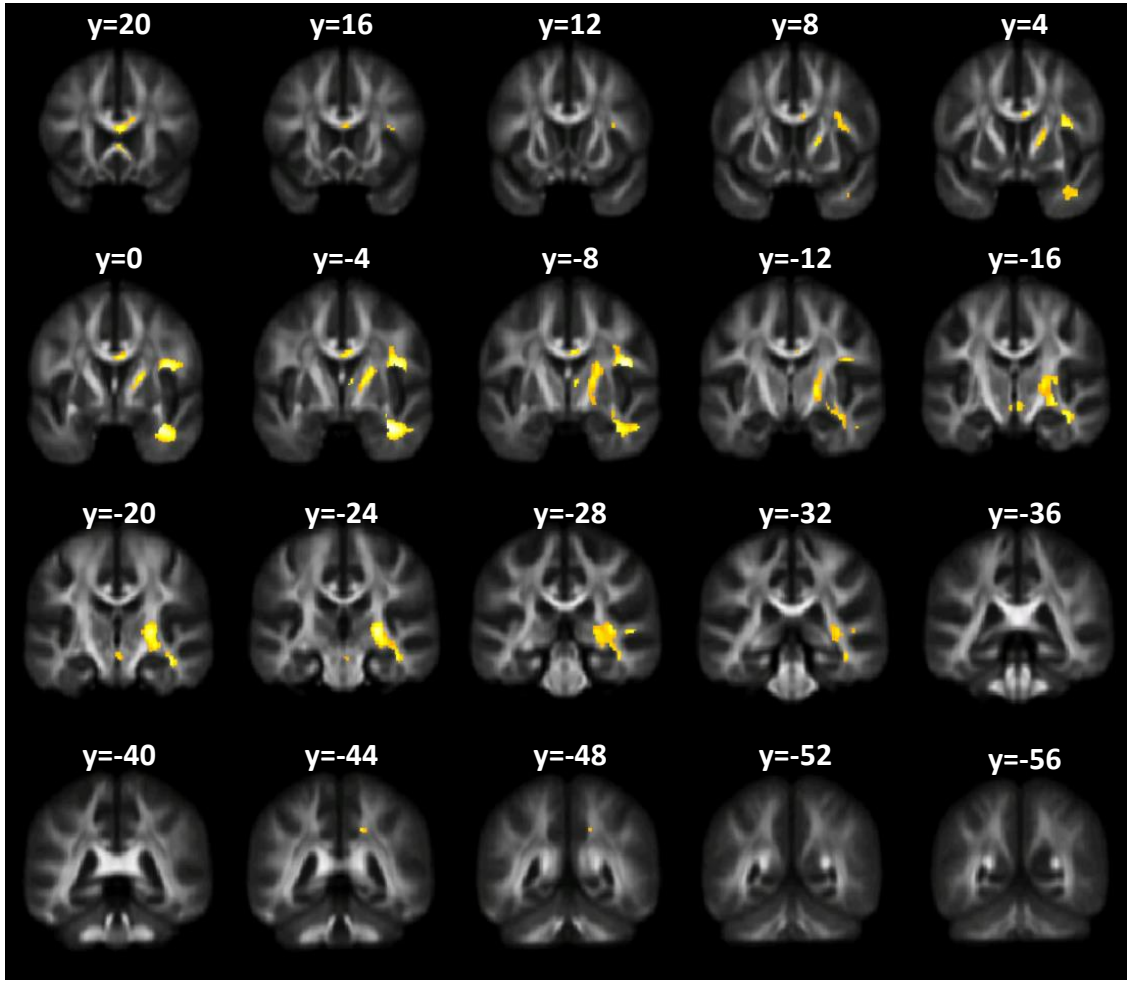
Human Brain Structural Change Related to Acute Single Exposure to Sarin

Hidenori Yamasue, MD, PhD,[1] Osamu Abe, MD, PhD,[2] Kiyoto Kasai, MD, PhD,[1] Motomu Suga, MD,[1]
Akira Iwanami, MD, PhD,[3] Haruyasu Yamada, MD, PhD,[2] Mamoru Tochigi, MD,[1]
Toshiyuki Ohtani, MD, PhD,[1] Mark A. Rogers, PhD,[1,4] Tsukasa Sasaki, MD, PhD,[1] Shigeki Aoki, MD, PhD,[2]
Tadafumi Kato, MD, PhD,[5] and Nobumasa Kato, MD, PhD[1]

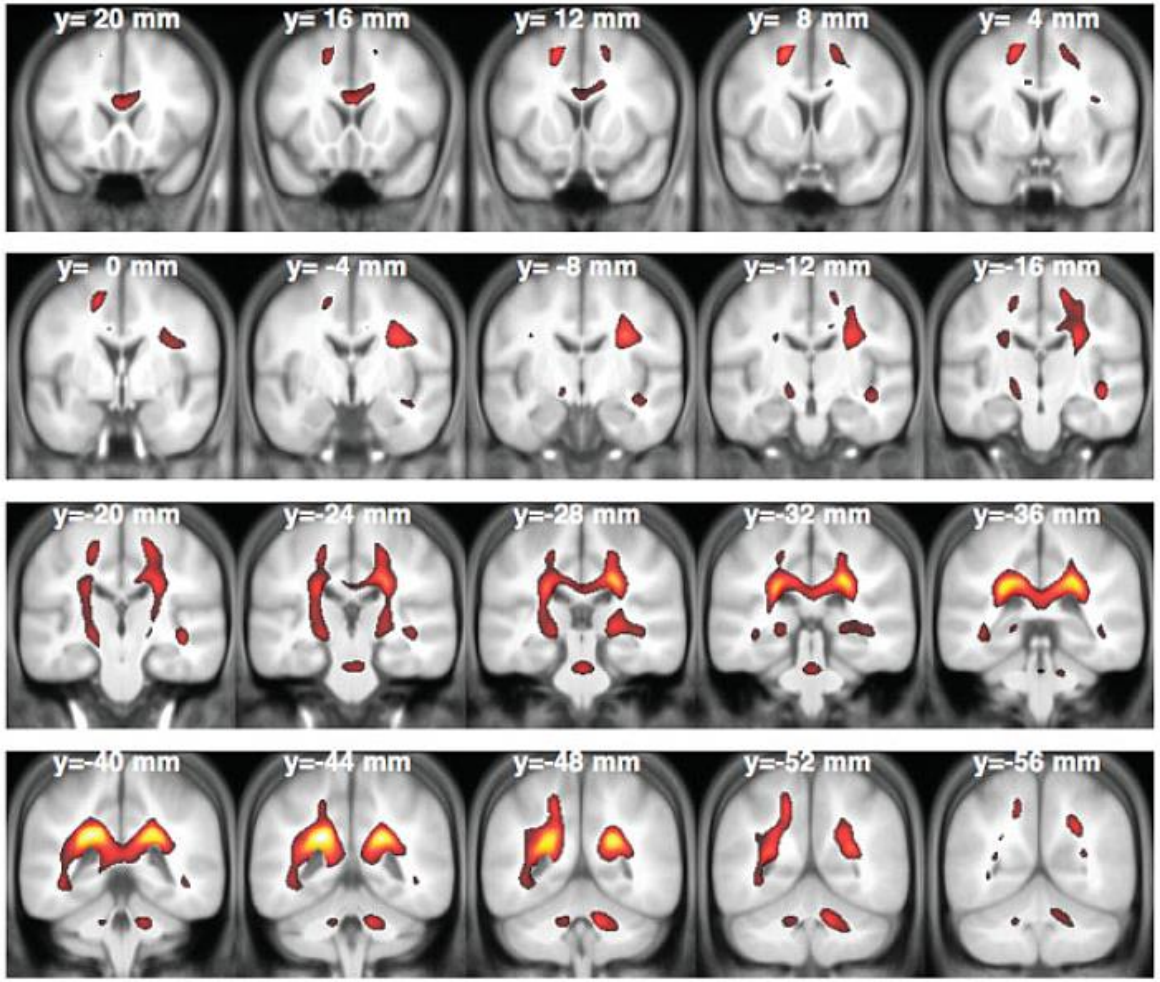


Regions of reduced FA in

GW veterans

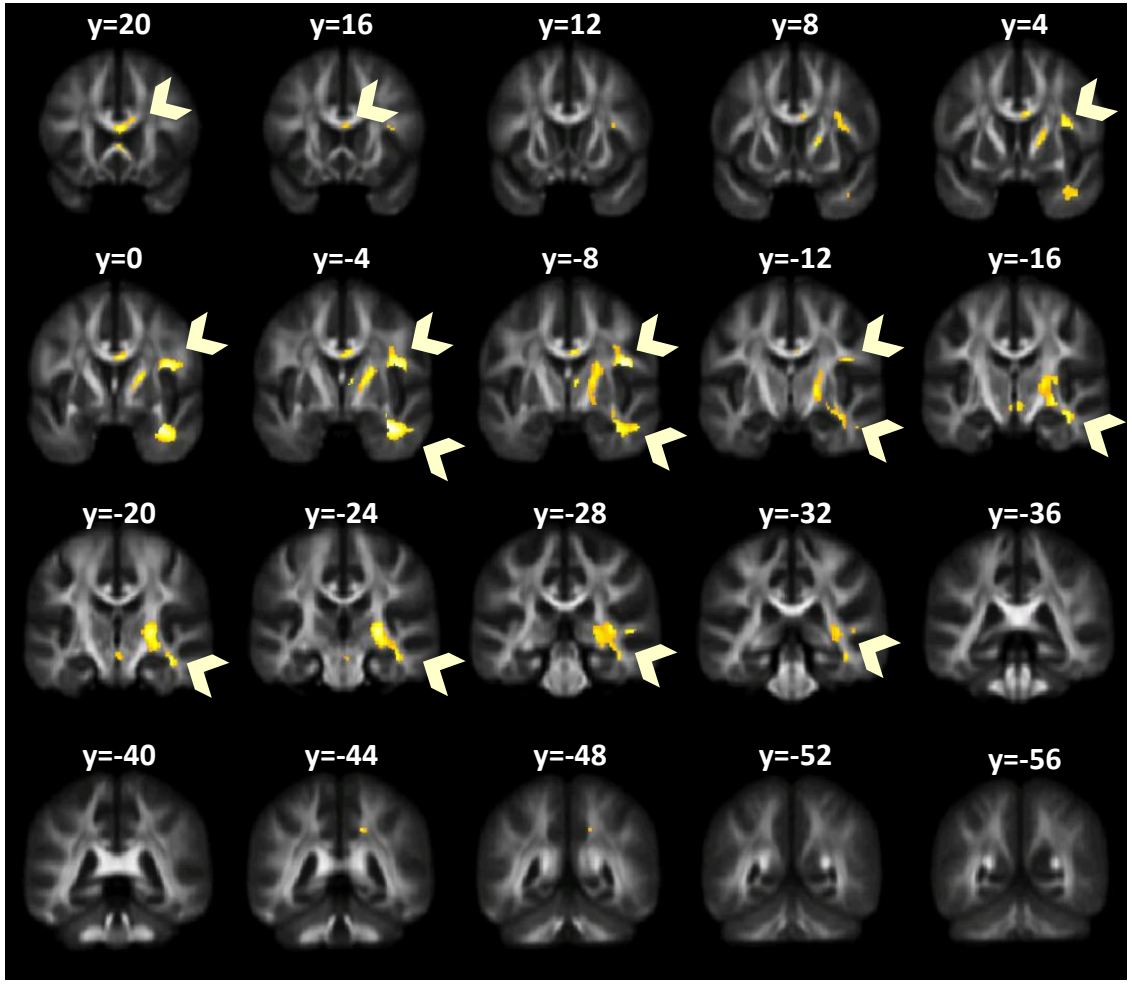


Tokyo sarin victims

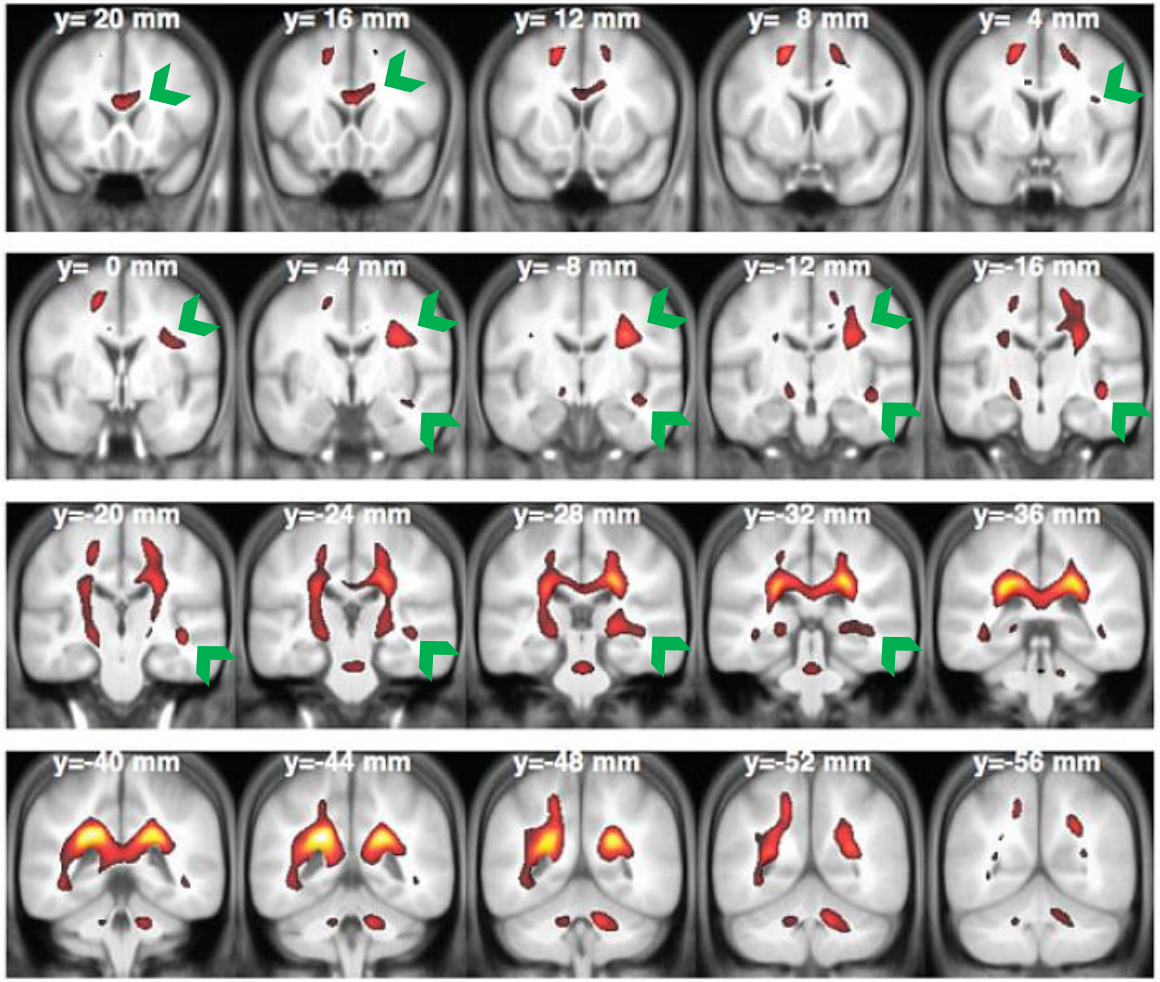


Regions of reduced FA in

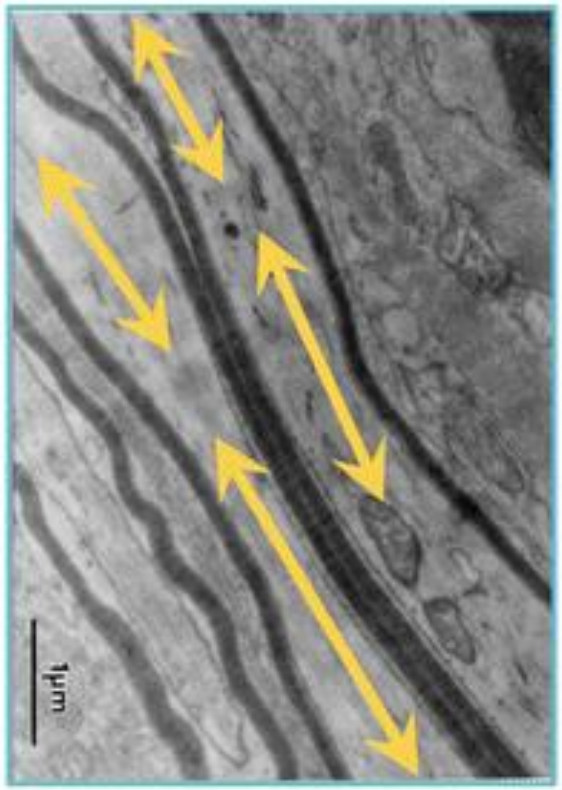
GW veterans

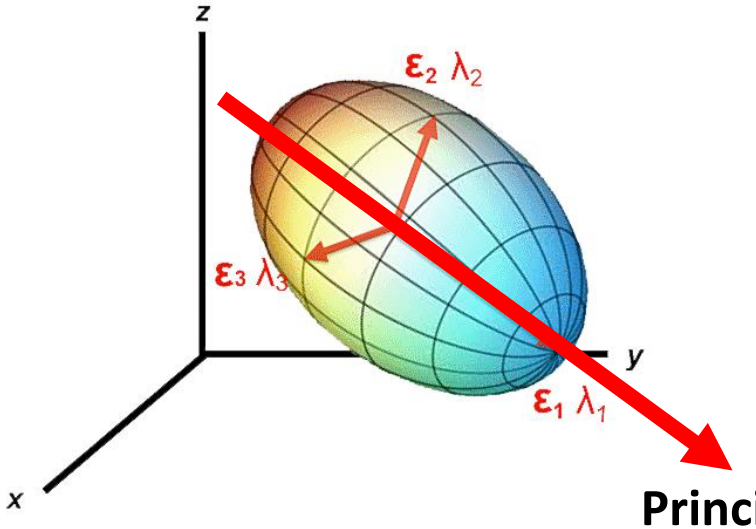


Tokyo sarin victims

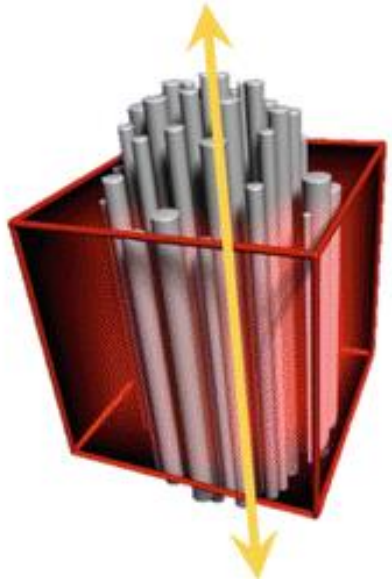


DIFFUSION TENSOR IMAGING

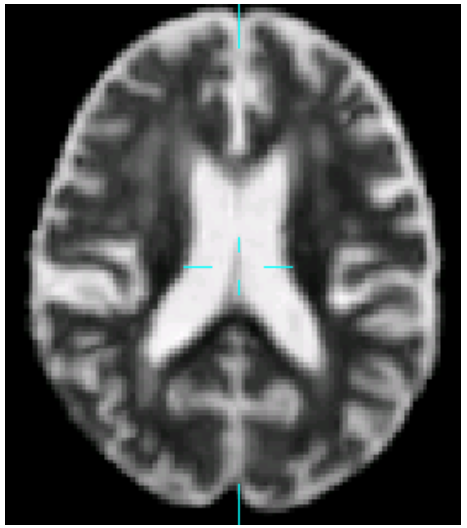




Principle direction of diffusion



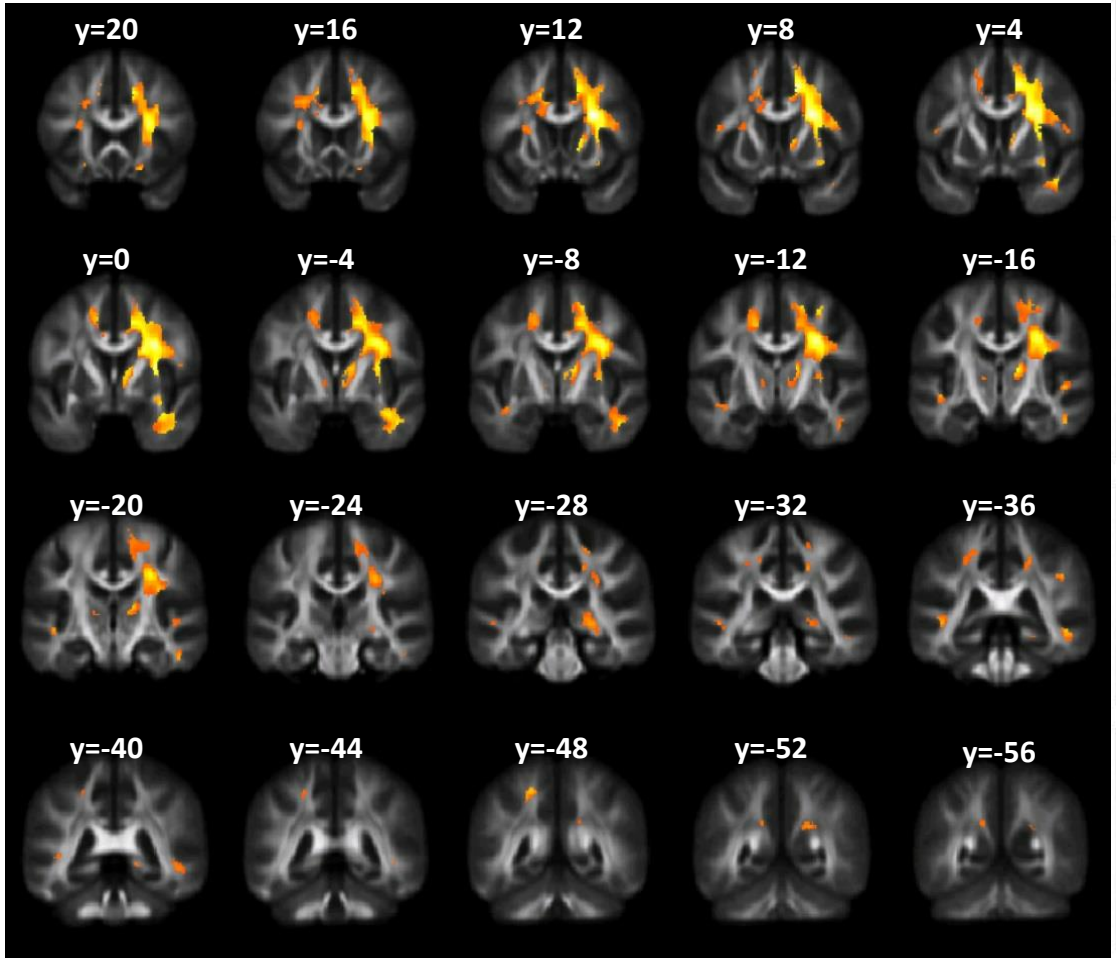
Axial Diffusivity (AD) = λ_1



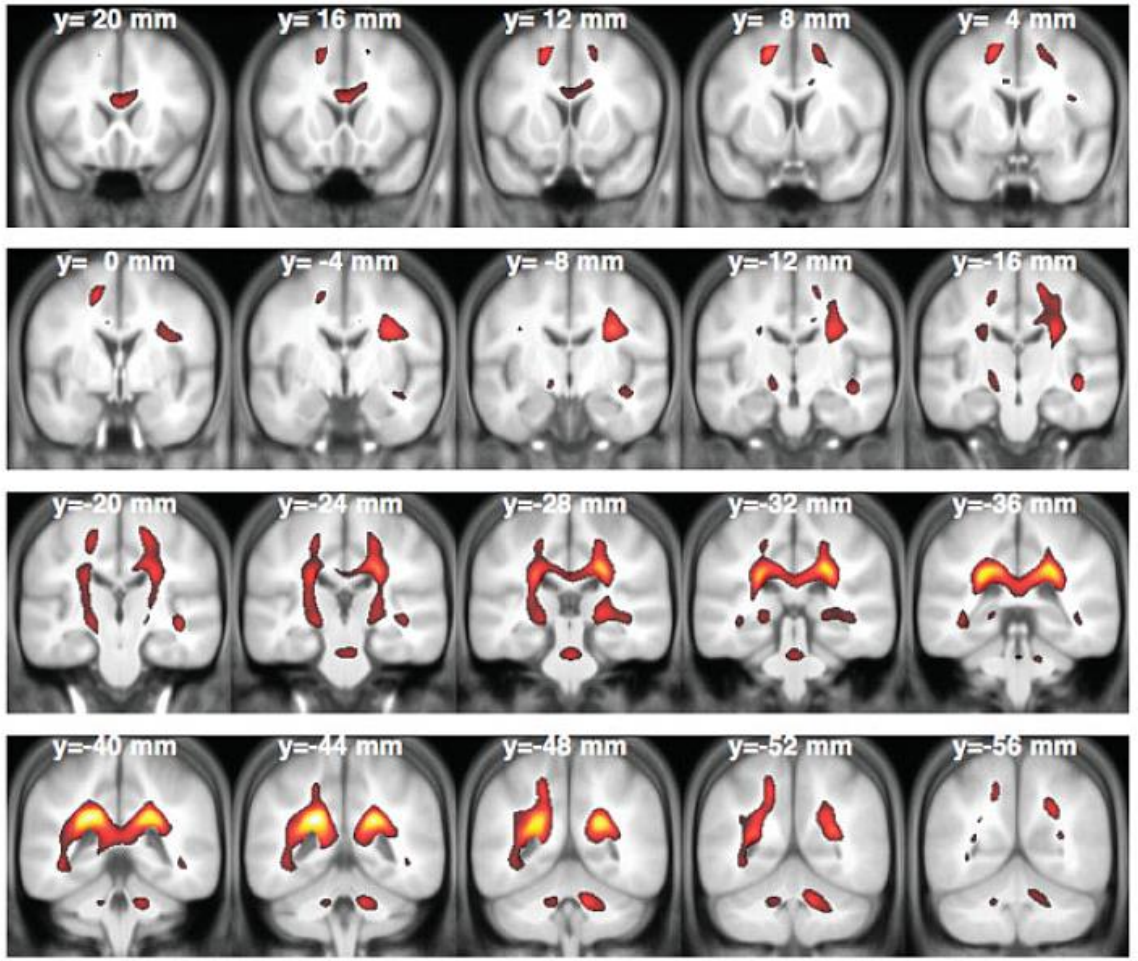
↑ AD is associated with axonal or myelin degeneration.

Regions of increased AD in

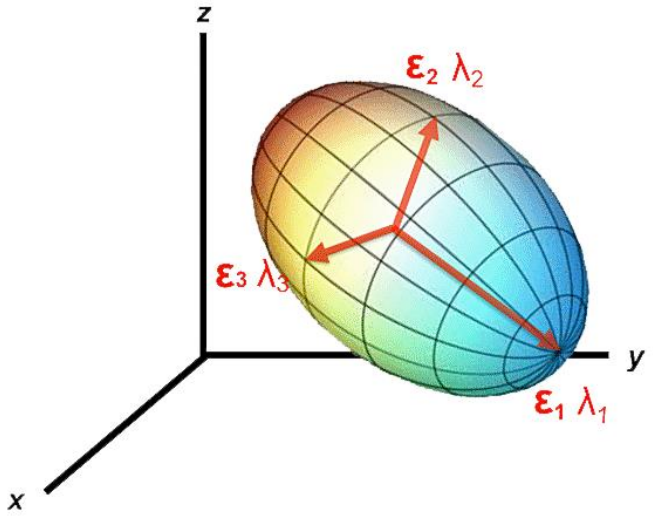
GW veterans



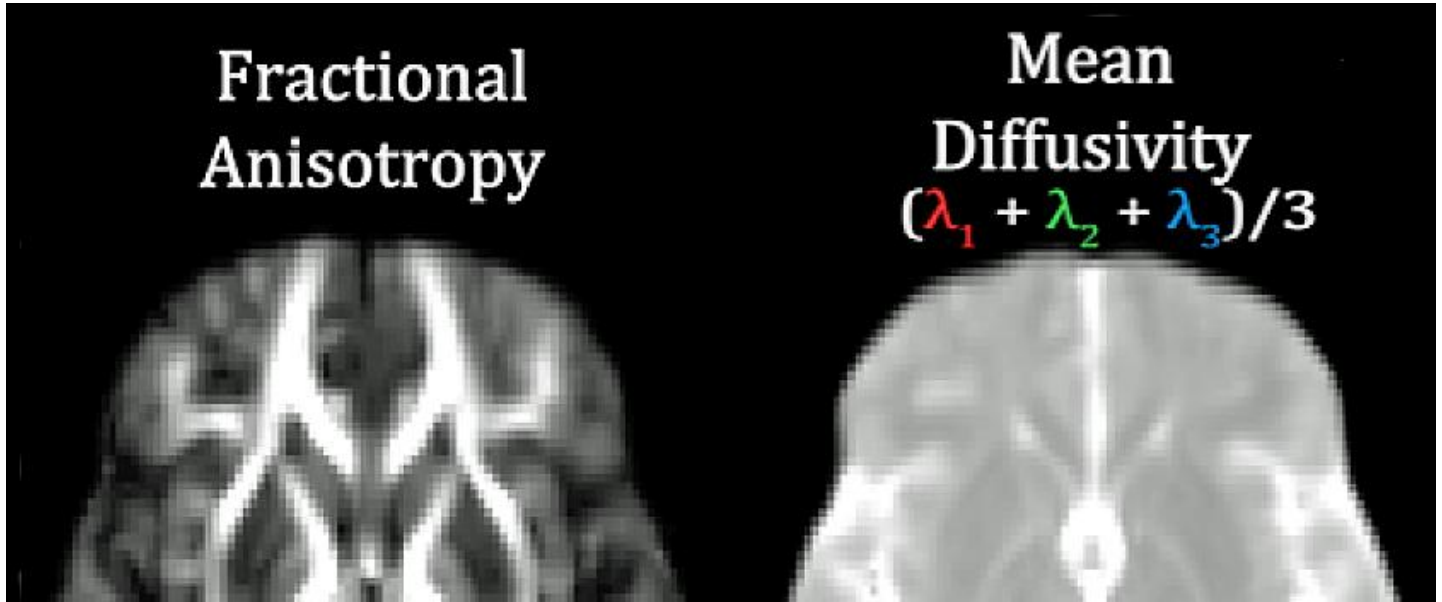
Tokyo sarin victims



DIFFUSION TENSOR IMAGING



- measures the magnitude of water movement
- ↑ MD reflects ↑ water movement, possibly due to loss of neurons.



Demographics of 3T DTI sample

	Exposed	Unexposed
N	81	89
No. Female (%)	13 (16%)	18 (20%)
Age, years	54.2 ± 8.3	53.5 ± 6.7
Education, years	15.3 ± 2.5	15.0 ± 2.5
No. current PTSD diagnosis (%)	9 (11%)	17 (19%)
No. current MDD diagnosis (%)	9 (11%)	10 (11%)
No. Kansas GWI cases (%)	35 (43%)	40 (45%)
No. CDC CMI cases (%)	65 (80%)	66 (74%)

PTSD: Posttraumatic Stress Disorder
MDD: Major Depressive Disorder
Kansas GWI, as defined by Steele, 2000
CDC CMI, as defined by Fukuda et al., 1998

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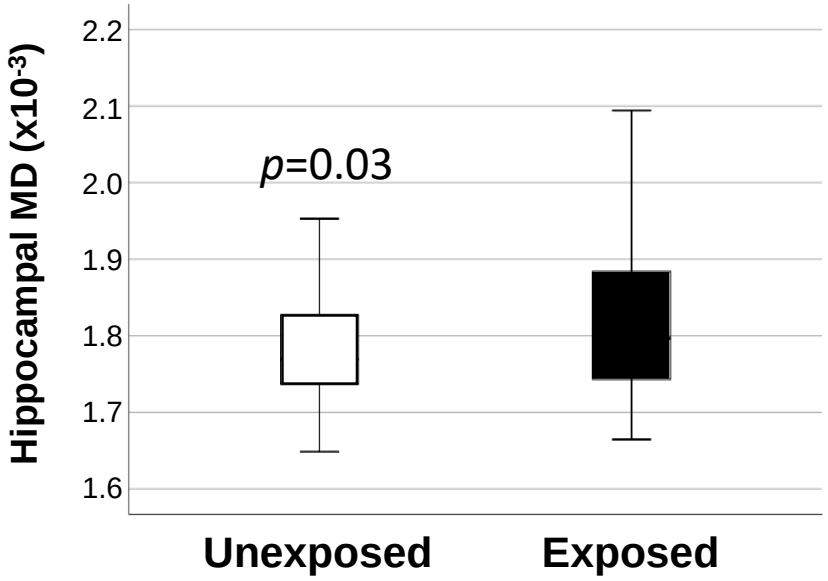
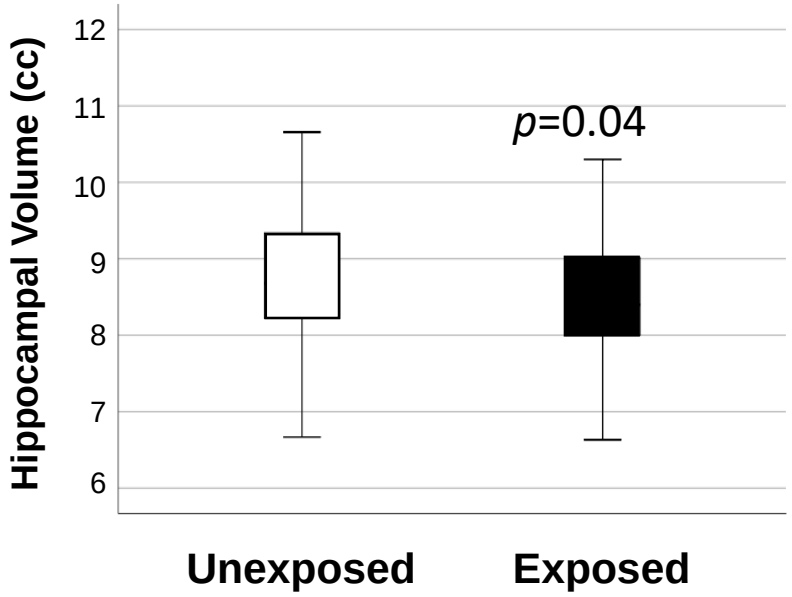
Effects of low-level sarin and cyclosarin exposure on hippocampal microstructure in Gulf War Veterans

Linda L. Chao[a,b,c,*], Yu Zhang[a]





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Effects of low-level sarin and cyclosarin exposure on hippocampal microstructure in Gulf War Veterans

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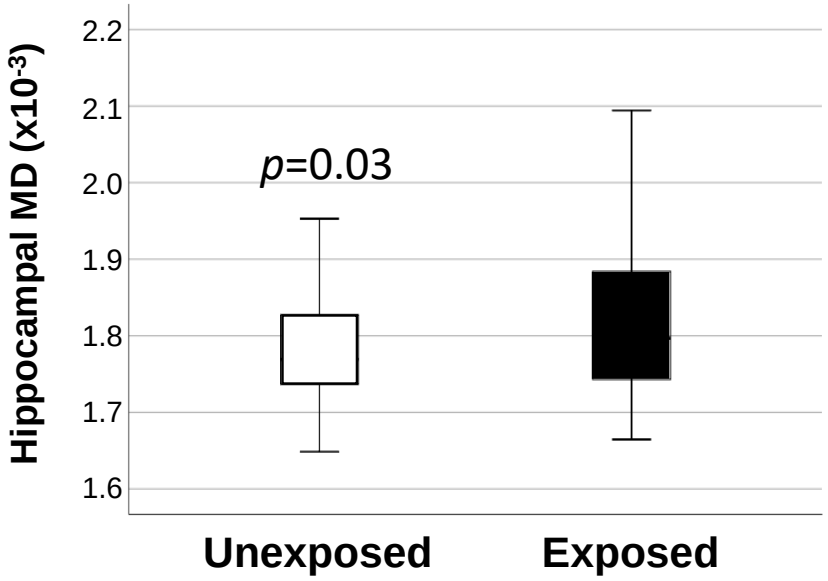
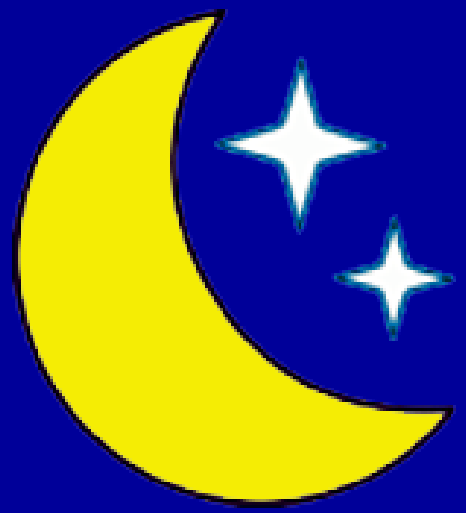


- Mean Diffusivity (MD) measures magnitude of H_2O movement
- ↑ MD reflects reflecting diminished tissue integrity

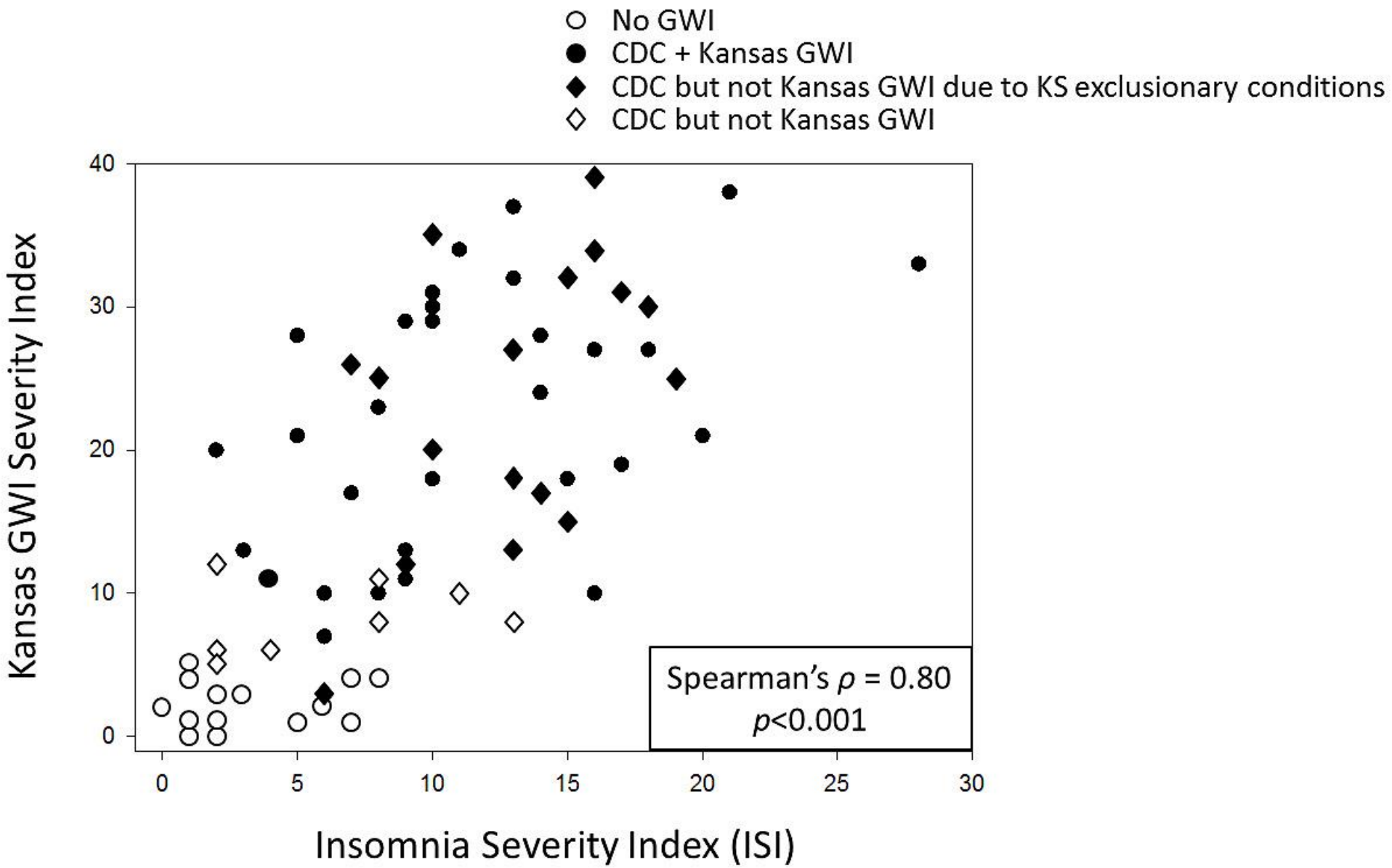
Effects of low-level sarin exposure in GW Veterans:

- Reduced gray matter volume throughout the brain.
- Compromised the macro (volume) and micro (↑ MD) structure of the hippocampus.
- Reduced white matter volume throughout the brain
- Compromised white matter (↓ FA) and axonal (↑ DA) integrity.

Part II. Effects of Cognitive Behavioral Therapy for Insomnia (CBTi) in Gulf War Veterans with GWI and Insomnia



Relationship between GWI symptoms and sleep



Gulf War Illness Severity Index

Symptoms	None (0)	Mild (1)	Moderate (2)	Severe (3)
• Fatigue				
• Feeling unwell after physical exertion				
• Problems falling/staying asleep				
• Unrefreshing sleep				
• Joint pain				
• Muscle pain				
• Bodily pain/hurt all over				
• Headaches				
• Feeling dizzy, faint, or light headed				
• Sensitivity to light				
•				
•				
•				

Hierarchical Regression analysis: ISI significantly predicted Kansas GWI cases

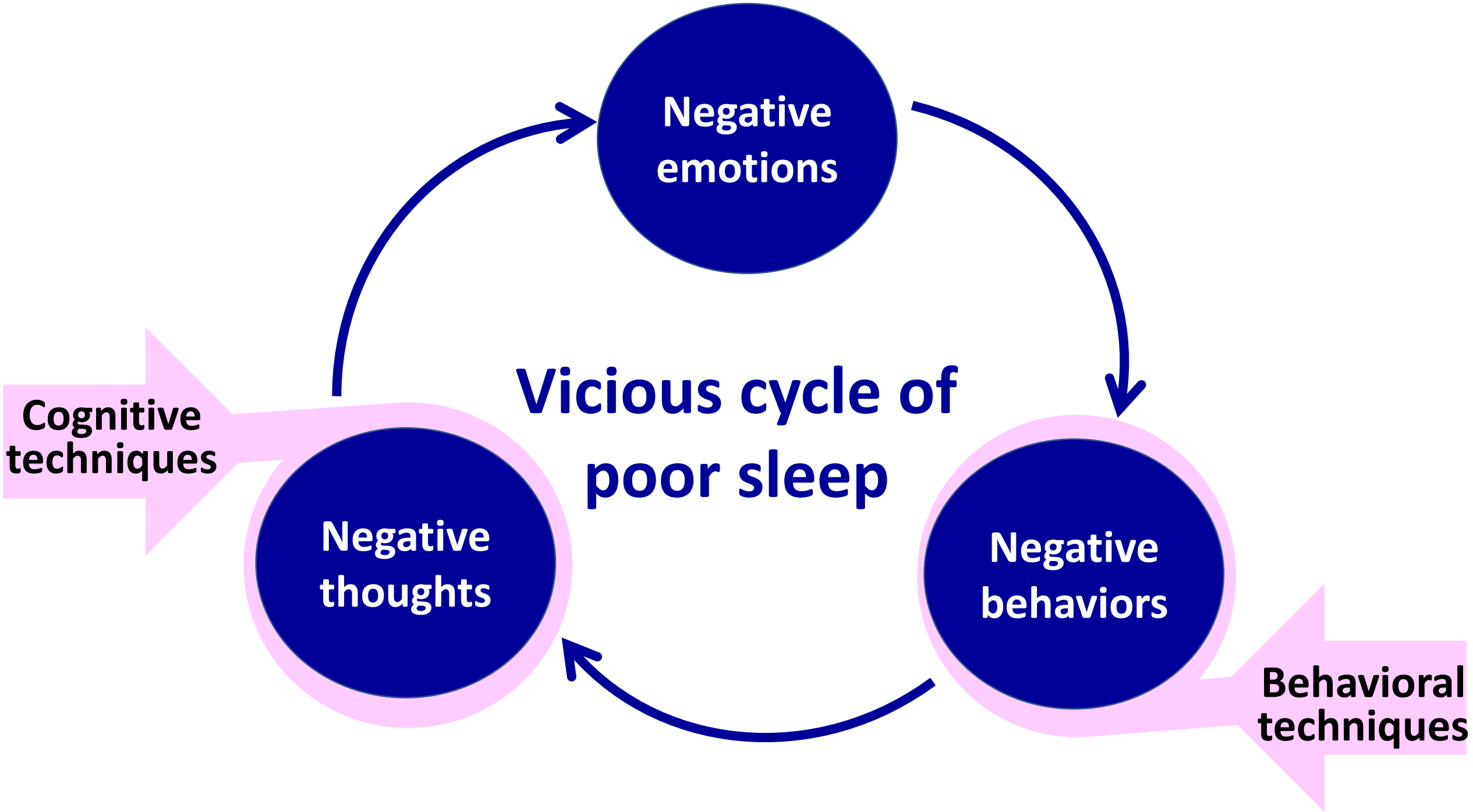
				Standardized Coefficient β for each step		
Independent variables	**ΔR^2**	**adjusted ΔR^2**	**ΔF**	**Step 1**	**Step 2**	**Step 3**
Step 1	0.069	0.040	2.33			
age				-0.11	-0.04	-0.02
male sex				0.08	0.13	0.11
years of education				-0.20	-0.14	-0.12
Step 2	0.136	0.153	5.20[a]			
current PTSD					0.29[a]	0.18
current MDD					0.20	0.13
predicted sarin exposure					-0.04	-0.06
Step 3	0.057	0.206	7.00[b]			
Insomnia Severity Index (ISI)						**0.28[b]**

[a] $p \leq 0.002$
[b] $p = 0.01$

Hierarchical Regression analysis: ISI significantly predicted CDC CMI cases

				Standardized Coefficient β for each step		
Independent variables	**ΔR^2**	**adjusted ΔR^2**	**ΔF**	**Step 1**	**Step 2**	**Step 3**
Step 1	0.074	0.044	2.49			
age				-0.20	-0.16	-0.13
male sex				0.06	0.08	0.04
years of education				-0.13	-0.10	-0.06
Step 2	0.030	0.044	1.75			
current PTSD					0.11	-0.09
current MDD					0.12	0.01
predicted sarin exposure					-0.03	-0.07
Step 3	0.191	0.239	5.35[a]			
Insomnia Severity Index (ISI)						**0.51[a]**

[a] $p<0.001$


Negative emotions
Vicious cycle of poor sleep
Cognitive techniques
Negative thoughts
Negative behaviors
Behavioral techniques

Pilot study of telephone-delivered CBT-I for veterans with GWI and Insomnia

N	64
No. Female (%)	16 (25%)
Age, years	53.0 ± 8.9
Education, years	15.4 ± 4.2
No. current PTSD diagnosis (%)	12 (19%)
No. current MDD diagnosis (%)	6 (10%)
Baseline ISI	20.0 ± 4.6
Baseline GWI severity Index	67.5 ± 15.5

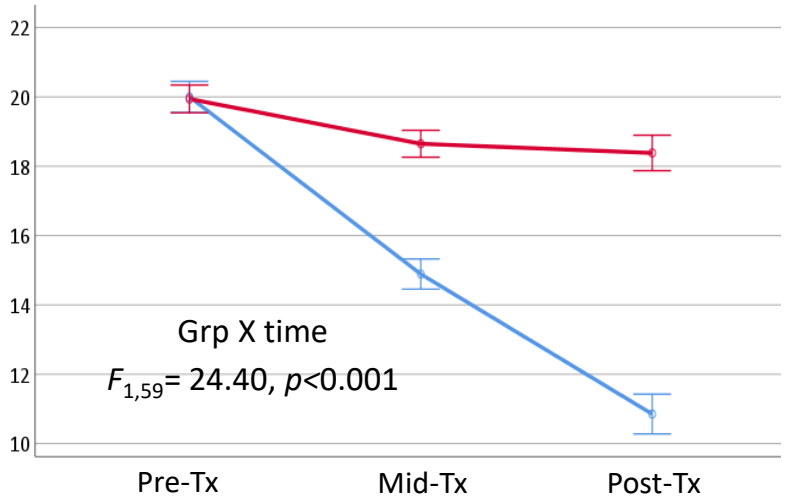
PTSD: Posttraumatic Stress Disorder
MDD: Major Depressive Disorder
Kansas GWI, as defined by Steele, 2000
CDC CMI, as defined by Fukuda et al., 1998

No group differences at baseline

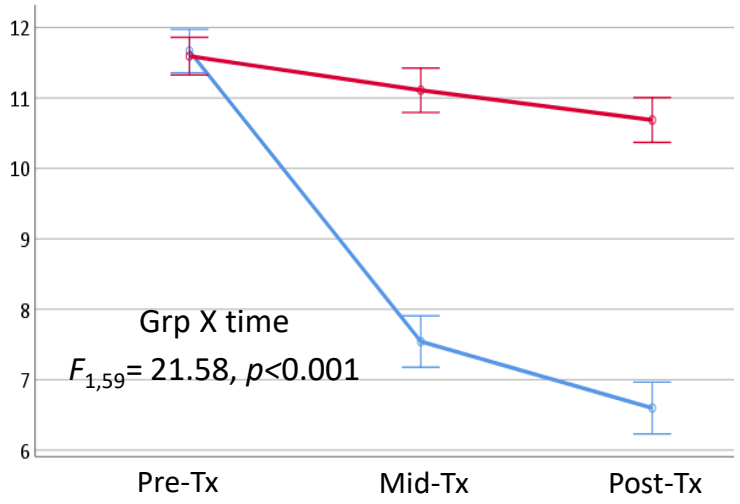
	Wait List	**CBT-I**
N	35	29
No. Female (%)	7 (20%)	8 (28%)
Age, years	54.5 ± 6.1	51.8 ± 11.4
Education, years	15.7 ± 4.8	14.9 ± 3.5
No. Caucasian (%)	27 (77%)	18 (62%)

Insomnia severity, subjective sleep quality GWI symptoms improved after CBT-I

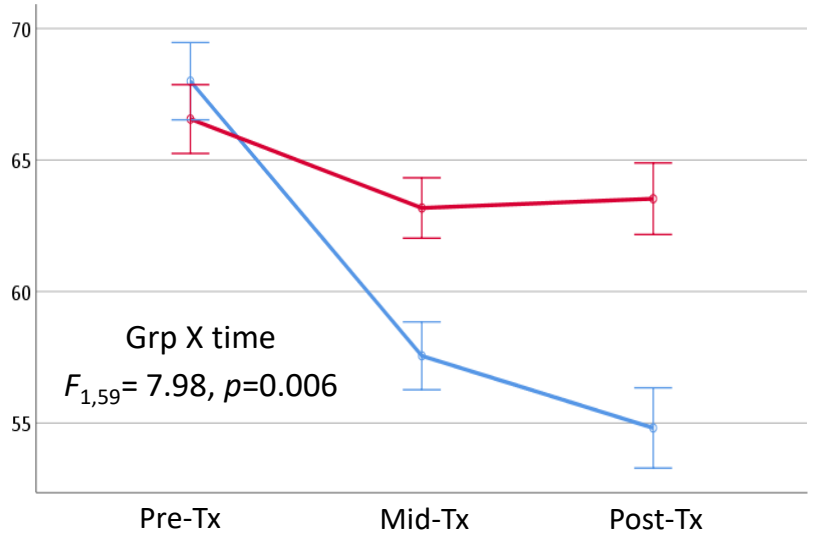
Insomnia Severity Index (ISI)



Subjective Sleep Quality (PSQI)



GWI Severity Index

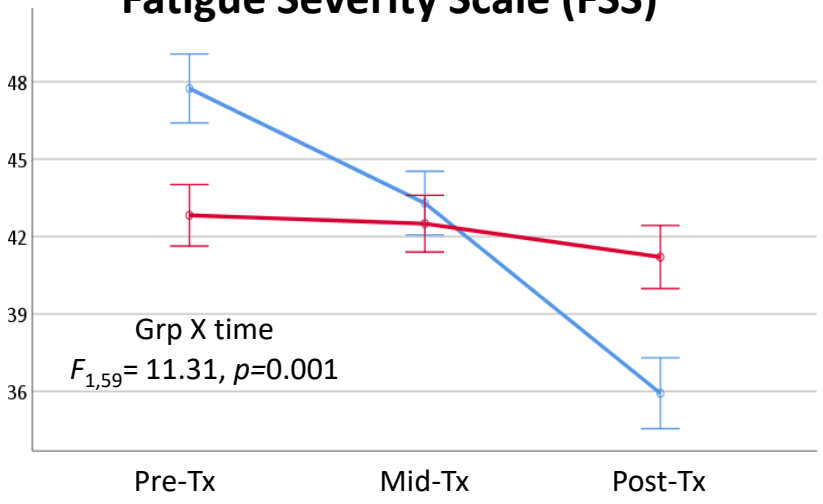


Wait List
CBT-I

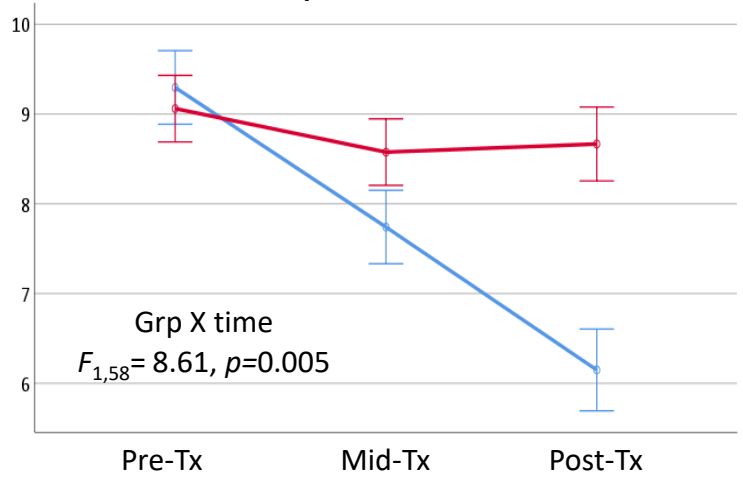
Fatigue, depression and anxiety decreased after CBT-I

Hospital Anxiety and Depression Scale (HADS)

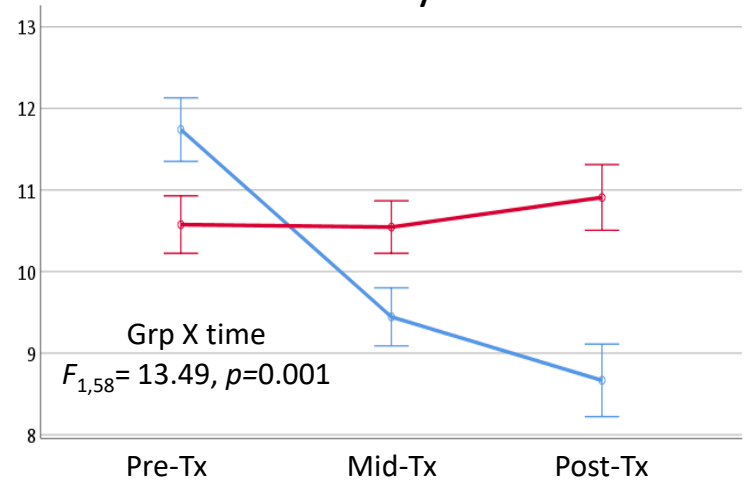
Fatigue Severity Scale (FSS)



Depression



Anxiety



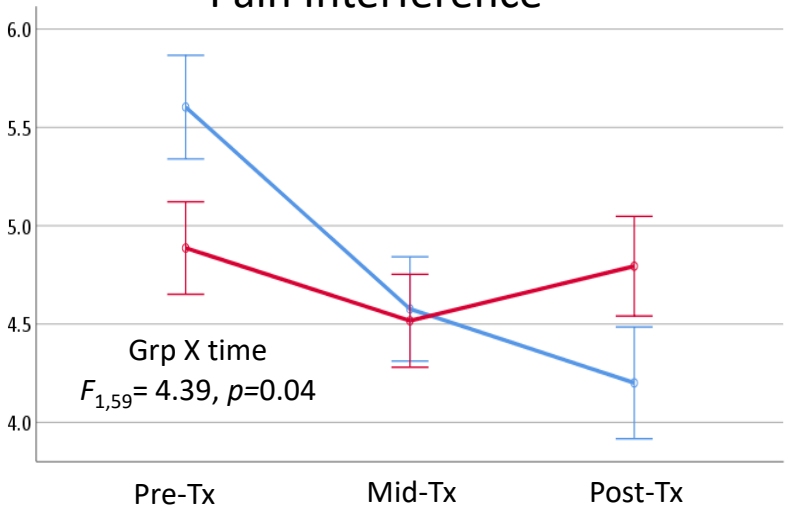
Wait List

CBT-I

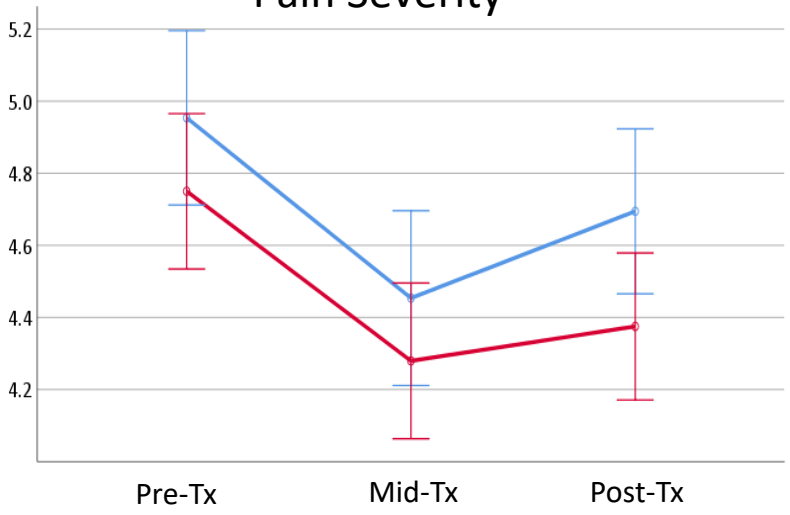
- Pain interfered less with daily activities after CBT-I.
- There were trends of self-reported improved cognitive function after CBT-I.

Brief Pain Inventory (BPI)

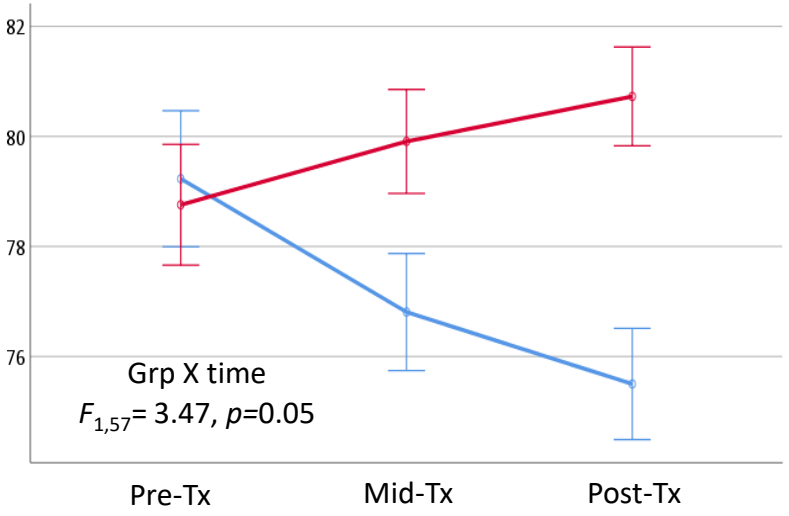
Pain Interference



Pain Severity



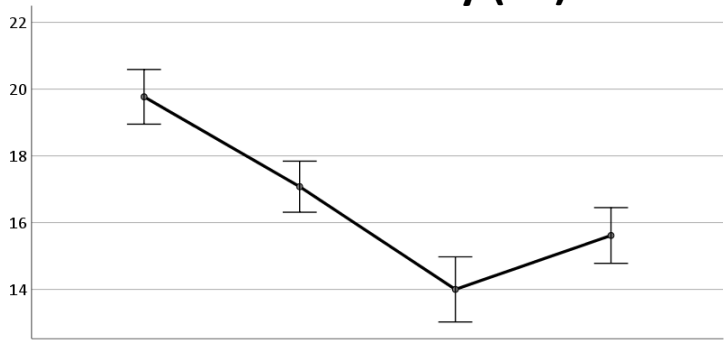
Multiple Ability Self-Report Questionnaire (MASQ - cognition)



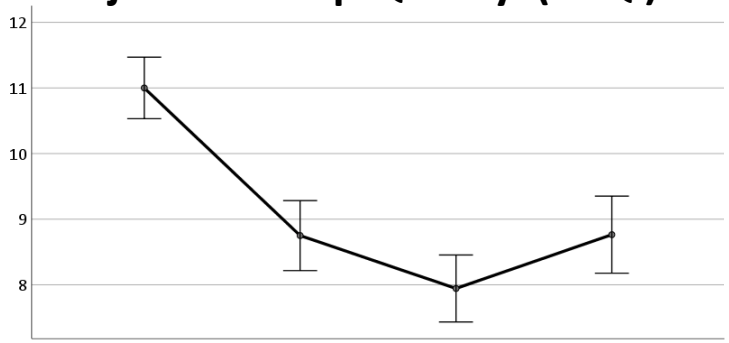
Wait List

CBT-I

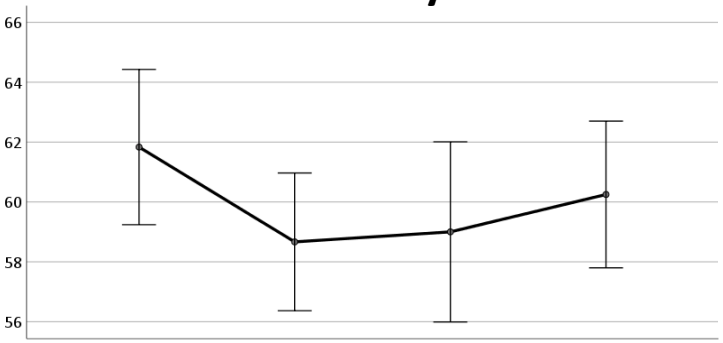
Insomnia Severity (ISI)



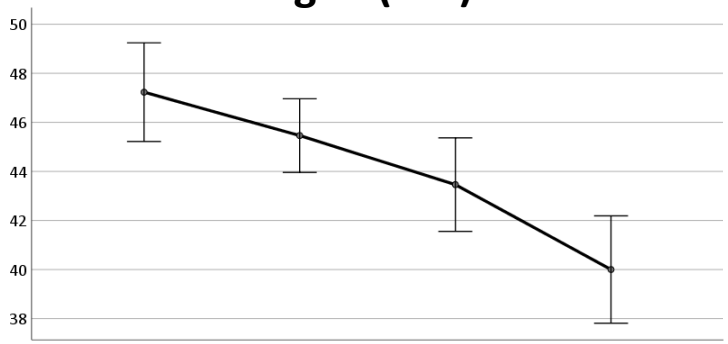
Subjective Sleep Quality (PSQI)



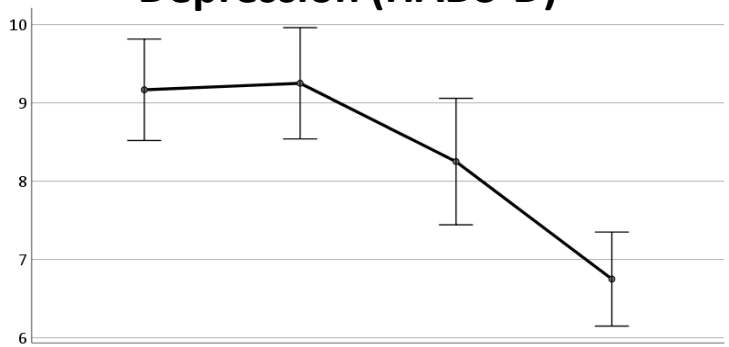
GWI Severity



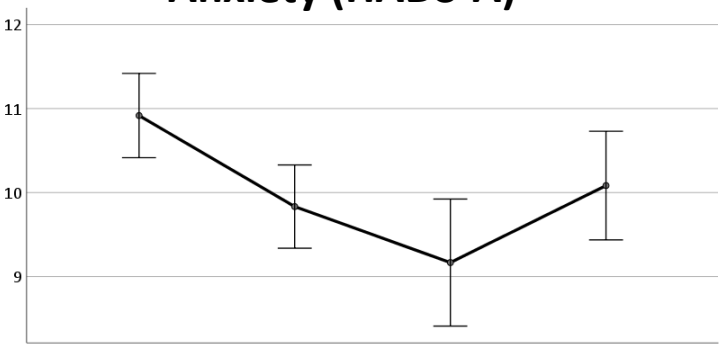
Fatigue (FSS)



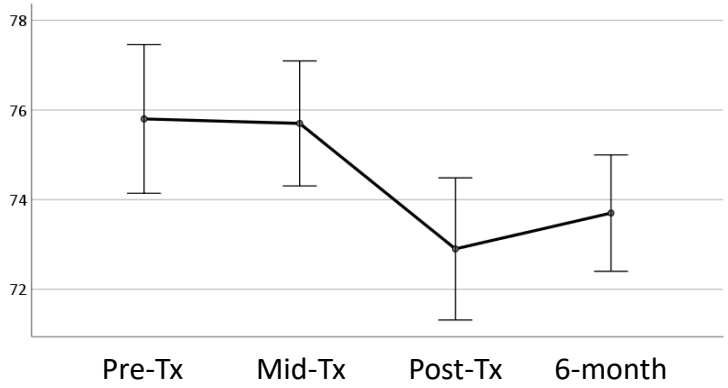
Depression (HADS-D)



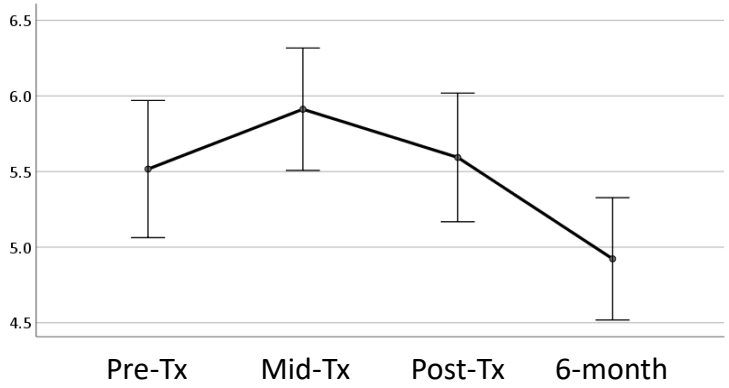
Anxiety (HADS-A)



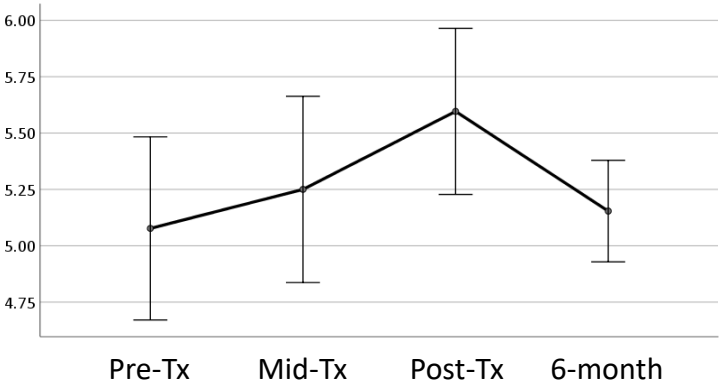
Cognitive Abilities (MASQ)



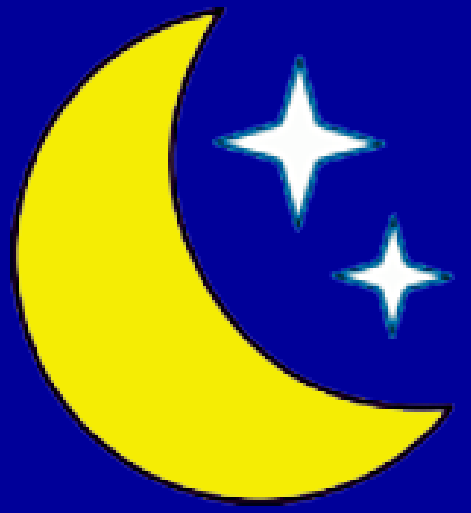
Pain Interference (BPI)



Pain Severity (BPI)



Effects of CBT-I in Gulf War Veterans:



- CBT-I is effective in helping GW Veterans with insomnia achieve better sleep.
- The Veterans' non-sleep GWI symptoms improved along with improved sleep.
- Veterans appeared to be able to maintain the gains they achieved after completing CBT-I.
- CBT-I may be a viable treatment for Veterans with GWI and insomnia.

Thank you!

- GW Veteran participants
- Michael Weiner
- Lea Steele
- Kimberly Sullivan
- Thomas Neylan
- Shira Maguen
- Jennifer Hlavin
- Jennifer Kanady
- Nicole Crocker
- Laura Straus
- Department of Veterans Affairs
- DMDC data request staff
- Force Readiness and Health Assurance Force Health Protection & Readiness Defense Health Agency Office of the Assistant Secretary of Defense (Health Affairs) Defense Health Headquarters