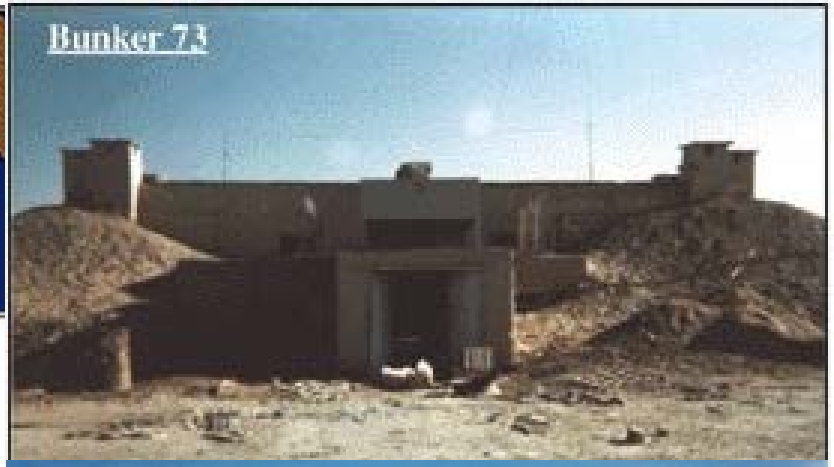
Neuroimaging studies of the effects of low-level sarin exposure on GW Veterans

Linda L. Chao, PhD

Center for Imaging of Neurodegenerative Diseases
San Francisco VAMC

Departments of Radiology, Biomedical Imaging, and Psychiatry
University of California, San Francisco

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



American Journal of Epidemiology

Vol. 158, No. 5
Printed in U.S.A.
DOI: 10.1093/aje/kwg178

Gulf War Veterans and Iraqi Nerve Agents at Khamisiyah: Postwar Hospitalization Data Revisited

Tyler C. Smith[1], Gregory C. Gray[2], J. Christopher Weir[3], Jack M. Heller[3], and Margaret A. K. Ryan[1]

[1] Department of Defense Center for Deployment Health Research, Naval Health Research Center, San Diego, CA.
[2] Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA.
[3] Deployment Environmental Surveillance Program, US Army Center for Health Promotion and Preventive Medicine, Aberdeen Proving Ground, MD.

Received for publication January 13, 2003; accepted for publication March 20, 2003.

Chemical warfare agents were demolished by US soldiers at Khamisiyah, Iraq, in March 1991. The authors investigated postwar morbidity for Gulf War veterans, contrasting those who may have been exposed to low gaseous levels of nerve agents and those unlikely to have been exposed. Cox regression modeling was performed for hospitalizations from all causes and hospitalizations from diagnoses within 15 categories during the period March 10, 1991, through December 31, 2000, for the duration of active-duty status. After adjustment for all variables in the model, only two of 37 models suggested that personnel possibly exposed to subclinical doses of nerve agents might be at increased risk for hospitalization from circulatory diseases, specifically cardiac dysrhythmias. Of the 724 hospitalizations for cardiac dysrhythmias, 203 were in the potentially exposed group, slightly higher than expected (risk ratio = 1.23, 95% confidence interval: 1.04, 1.44). The increase was small in comparison with potential observational variability, but the findings are provocative and warrant further evaluation. Veterans possibly exposed to nerve agents released by the Khamisiyah demolition were not found to be at increased risk for hospitalizations from any other chronic diseases nearly 10 years after the Gulf War.

exposure, environmental; exposure, occupational; hospitalization; military medicine; morbidity; Persian Gulf syndrome; veterans

American Journal of Public Health | August 2005, Vol 95, No. 8

RESEARCH AND PRACTICE

Mortality in US Army Gulf War Veterans Exposed to 1991 Khamisiyah Chemical Munitions Destruction

Tim A. Bullman, MA, Clare M. Mahan, PhD, Han K. Kang, DrPH, William F. Page, PhD

On March 4 and 10, 1991, combat engineer and explosive ordnance disposal units of the US Army XVIII Corps destroyed 2 large Iraqi weapons caches at Khamisiyah, Iraq. In October 1991, March 1992, May 1992, and May 1998, representatives from the United Nations Special Commission inspected Khamisiyah and detected the existence of sarin and cyclosarin in both intact and damaged rockets in the bunker and pit. Military personnel who were possibly exposed to chemical warfare agents at Khamisiyah were identified by environmental and climatological modeling of the plume dispersion.

Sarin is a toxic nerve agent produced for chemical warfare. Sarin can be inhaled or absorbed via the mucous membranes, skin, or

Objectives. We investigated whether US Army Gulf War veterans who were potentially exposed to nerve agents during the March 1991 weapons demolitions at Khamisiyah, Iraq, are at increased risk of cause-specific mortality.

Methods. The cause-specific mortality of 100 487 exposed US Army Gulf War veterans was compared with that of 224 980 unexposed US Army Gulf War veterans. Exposure was determined with the Department of Defense 2000 plume model. Relative risk estimates were derived from Cox proportional hazards models.

Results. The risks of most disease-related mortality were similar for exposed and unexposed veterans. However, exposed veterans had an increased risk of brain cancer deaths (relative risk [RR] = 1.94; 95% confidence interval [CI] = 1.12, 3.34). The risk of brain cancer death was larger among those exposed 2 or more days than those exposed 1 day when both were compared separately to all unexposed veterans (RR = 3.26; 95% CI = 1.33, 7.96; RR = 1.72; 95% CI = 0.95,3.10, respectively).

Conclusions. Exposure to chemical munitions at Khamisiyah may be associated with an increased risk of brain cancer death. Additional research is required to confirm this finding. (*Am J Public Health.* 2005;95:1382–1388. doi:10.2105/AJPH.2004.045799)

Neurological Mortality Among U.S. Veterans of the Persian Gulf War: 13-Year Follow-Up

Shannon K. Barth, MPH,[1]* Han K. Kang, DrPH,[1] Tim A. Bullman, MS,[1] and Mitchell T. Wallin, MD, MPH[2]

Background *This study focuses on long-term mortality, specifically brain cancer, amyotrophic lateral sclerosis (ALS), Parkinson's disease, and multiple sclerosis (MS) of 621,902 veterans who served in the 1990–1991 Persian Gulf War (GW), and 746,248 non-GW veterans.*

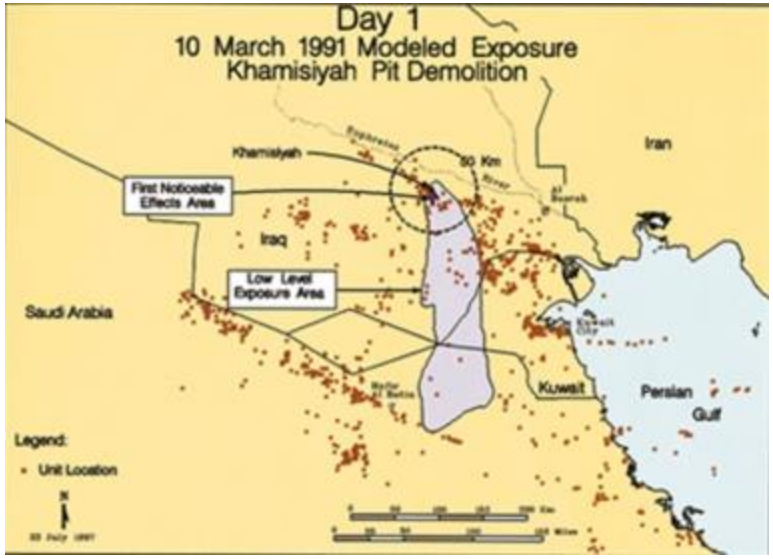
Methods *Follow-up began with the date the veteran left the GW theater or May 1, 1991 and ended with the date of death or December 31, 2004. Cox proportional hazard models were used for analyses.*

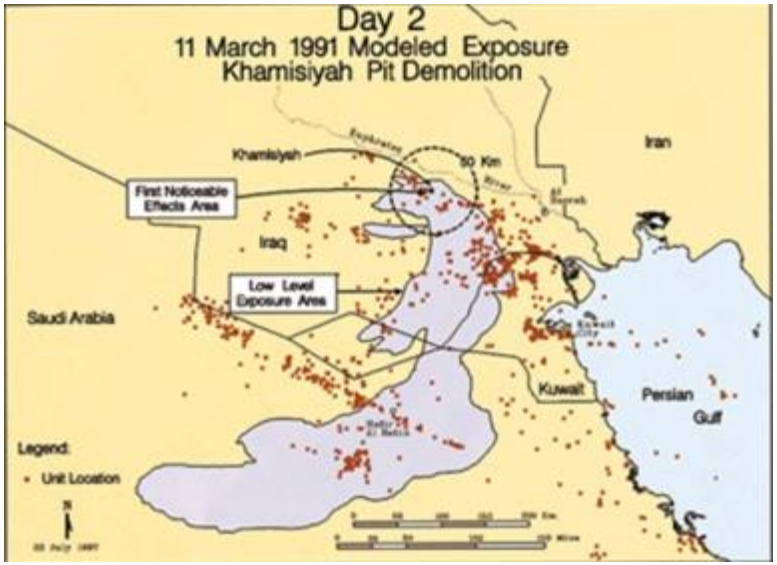
Results *Adjusted mortality rate ratios (aRR) of GW veterans compared to non-GW veterans were not statistically significant for brain cancer (aRR = 0.90, 95% confidence interval (CI): 0.73, 1.11), MS (aRR = 0.61, 95% CI: 0.23, 1.63), Parkinson's disease (aRR = 0.71, 95% CI: 0.17, 2.99), or ALS (aRR = 0.96, 95% CI: 0.56, 1.62). GW veterans potentially exposed to nerve agents for 2 or more days and GW veterans exposed to oil well fire smoke were at increased risk for brain cancer mortality (aRR = 2.71, 95% CI: 1.25, 5.87; aRR = 1.81, 95% CI: 1.00, 3.27; respectively).*

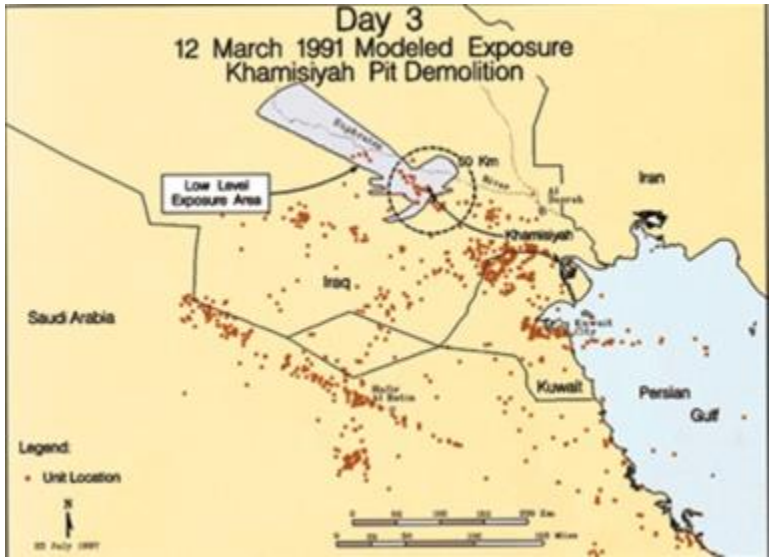
Conclusions *The risk of death due to ALS, MS, Parkinson's disease, and brain cancer was not associated with 1991 GW service in general. However, GW veterans potentially exposed to nerve agents at Khamisiyah, Iraq, and to oil well fire smoke had an increased risk of mortality due to brain cancer.* Am. J. Ind. Med. 52:663–670, 2009. © *2009 Wiley-Liss, Inc.*

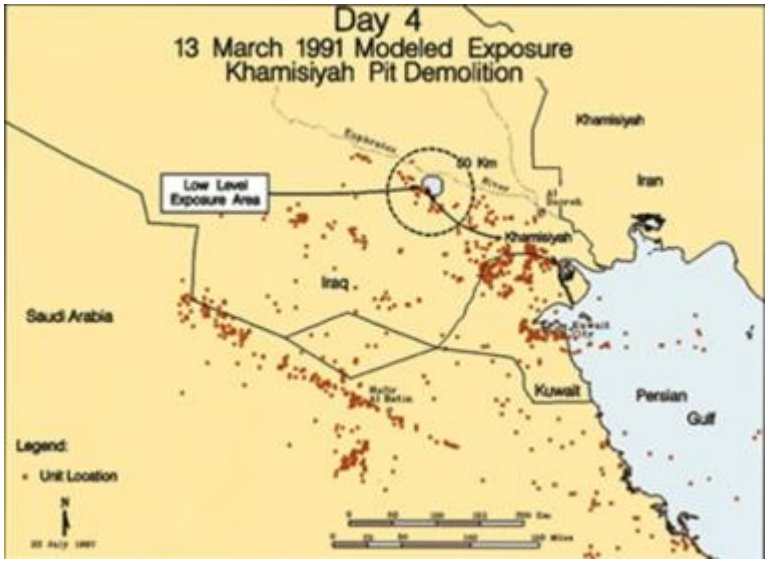
KEY WORDS: Gulf War; mortality; sarin; sex; United States Department of Veterans Affairs; veterans; amyotrophic lateral sclerosis; Parkinson's disease; brain cancer; multiple sclerosis

Modeling of the potential hazard area at Khamisiyah.









ELSEVIER

Available online at www.sciencedirect.com

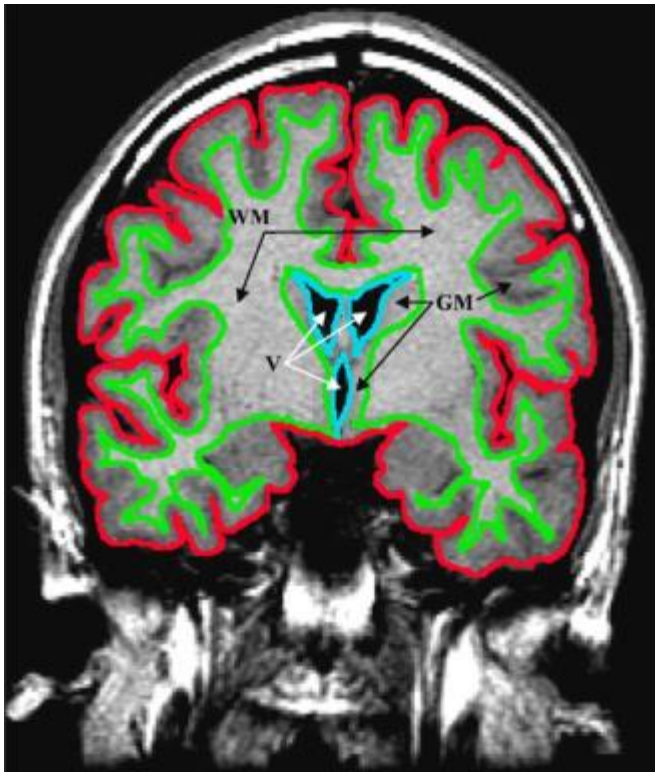
ScienceDirect

NeuroToxicology 28 (2007) 761–769

NeuroToxicology

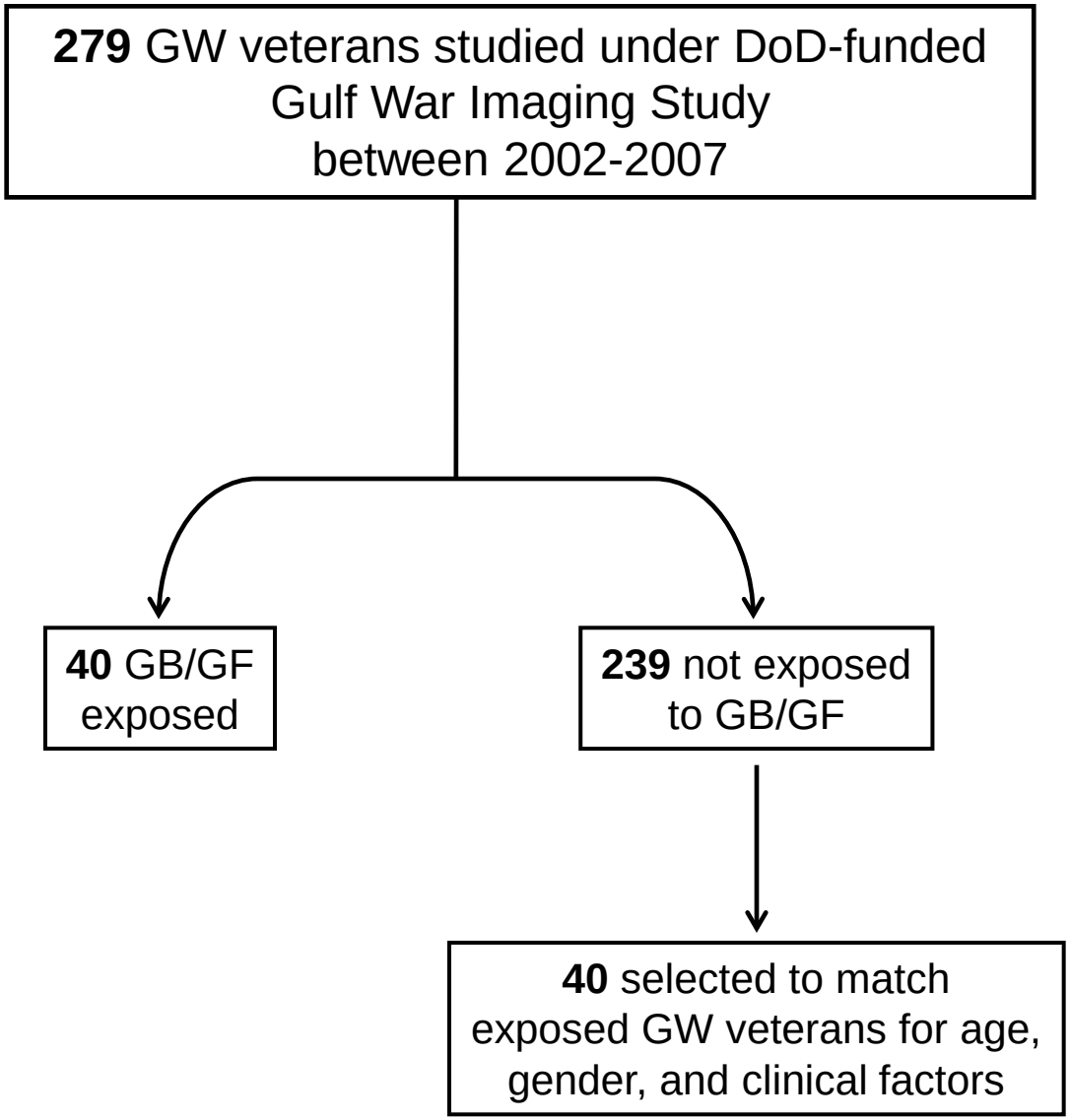
Quantitative magnetic resonance brain imaging in US army veterans of the 1991 Gulf War potentially exposed to sarin and cyclosarin

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).

1.5 Tesla Study Sample



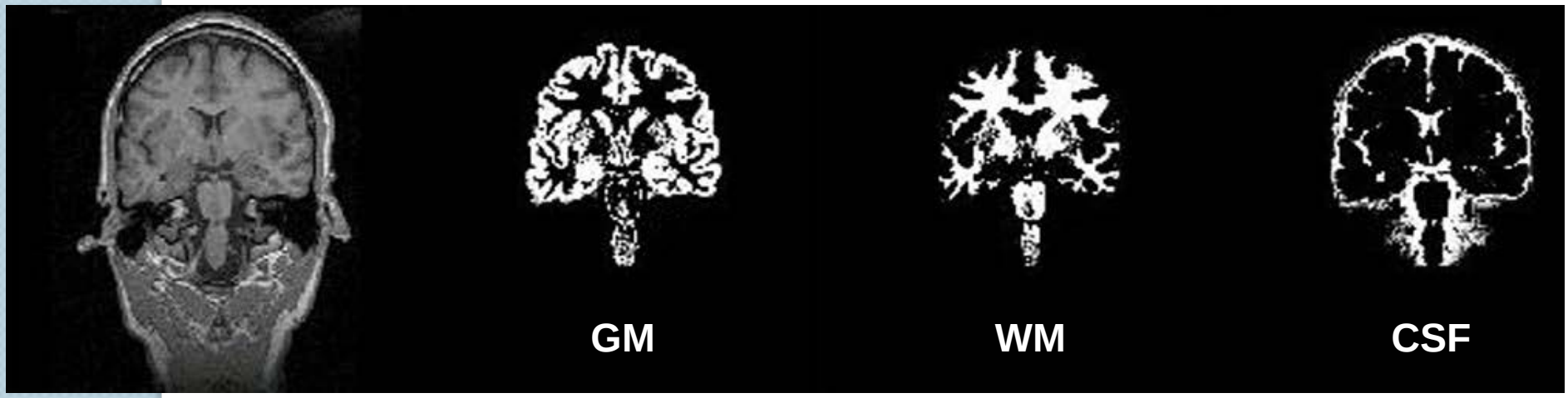
Demographics of 1.5T sample

	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. CMI cases (%)	21 (54%)	23 (59%)

PTSD: Posttraumatic Stress Disorder
MDD: Major Depressive Disorder
CMI: Chronic Multisymptom Illness as defined by Fukuda et al. (1998)

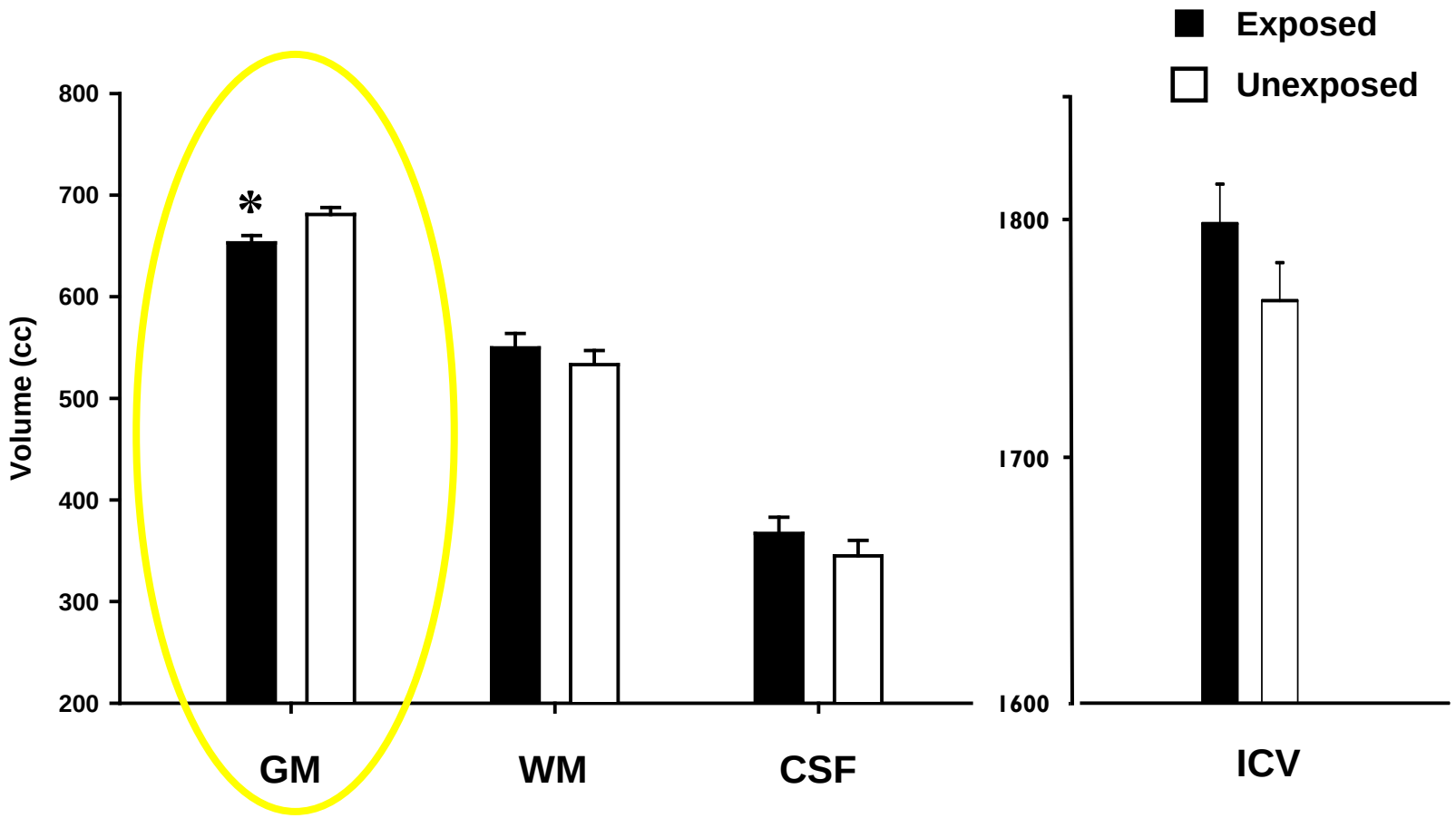
1.5T MRI methods

Cortical gray matter (GM), white matter (WM), and cerebral spinal fluid (CSF) were automatically classified with SPM8 segmentation.



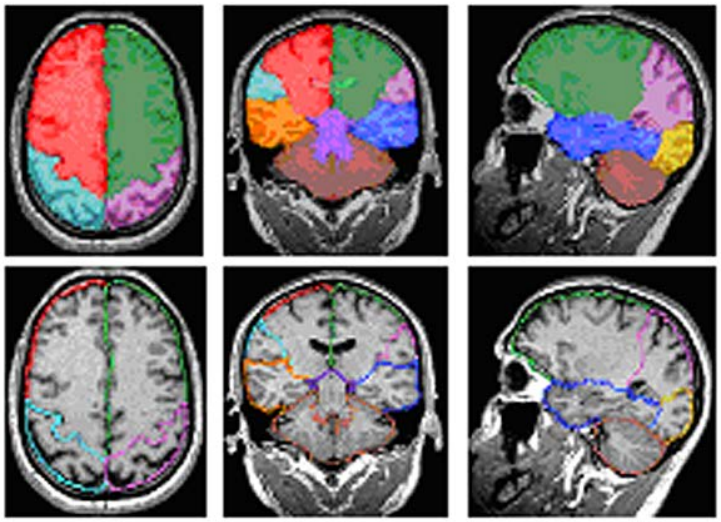
1.5T MRI Results

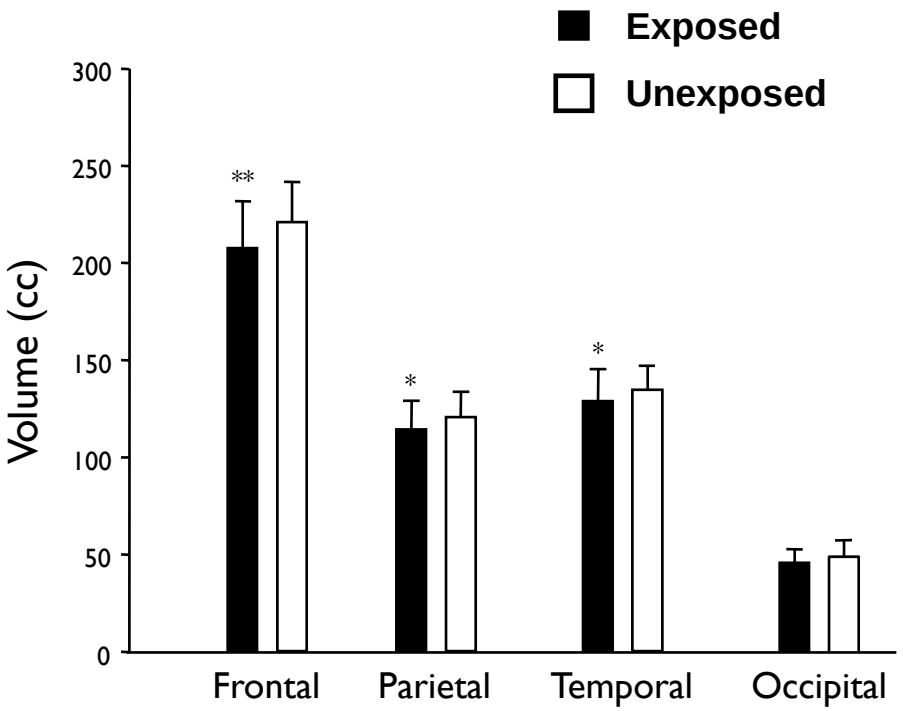
- After accounting for ICV, age, and gender, exposed veterans had smaller total brain GM volume than unexposed veterans.



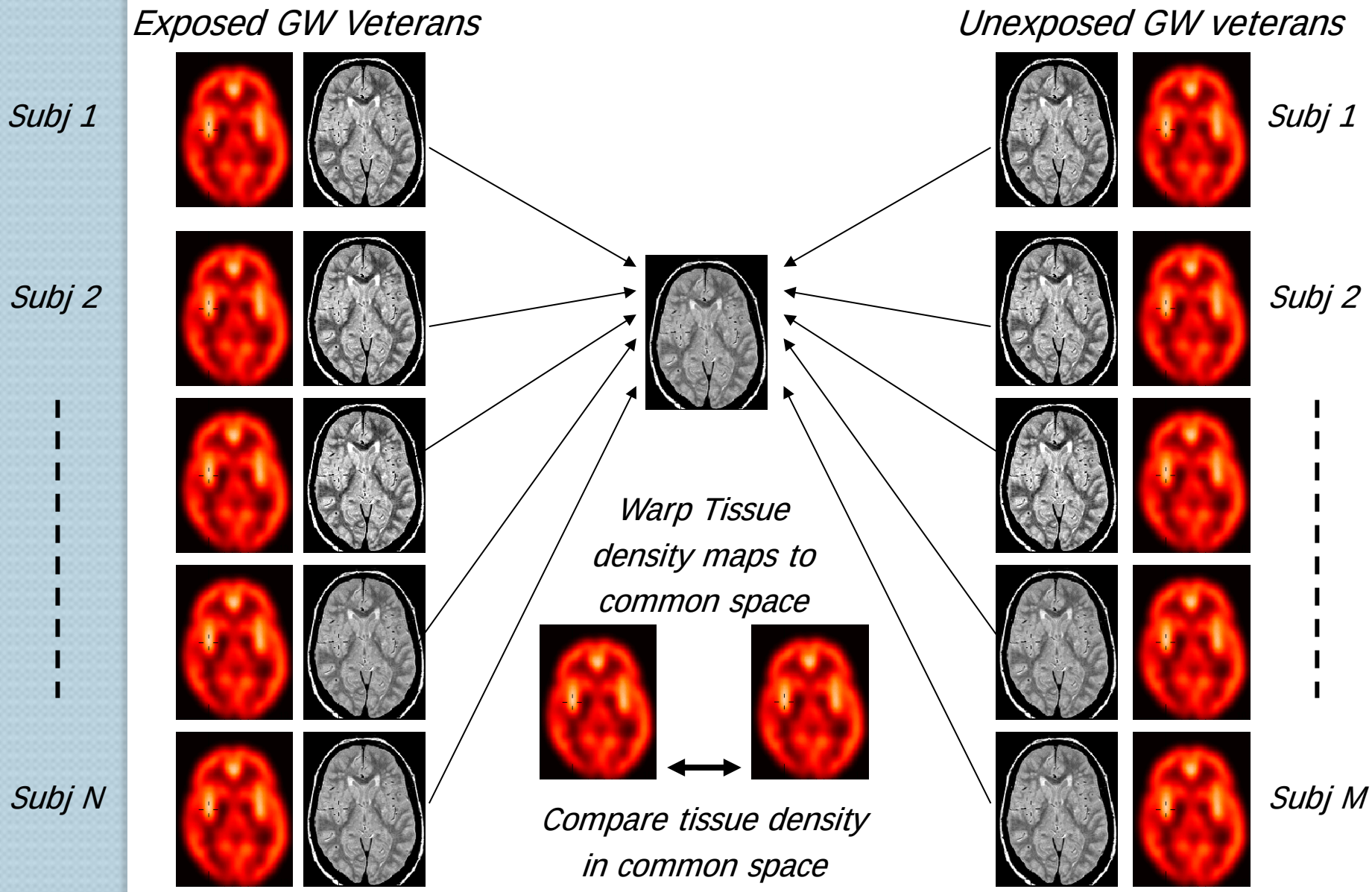
1.5T MRI Results

- In post-hoc analyses, we examined group differences in regional lobar GM volume.



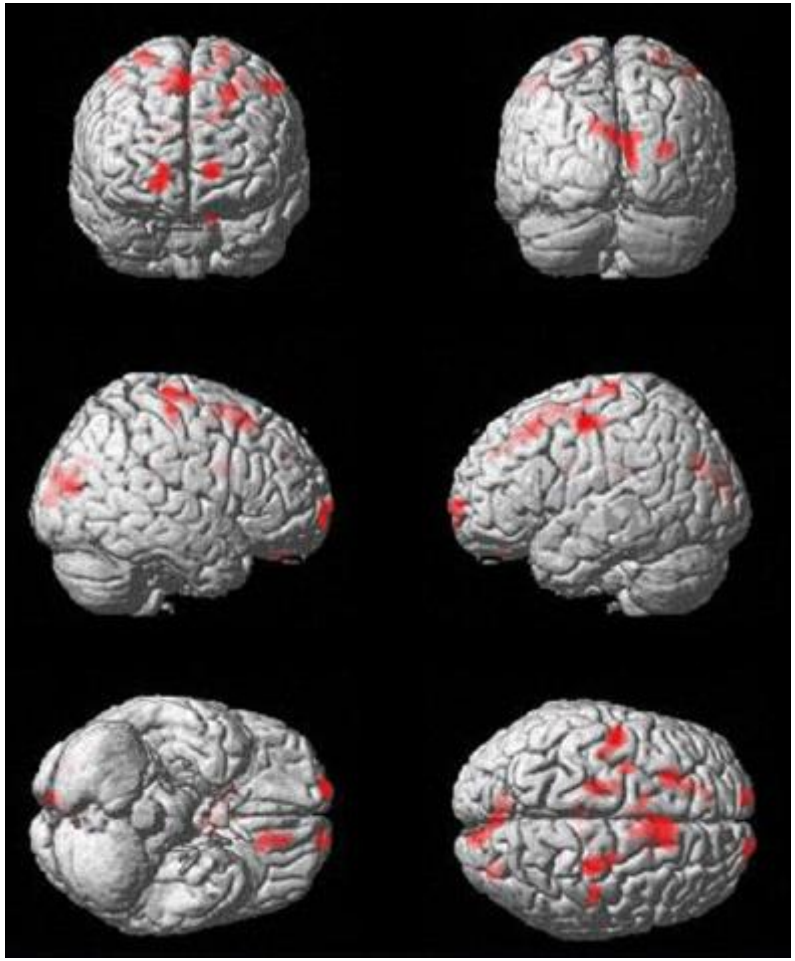


VBM: Group comparison of local gray matter density



1.5T VBM Results

- Nothing from the VBM analyses of the GM segmentation maps survived correction for multiple comparisons.



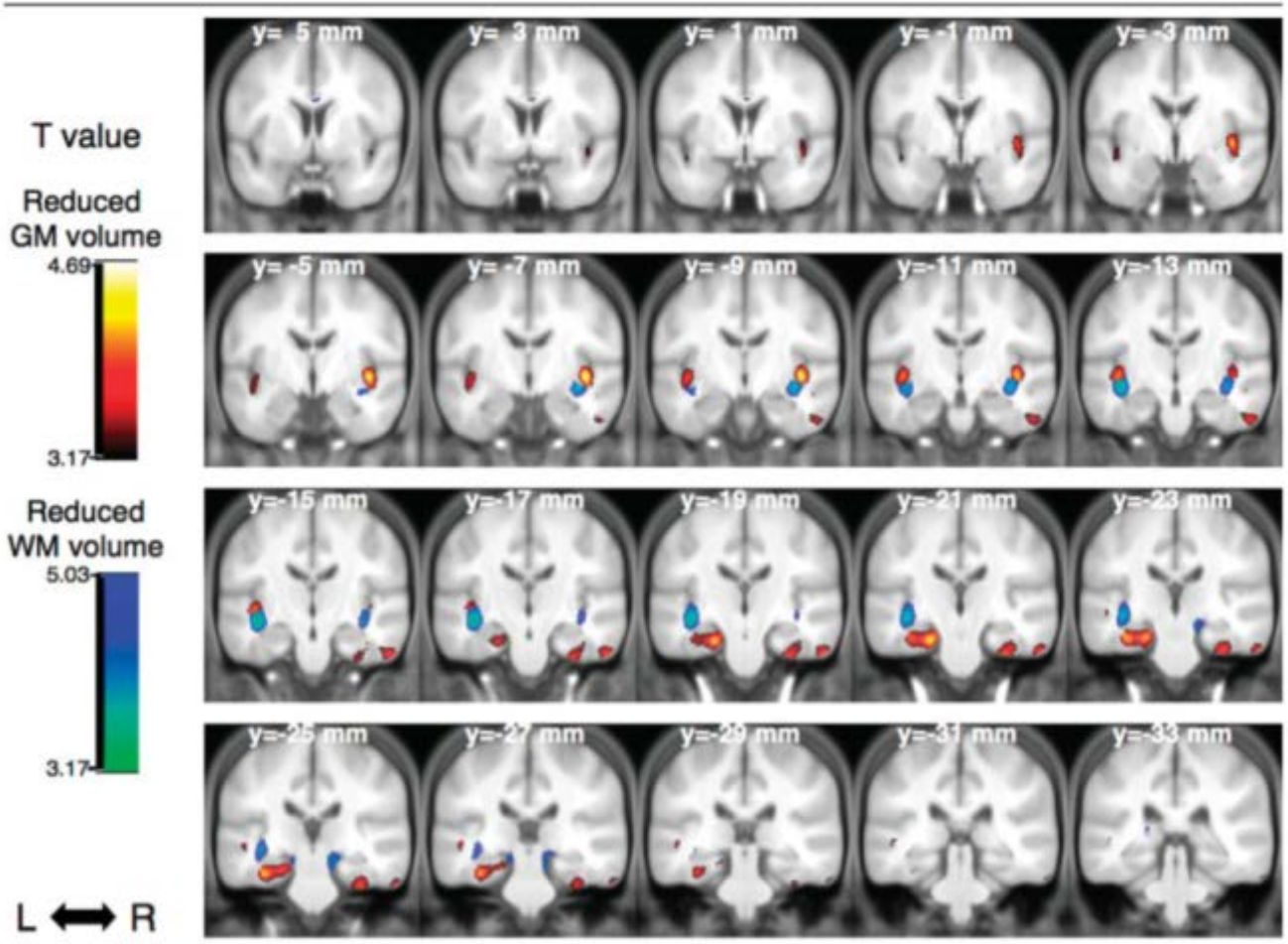
$p < 0.001$, uncorrected

1995 Tokyo subway sarin attack

Ann Neurol 2007;61:37–46

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]



Organophosphate poisoning affects mammalian hippocampus

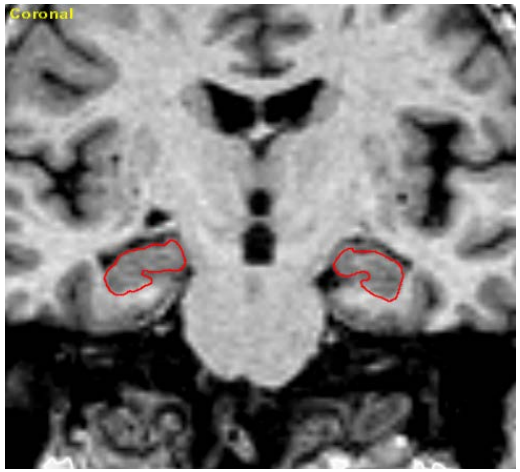
- Veronesi B, Jones K, Pope C. Electrophysiological and biochemical effects of single and multiple doses of the organophosphate diazinon in the mouse. *Toxicol Appl Pharmacol* 1990; 104:440-56.

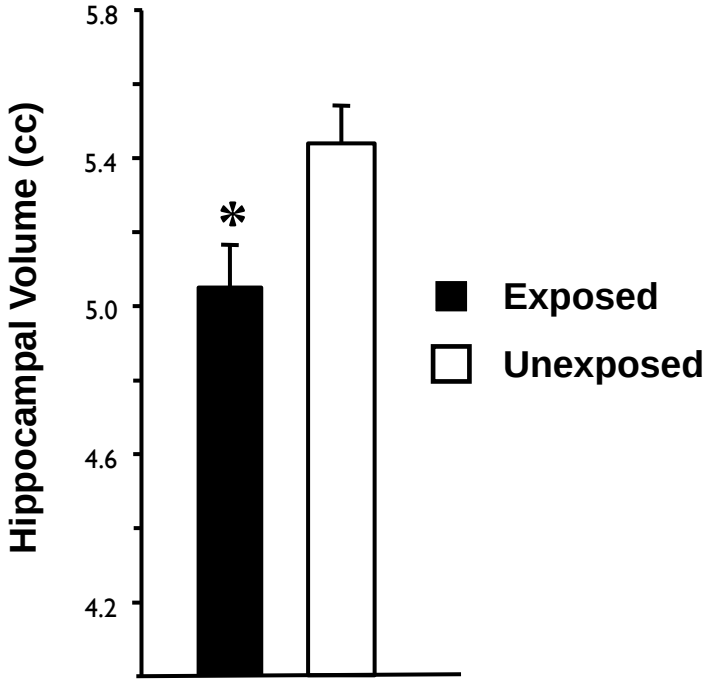
- Pazdernik TL, Emerson MR, Cross R, Nelson SR, Samson FE. Soman-induced seizures: limbic activity, oxidative stress, and neuroprotective proteins. *J Appl Toxicol* 2001; 21:S87-S94.

- Abdel-Rahman A, Shetty AK, Abou-Donia MB. Acute exposure to sarin increases blood brain barrier permeability and induces neuropathological changes in the rat brain: dose-response relationships. *Neuroscience* 2002; 113:721–41.

1.5T MRI Results

- Hippocampal volume (HV) was quantified with a semi-automatic high dimensional brain mapping tool (Medtronic Surgical Navigation Technologies, SNT).
- After accounting for ICV, age, and gender, exposed veterans had smaller HV than unexposed veterans.





NeuroToxicology 31 (2010) 493–501

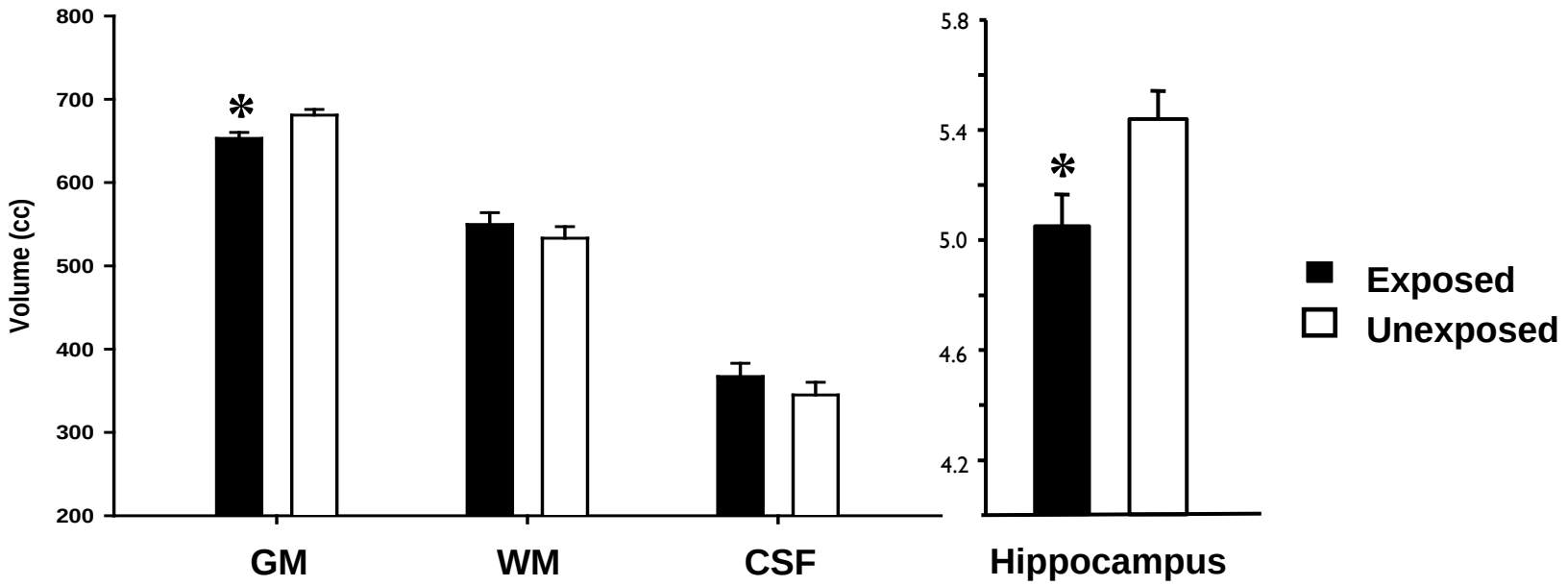
Contents lists available at ScienceDirect

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]

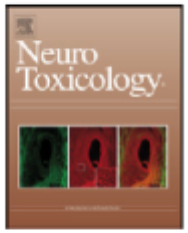
[a] Center for Imaging of Neurodegenerative Diseases, San Francisco Veterans Affairs Medical Center, 4150 Clement Street, 114 M, San Francisco, CA, 94121, United States
[b] Department of Psychiatry, University of California, San Francisco, San Francisco, CA, United States
[c] Department of Radiology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



NeuroToxicology 32 (2011) 814–822

Contents lists available at ScienceDirect

NeuroToxicology



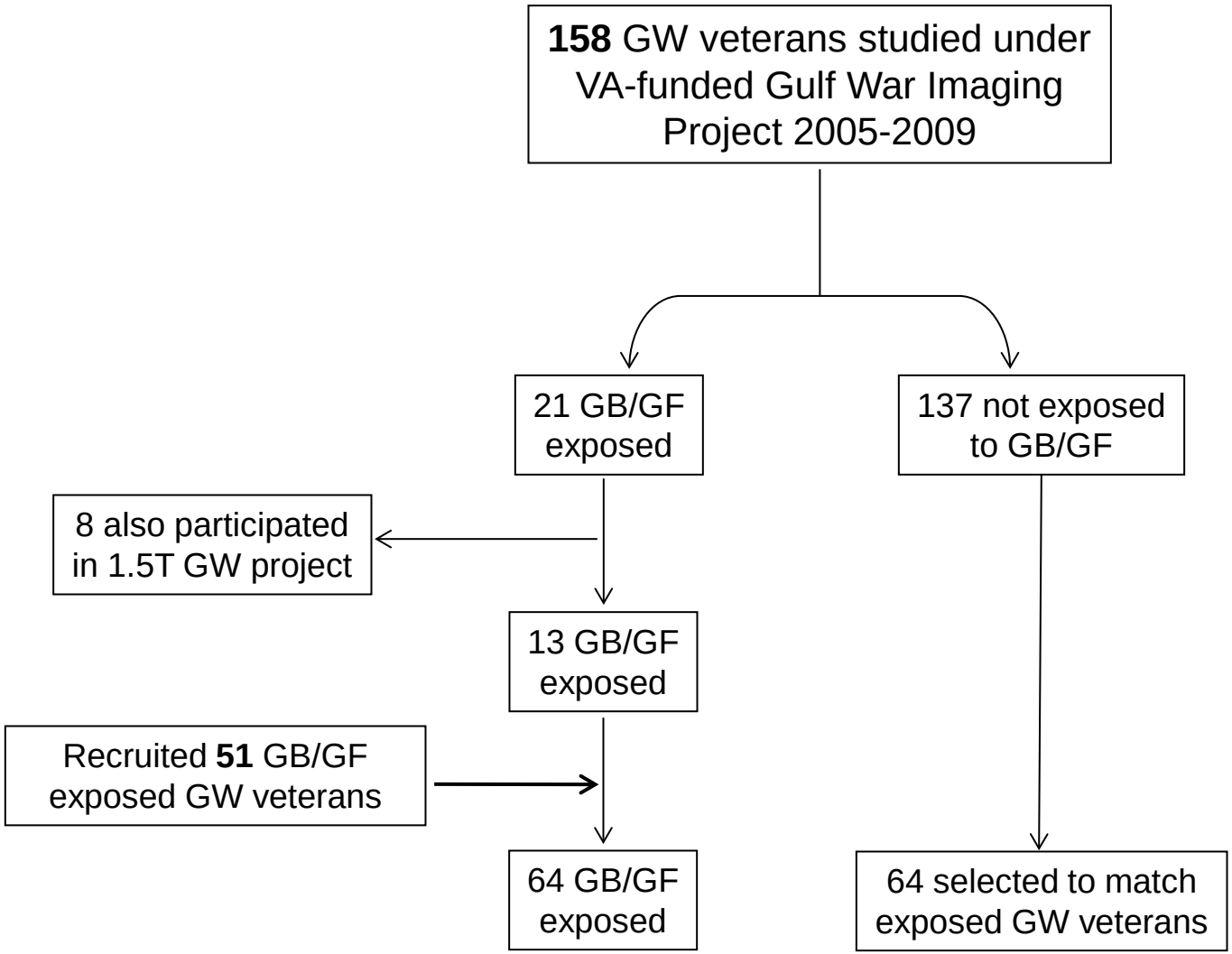
Effects of low-level sarin and cyclosarin exposure and Gulf War Illness on Brain Structure and Function: A study at 4 T

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

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

- Follow-up study with more subjects (N=64) imaged at higher magnetic field strength (4T) to determine if we could replicate and extend our previous finding in an independent cohort of GW veterans with predicted GB/GF exposure.

4 Tesla Study Sample



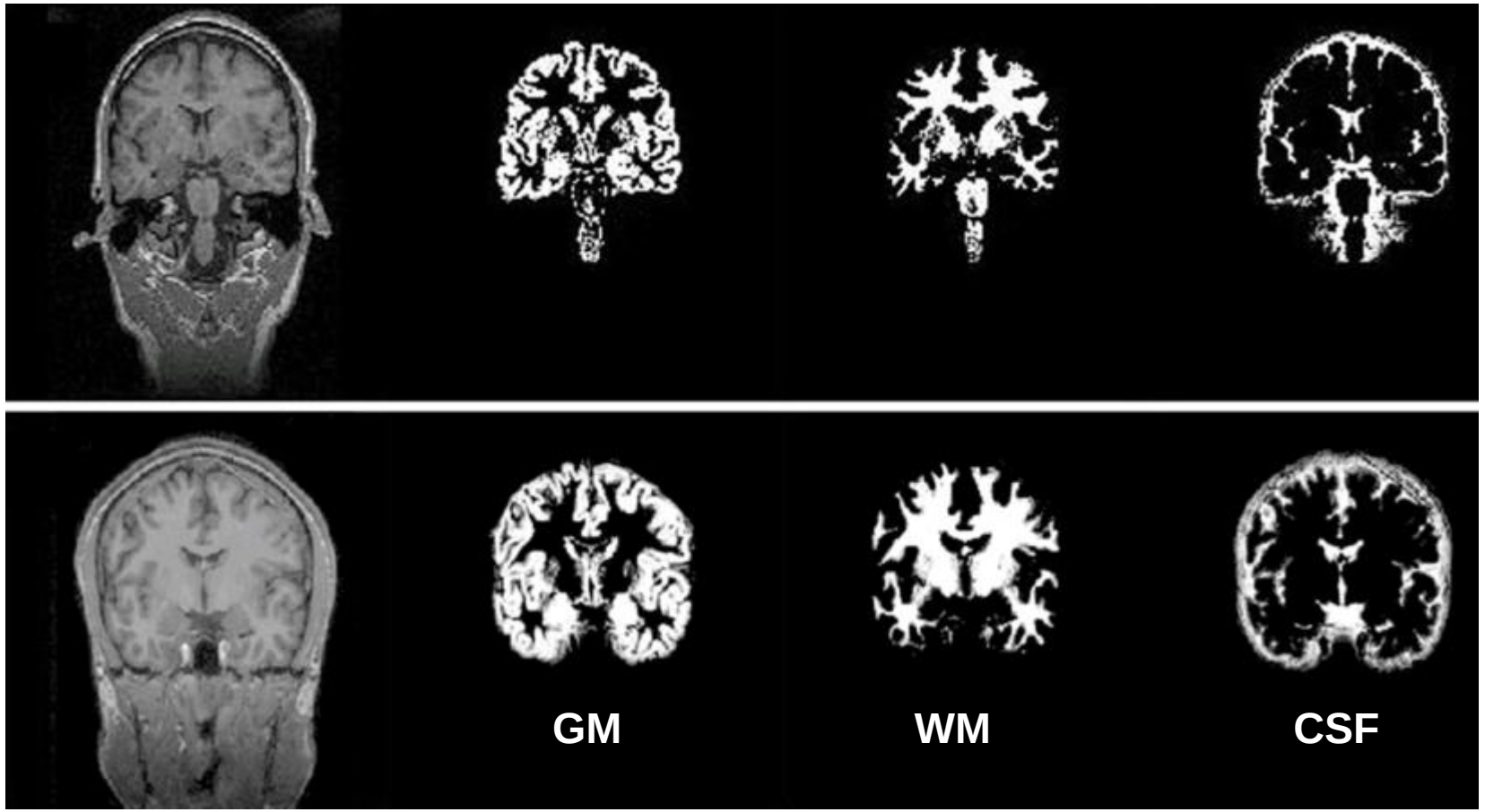
Demographics of 4T sample

	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. CMI cases (%)	33 (52%)	33 (52%)

PTSD: Posttraumatic Stress Disorder
MDD: Major Depressive Disorder
CMI: Chronic Multisymptom Illness as defined by Fukuda et al. (1998)

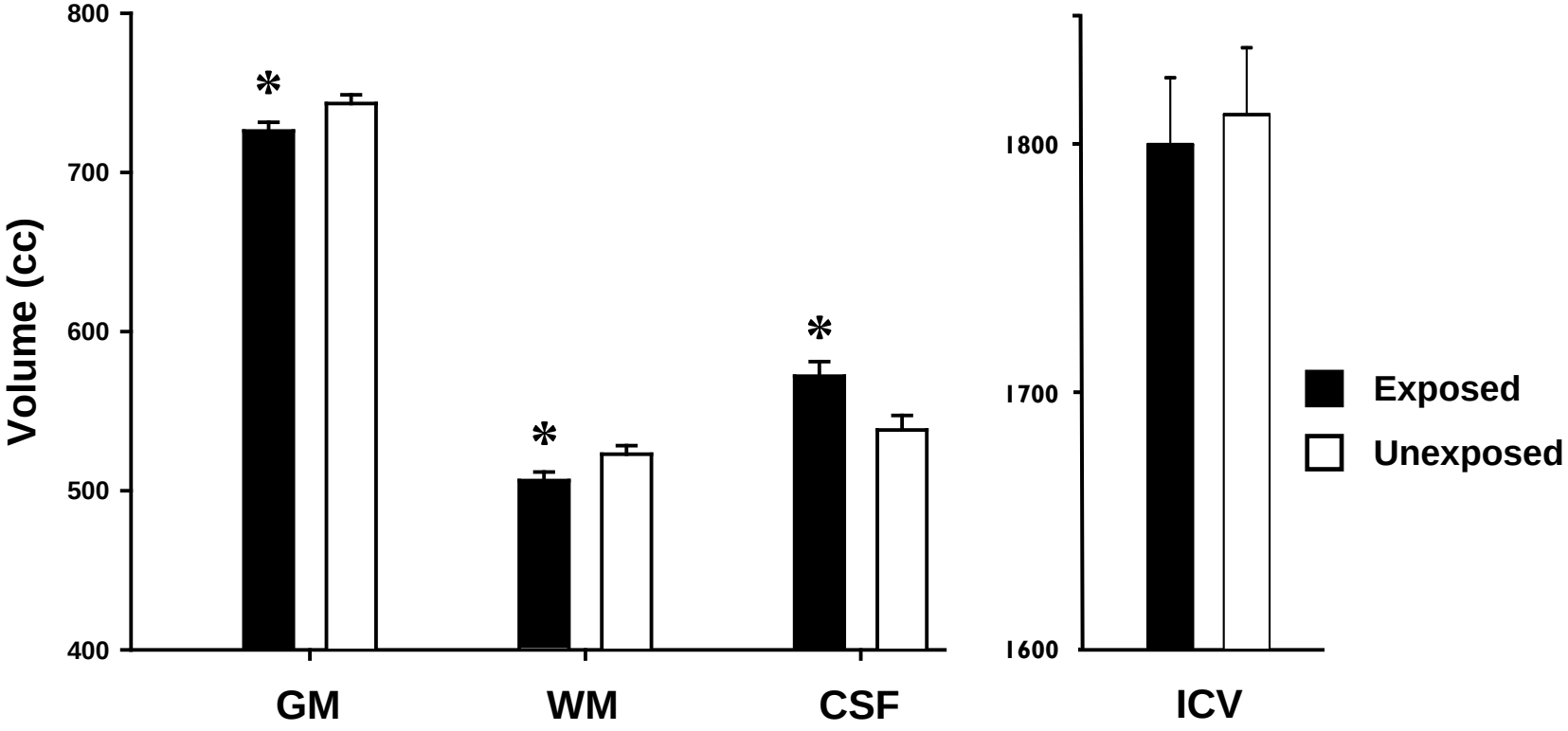
4T MRI methods

Cortical GM, WM, and CSF were automatically classified with SPM8 segmentation.

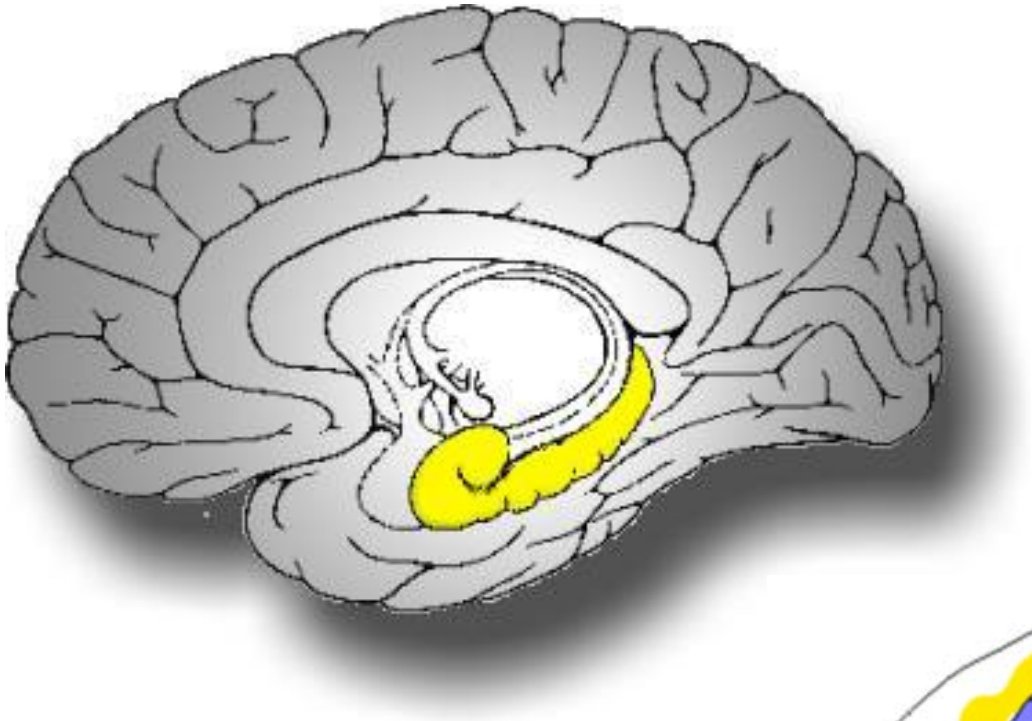


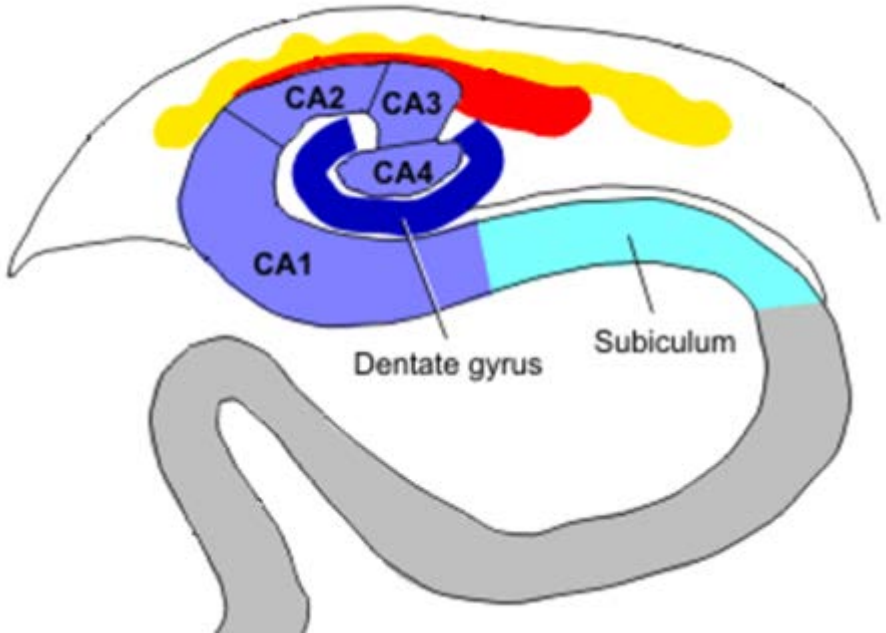
4T MRI Results

- After accounting for ICV, age, and gender, exposed veterans had smaller total brain GM and WM volume and larger CSF volume compared to unexposed veterans.

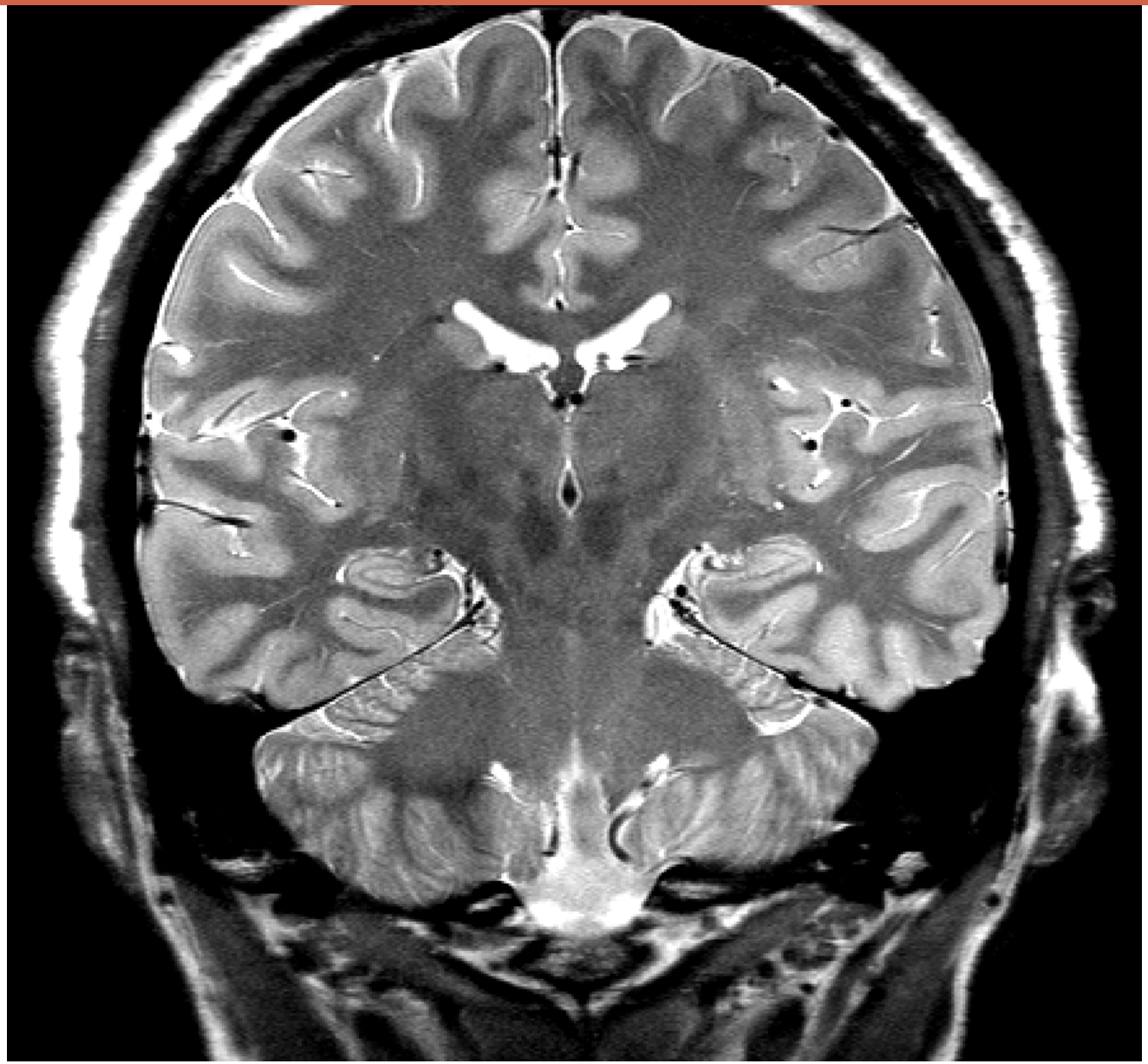


Hippocampal Anatomy



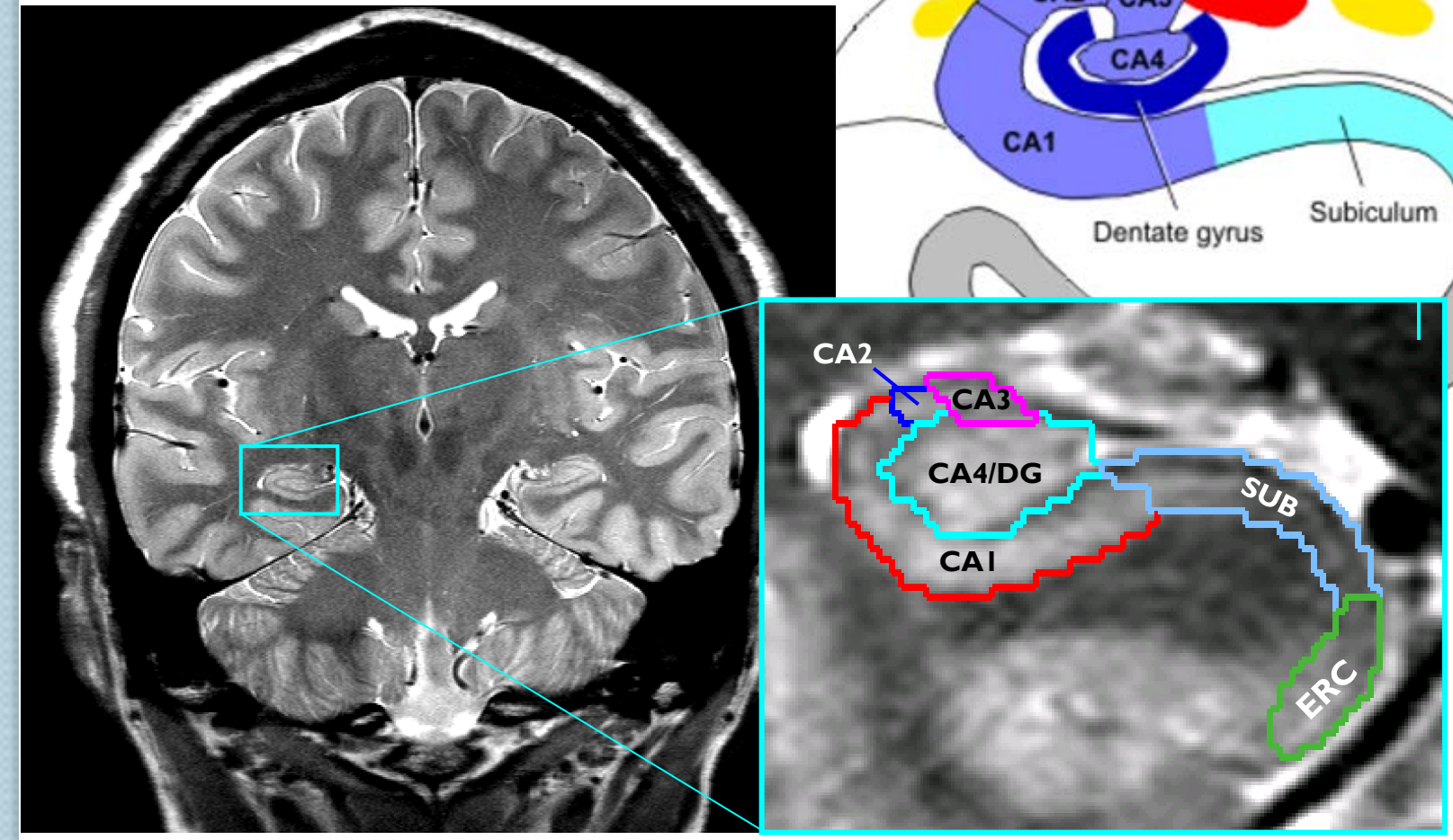


High Resolution T2-weighted 4T Image



Manual Hippocampal Subfield Marking Scheme

S.G. Mueller et al. Measurement of hippocampal subfields and age-related changes with high resolution MRI at 4T. 2007; Neurobiol Aging 28(5):719-26



NeuroImage 53 (2010) 1208–1224

Contents lists available at ScienceDirect

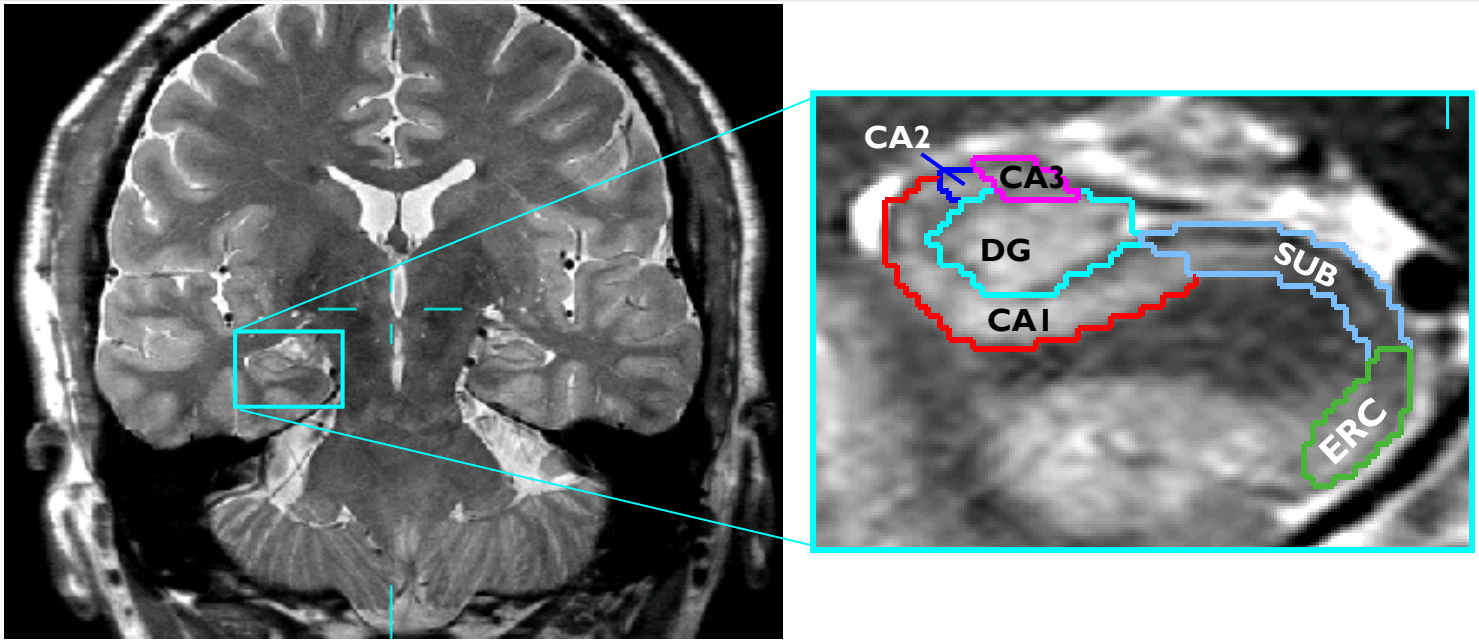
NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

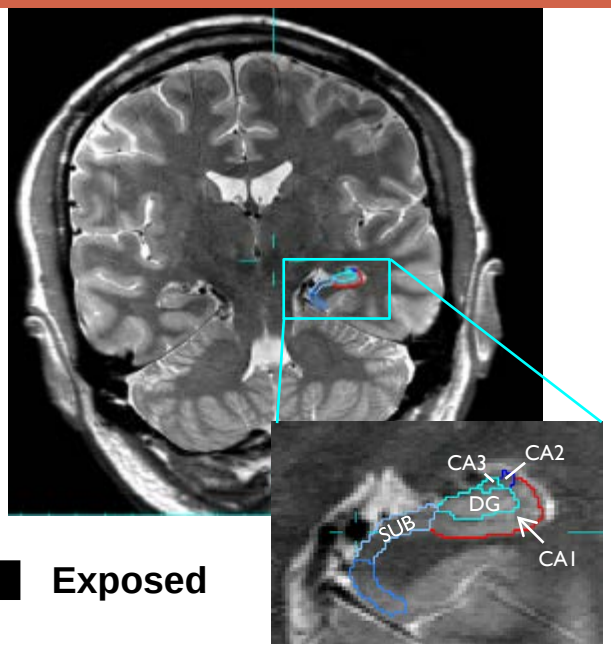
Nearly automatic segmentation of hippocampal subfields in *in vivo* focal T2-weighted MRI

Paul A. Yushkevich [a,*], Hongzhi Wang [a], John Pluta [a,b], Sandhitsu R. Das [a], Caryne Craige [a], Brian B. Avants [a], Michael W. Weiner [c], Susanne Mueller [c]

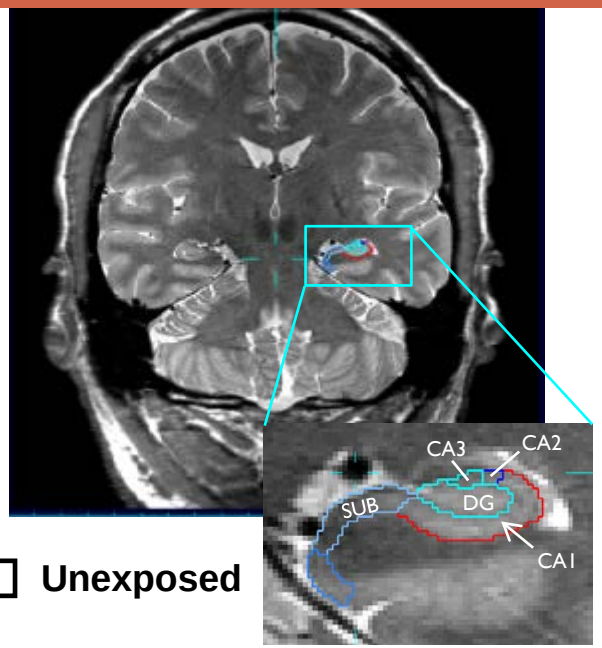
[a] Penn Image Computing and Science Laboratory, Department of Radiology, University of Pennsylvania, Philadelphia, USA
[b] Center for Functional Neuroimaging, Departments of Neurology and Radiology, University of Pennsylvania, Philadelphia, USA
[c] Department of Veterans Affairs Medical Center, University of California at San Francisco and Center for Imaging of Neurodegenerative Diseases, San Francisco, CA, USA



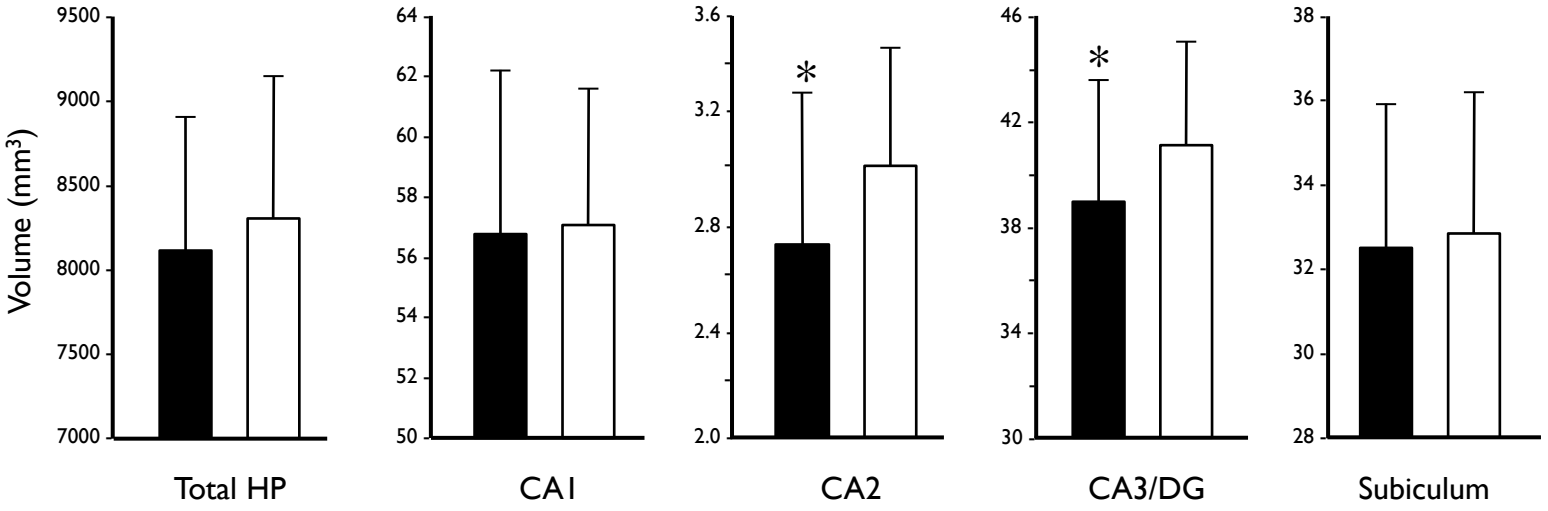
4T MRI Results



■ **Exposed**



□ **Unexposed**



Reduce WM volume with GB/GF exposure

In GW Veterans:

- Heaton KJ, Palumbo CL, Proctor SP, Killiany RJ, Yurgelund-Todd DA, White RF. (2007) *Neurotoxicology*, 28:761-9.

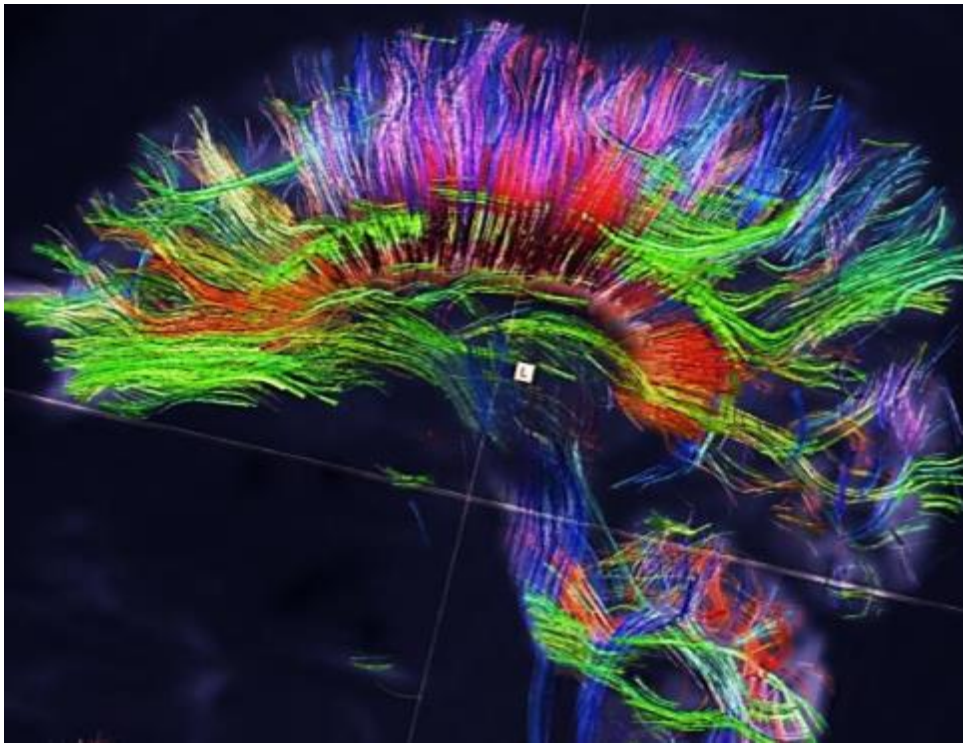
- Chao LL, Rothlind JC, Cardenas VA, Meyerhoff DJ, Weiner MW (2010). *Neurotoxicology,* 31:493-501.

In Tokyo Subway Sarin Attack Victims:

- Yamasue H, Abe O, Kasai K, Suga M, Iwanami A, Yamada H, et al. (2007) *Ann Neurol.* 62:37–46.

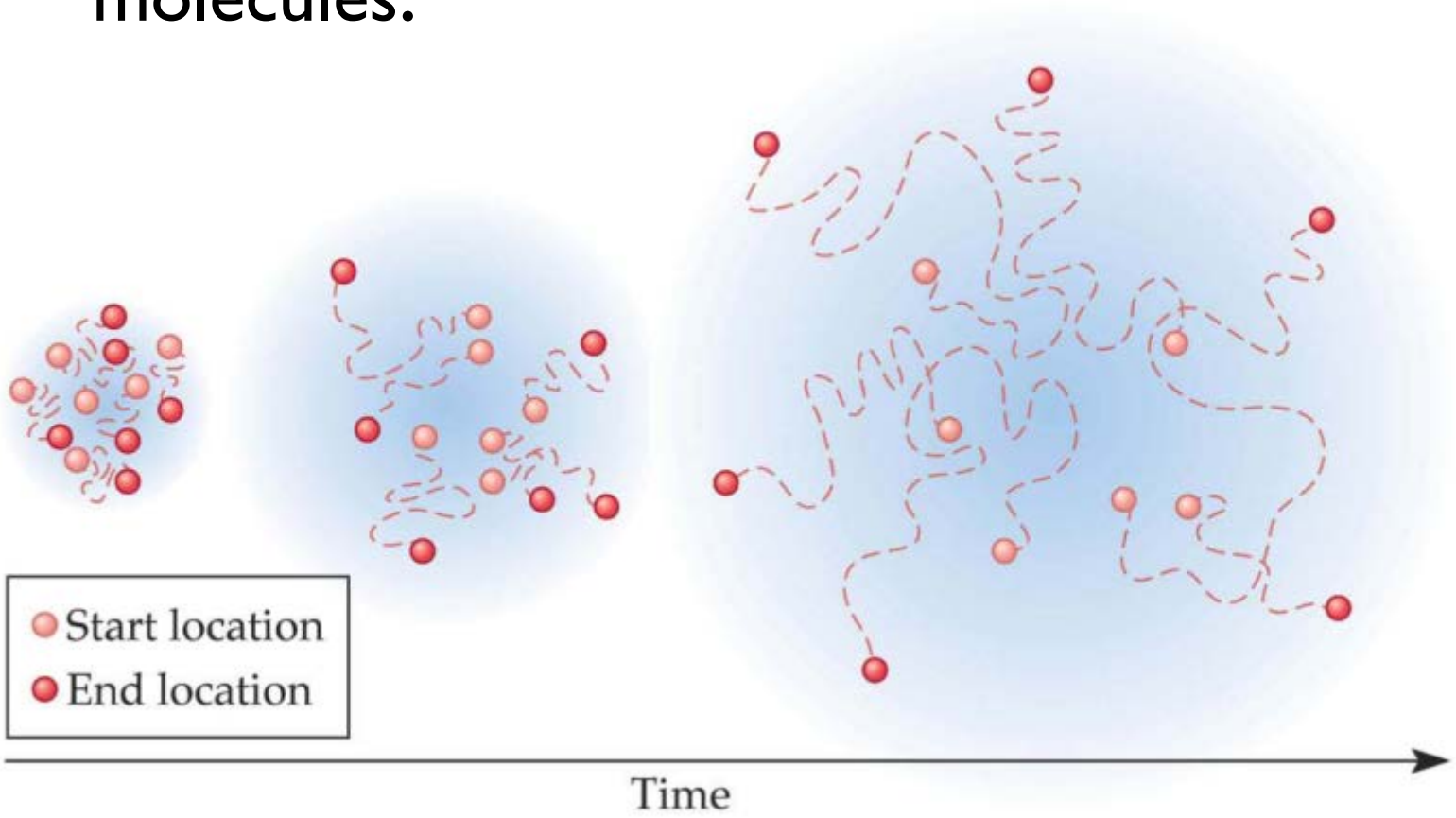
DIFFUSION TENSOR IMAGING

- Non-invasive method of quantifying WM tracks in the brain.



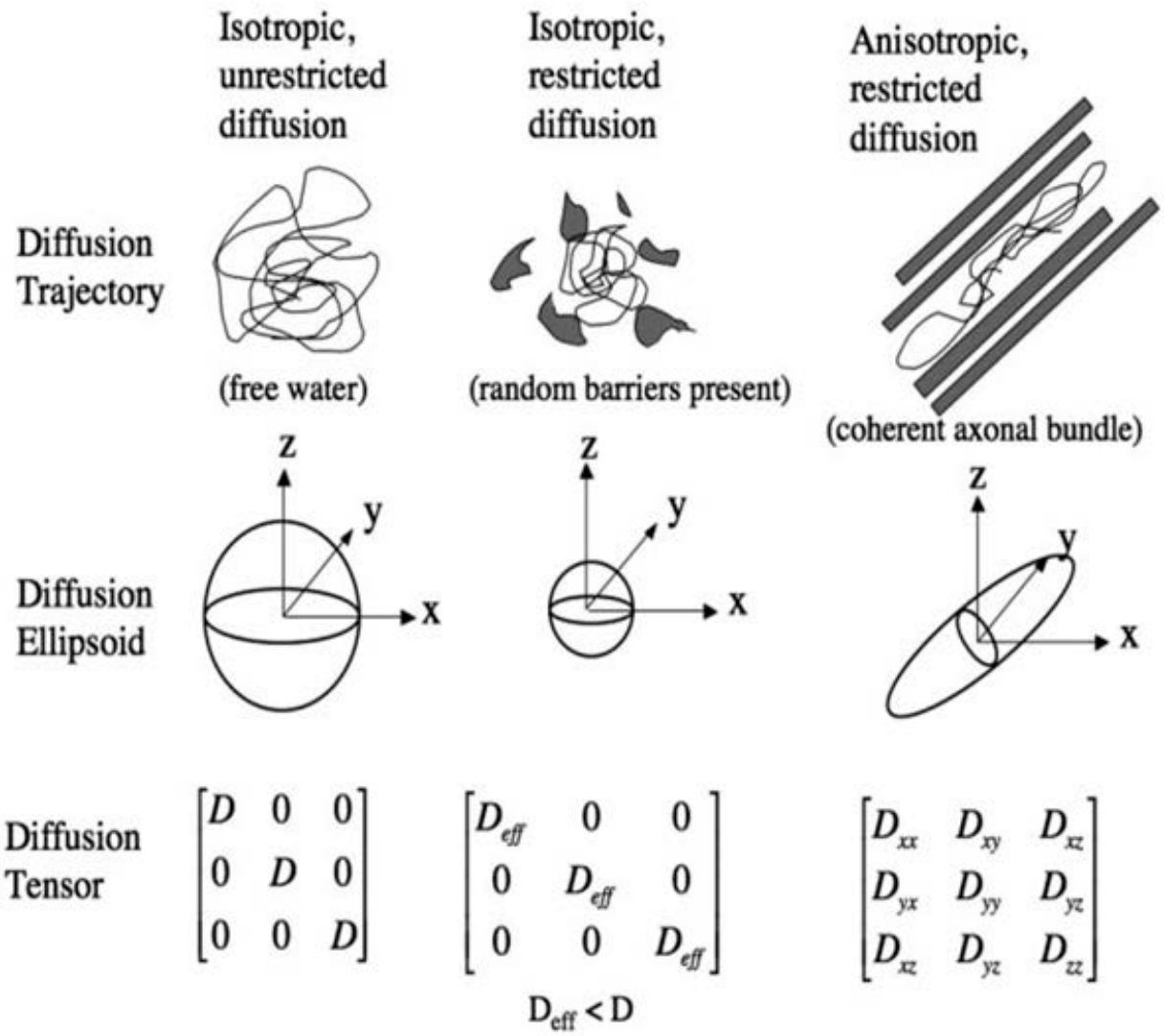
DIFFUSION TENSOR IMAGING

- measures the random movement of water molecules.

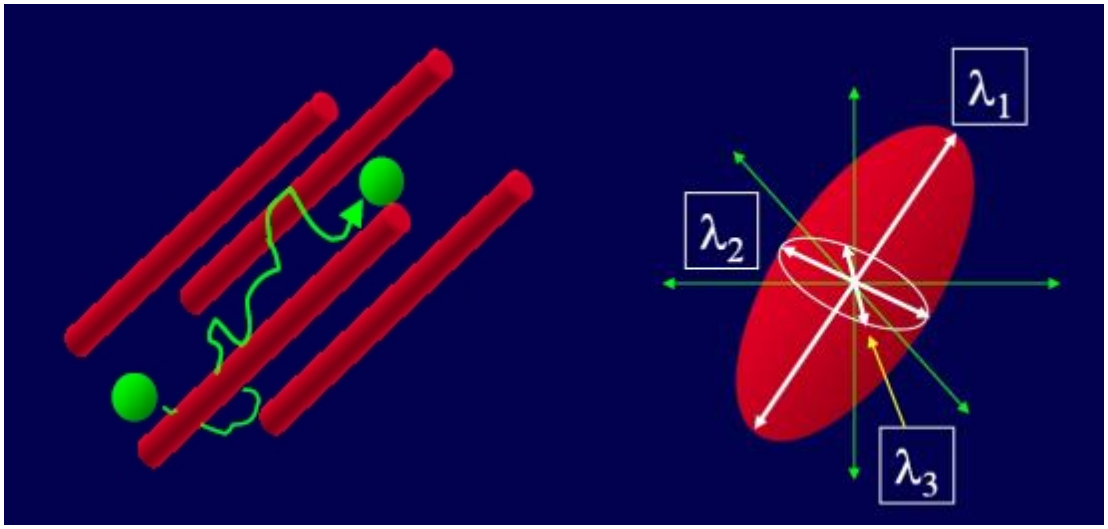


From Functional Magnetic Resonance Imaging, Figure 5.17 © 2004 Sinauer Associates, Inc.

DIFFUSION TENSOR IMAGING

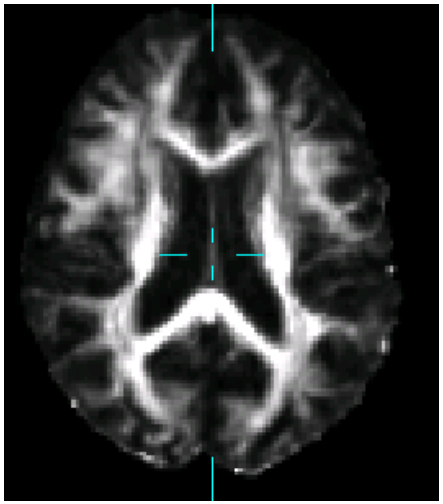


DIFFUSION TENSOR IMAGING



Diffusion Tensor

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



Fractional Anisotropy (FA)

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

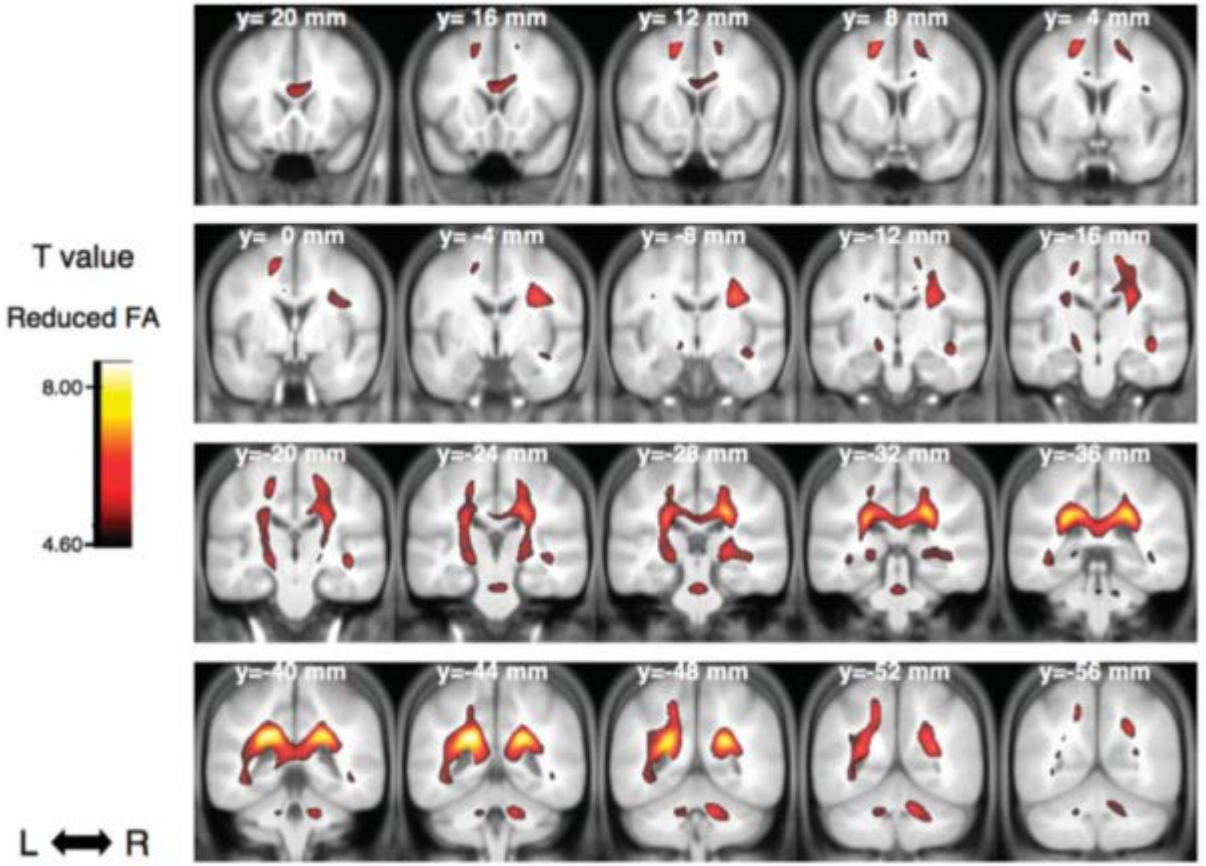
0 (spherical) to 1 (linear)

Lower FA is associated with reduced WM integrity.

Ann Neurol 2007;61:37–46

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]

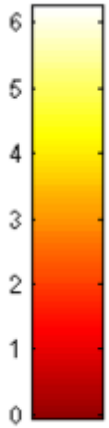


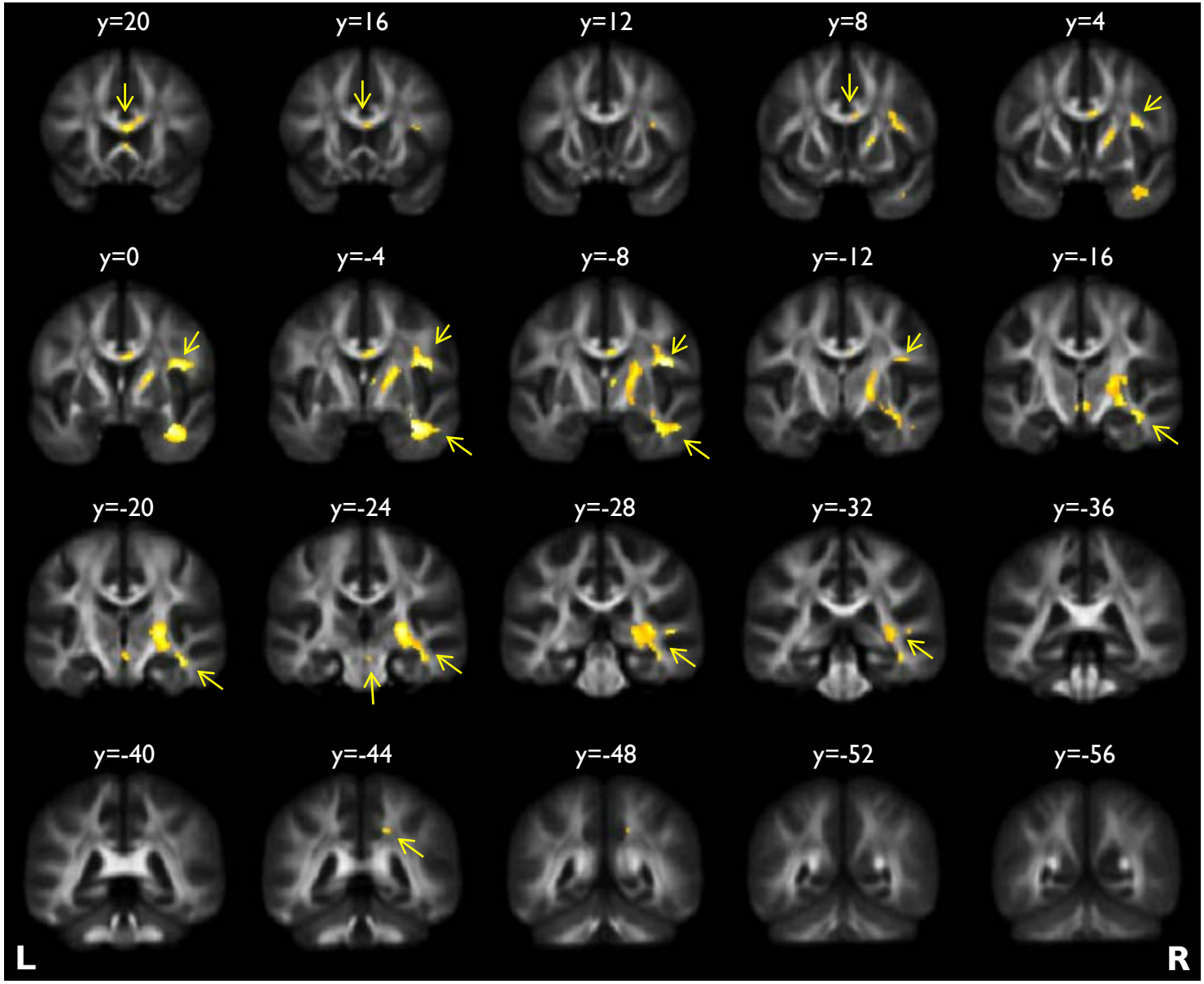
Demographics of 4T DTI sample

	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 ± 2.2	15.6 ± 2.2
No. current PTSD diagnosis (%)	4 (7%)	4 (7%)
No. CMI cases (%)	36 (61%)	36 (61%)

PTSD: Posttraumatic Stress Disorder
CMI: Chronic Multisymptom Illness as defined by Fukuda et al. (1998)

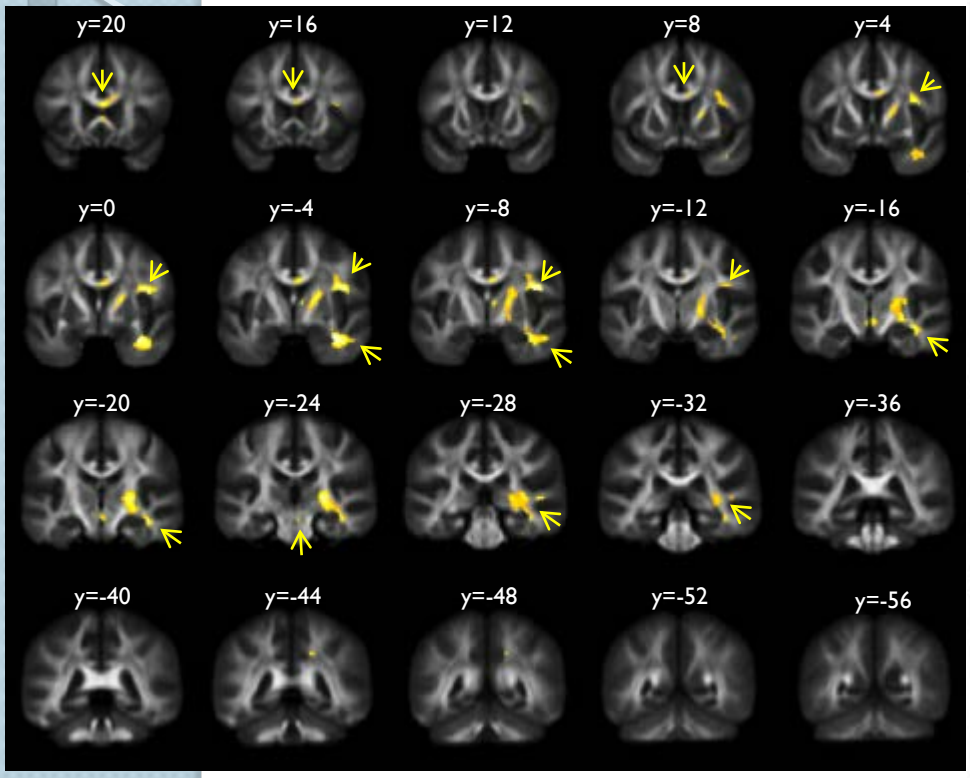
Regions of reduced FA in GB/GF exposed veterans vs. unexposed Veterans



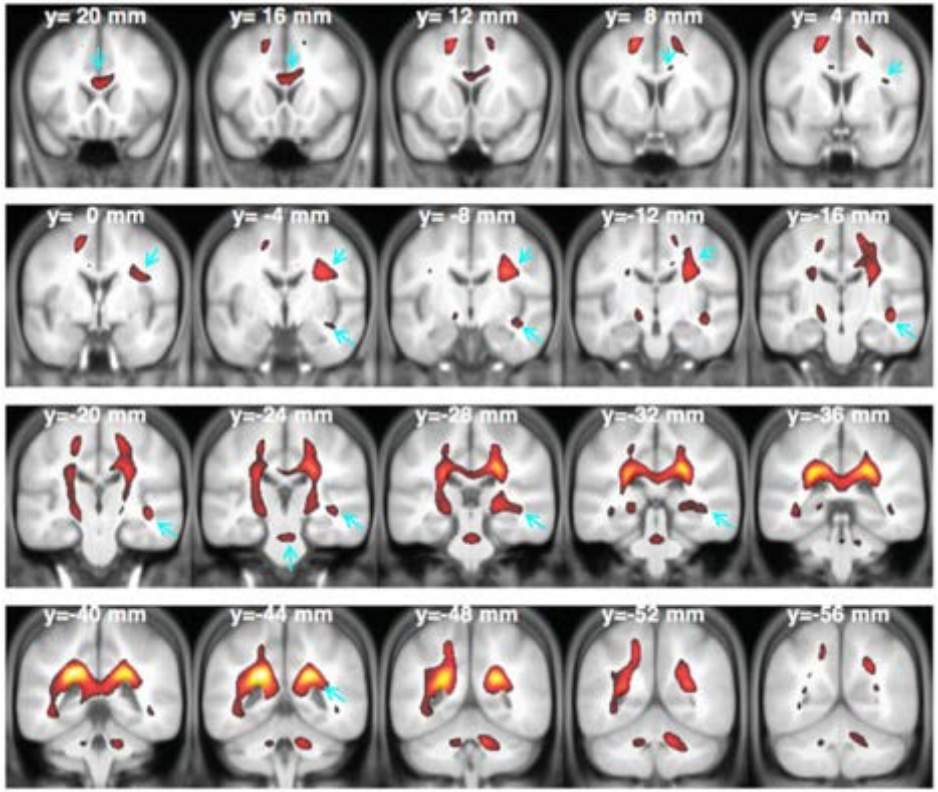


Regions of reduced FA in GW Veterans & TSSA victims

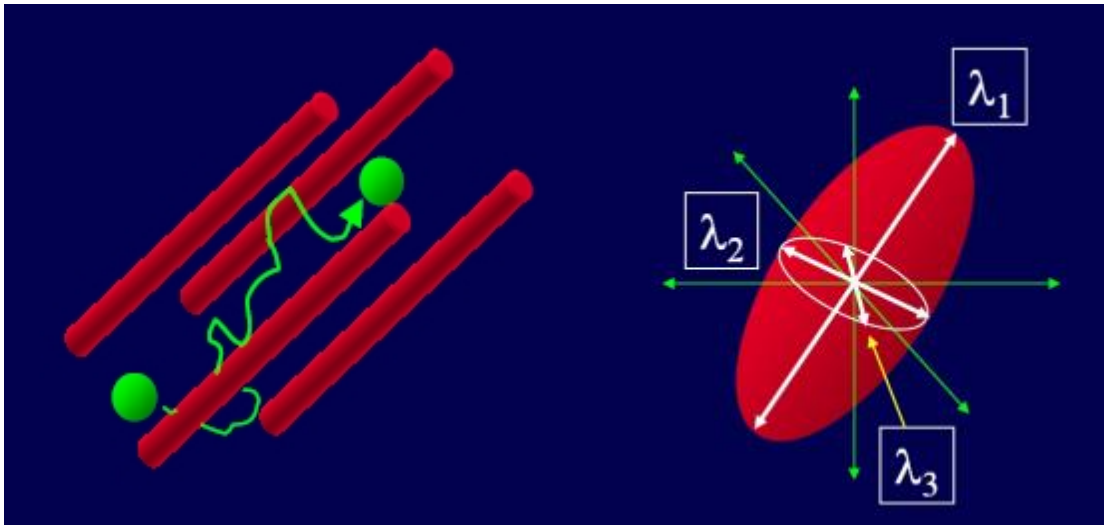
4T FA results



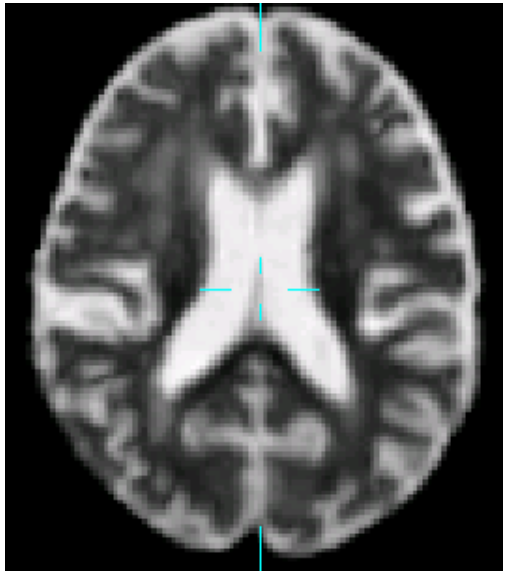
Yamasue et al., Ann Neurol. 2007; 61:37-46



DIFFUSION TENSOR IMAGING



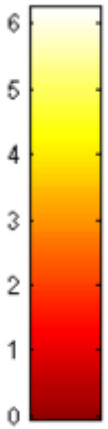
Calculate shape of the ellipsoid

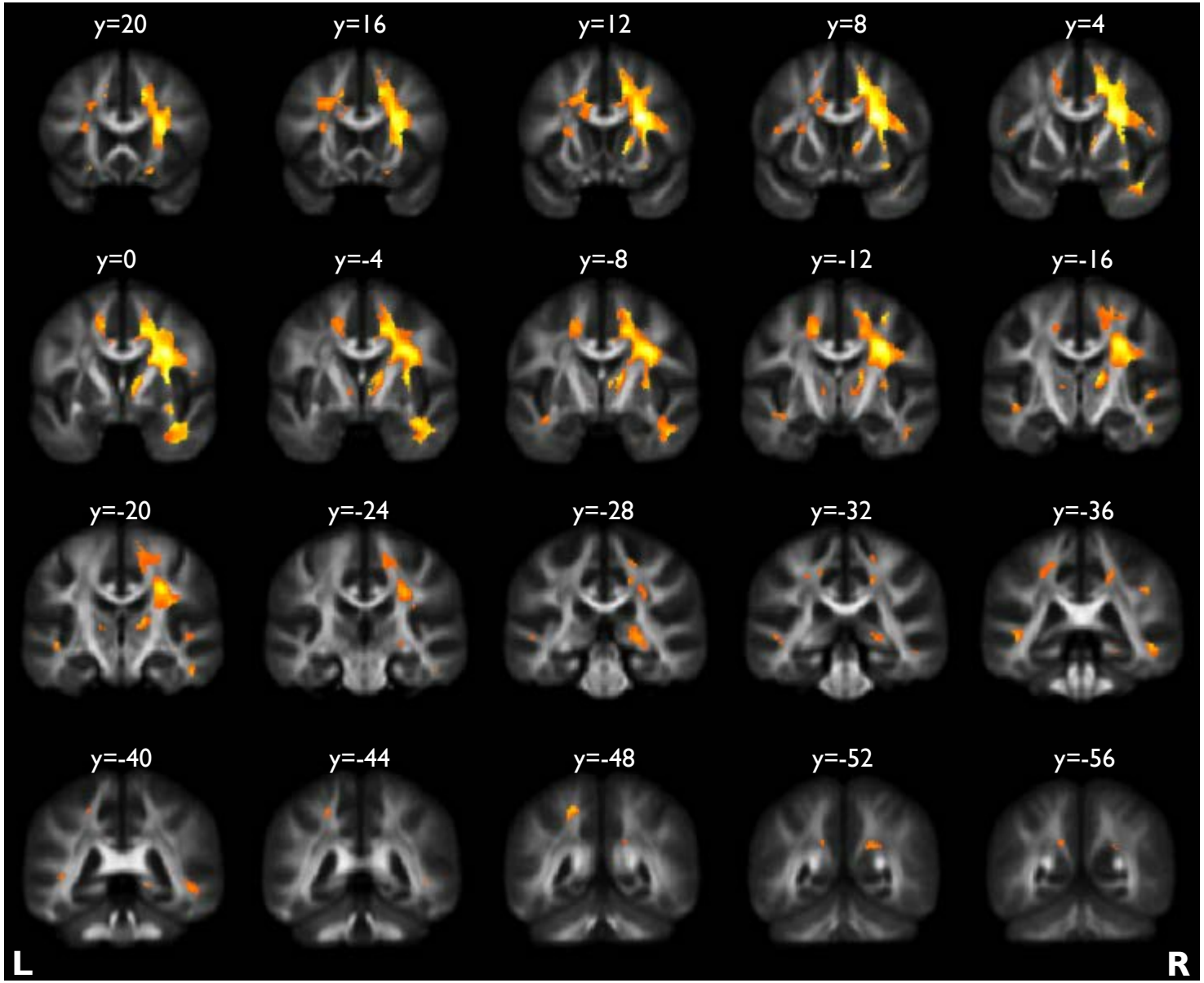


Axial Diffusivity (AD) = λ_1

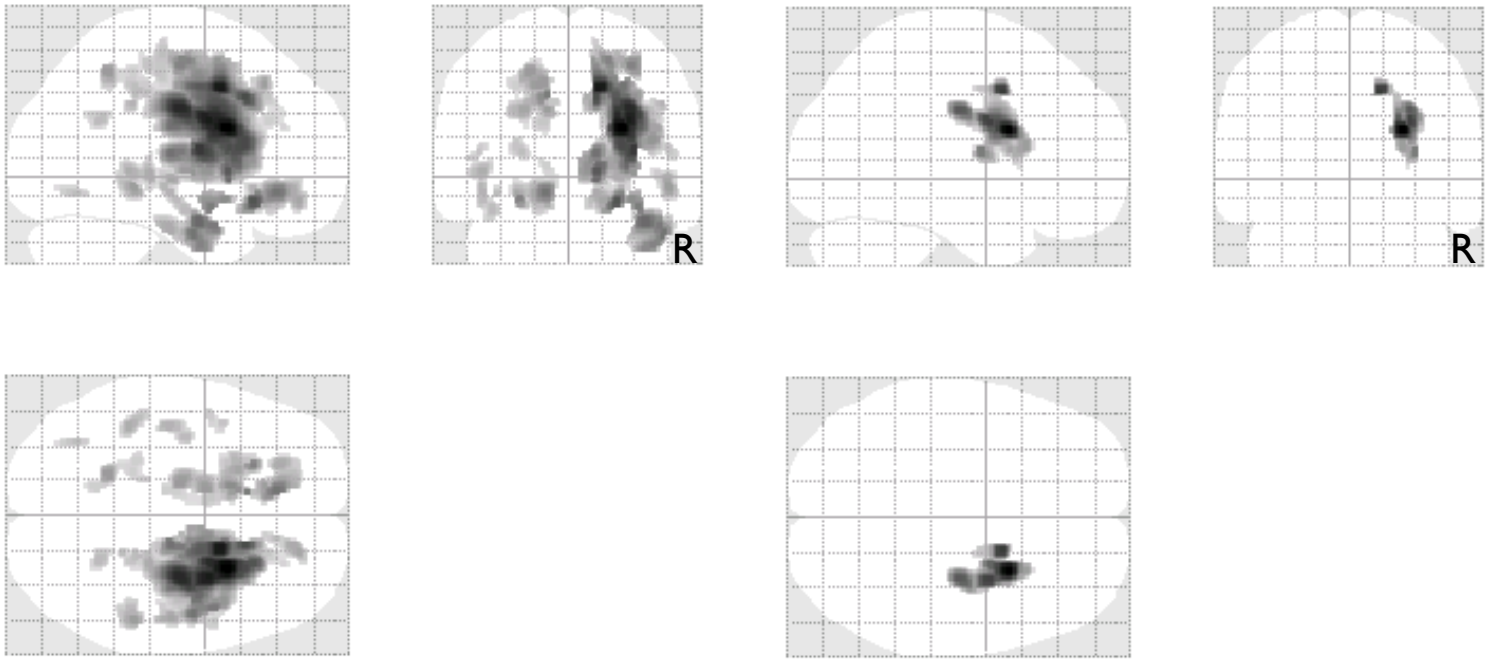
Higher AD has been associated with greater axonal degeneration.

Regions of increased AD in GB/GF exposed veterans vs. unexposed Veterans





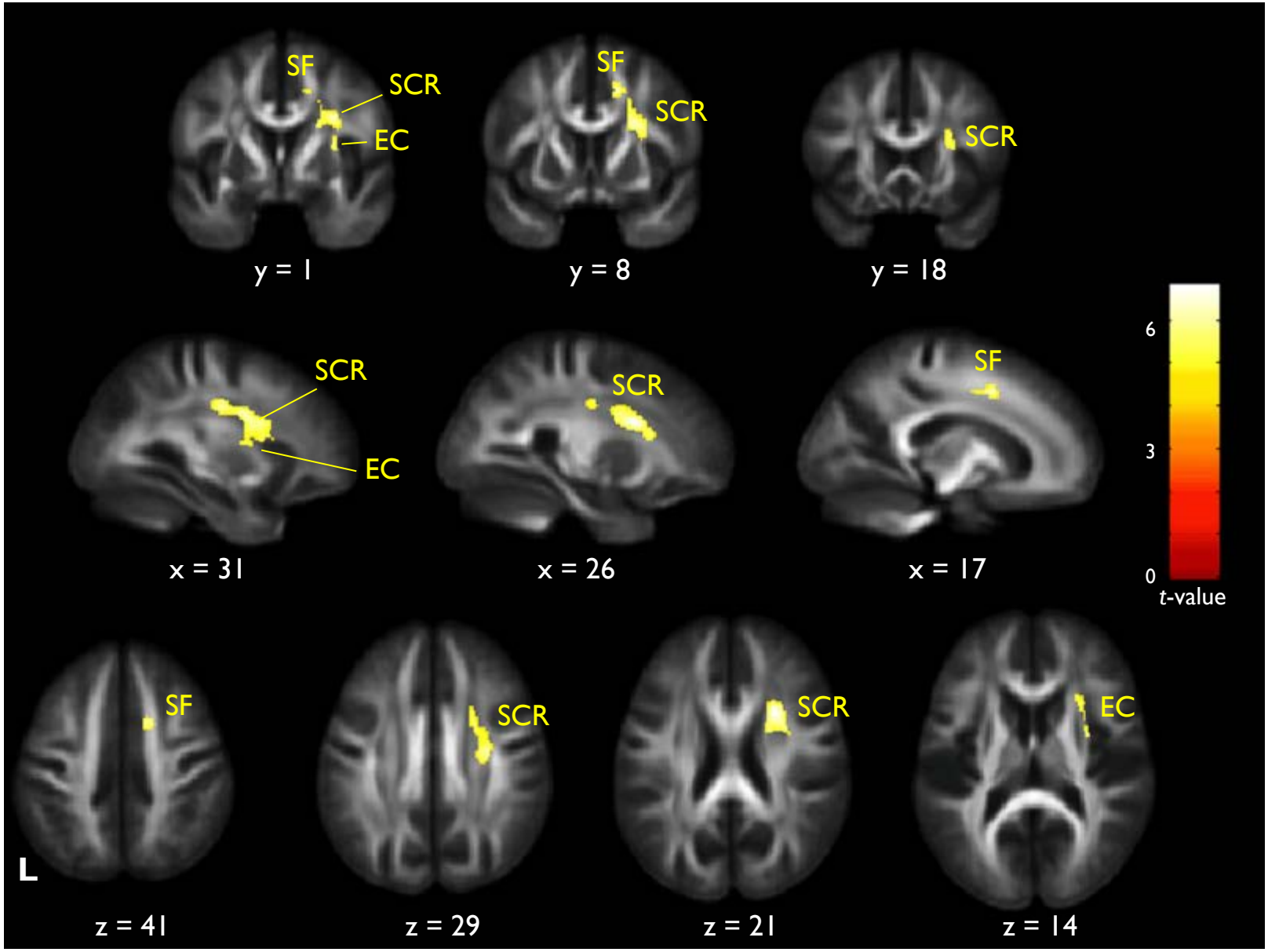
Effects of GB/GF exposure on Axial Diffusivity



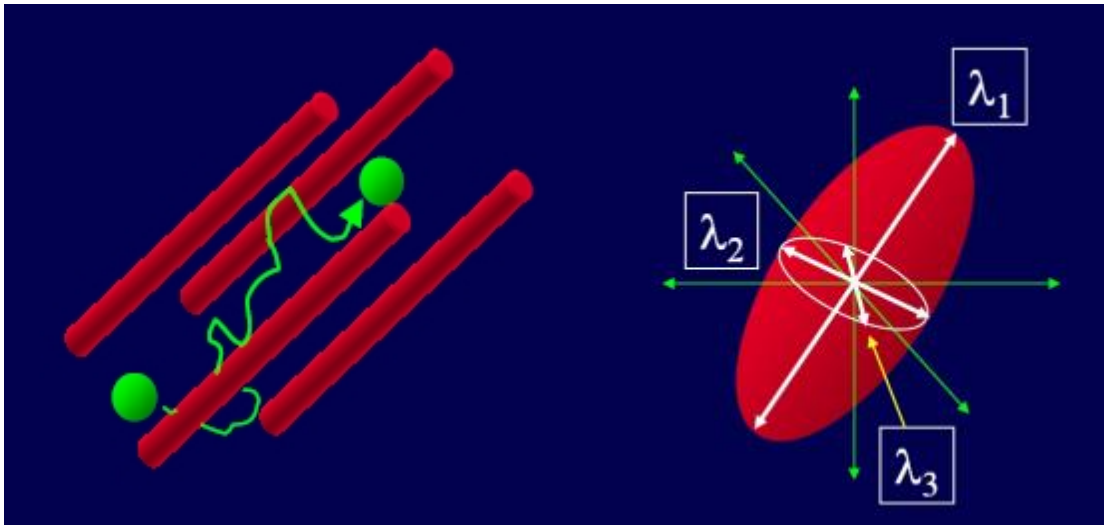
$T \geq 2.46, P_{FDR} = 0.05$

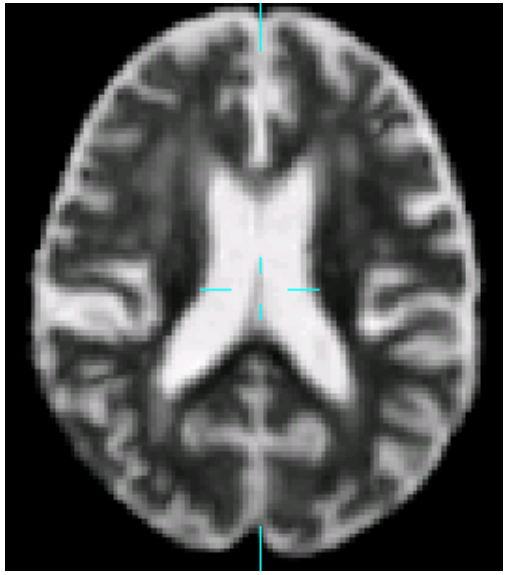
$T \geq 4.72, P_{FWE} = 0.05$

Effects of GB/GF exposure on Axial Diffusivity



DIFFUSION TENSOR IMAGING

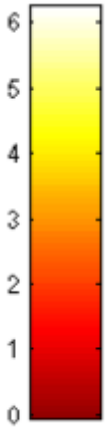


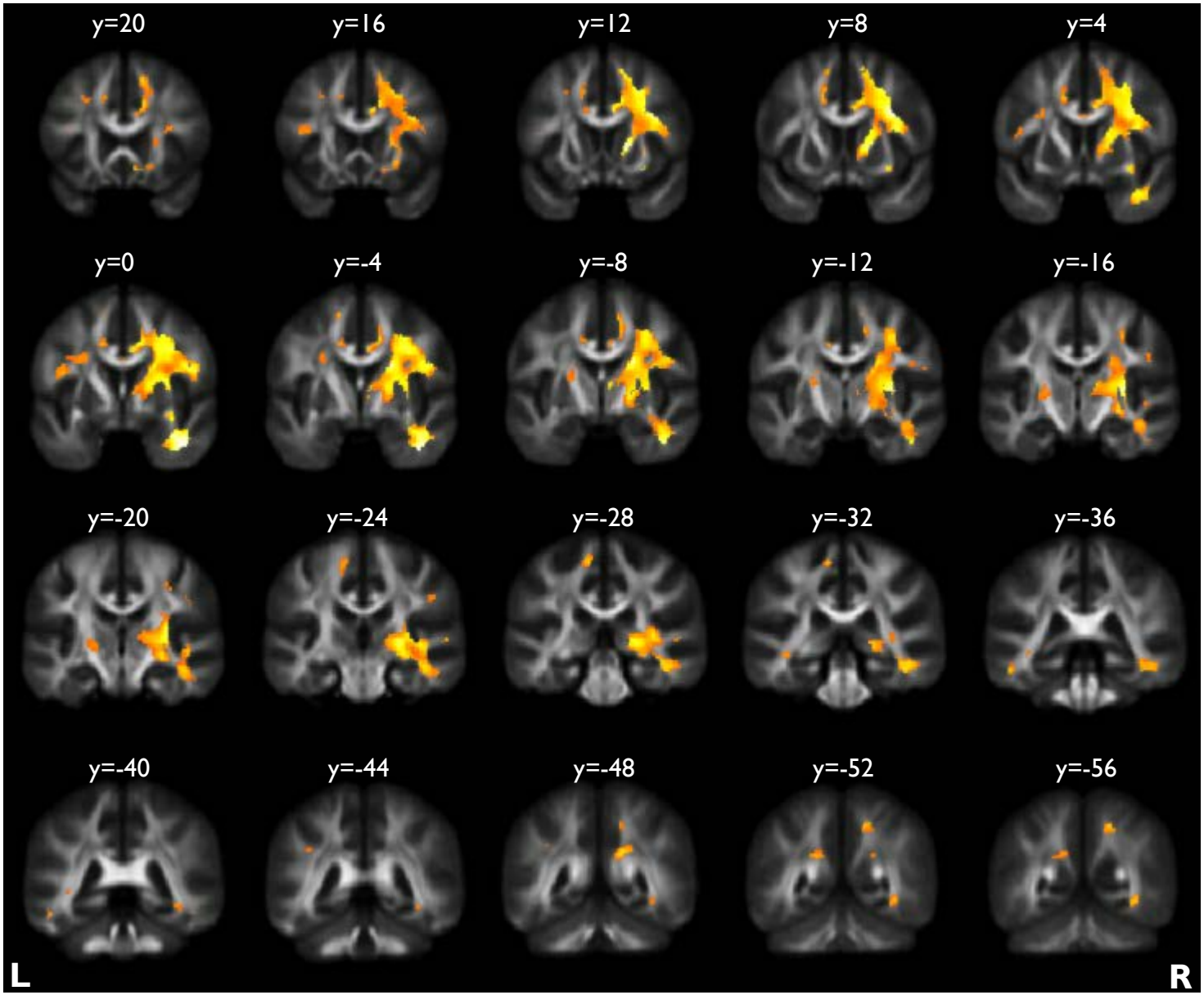


Radial Diffusivity (RD) = $(\lambda_2 + \lambda_3)/2$

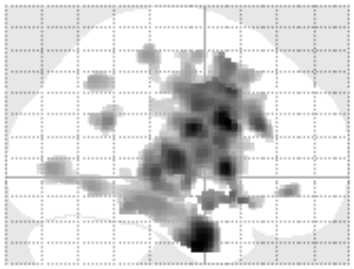
Higher RD has been associated with demyelination and neuroinflammation.

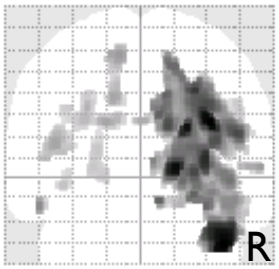
Regions of increased RD in GB/GF exposed veterans vs. unexposed Veterans

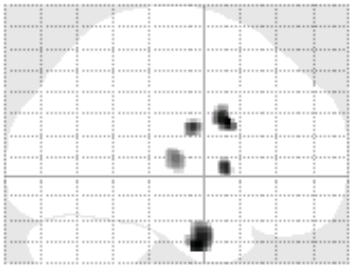


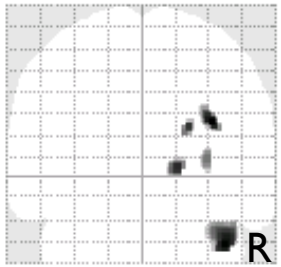


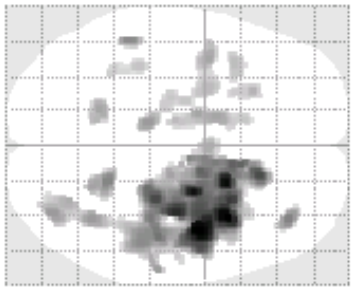
Effects of GB/GF exposure on Radial Diffusivity

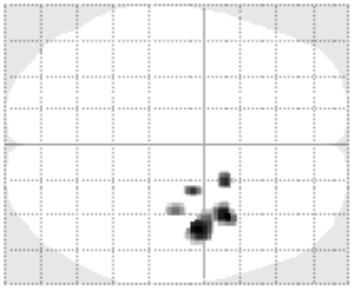








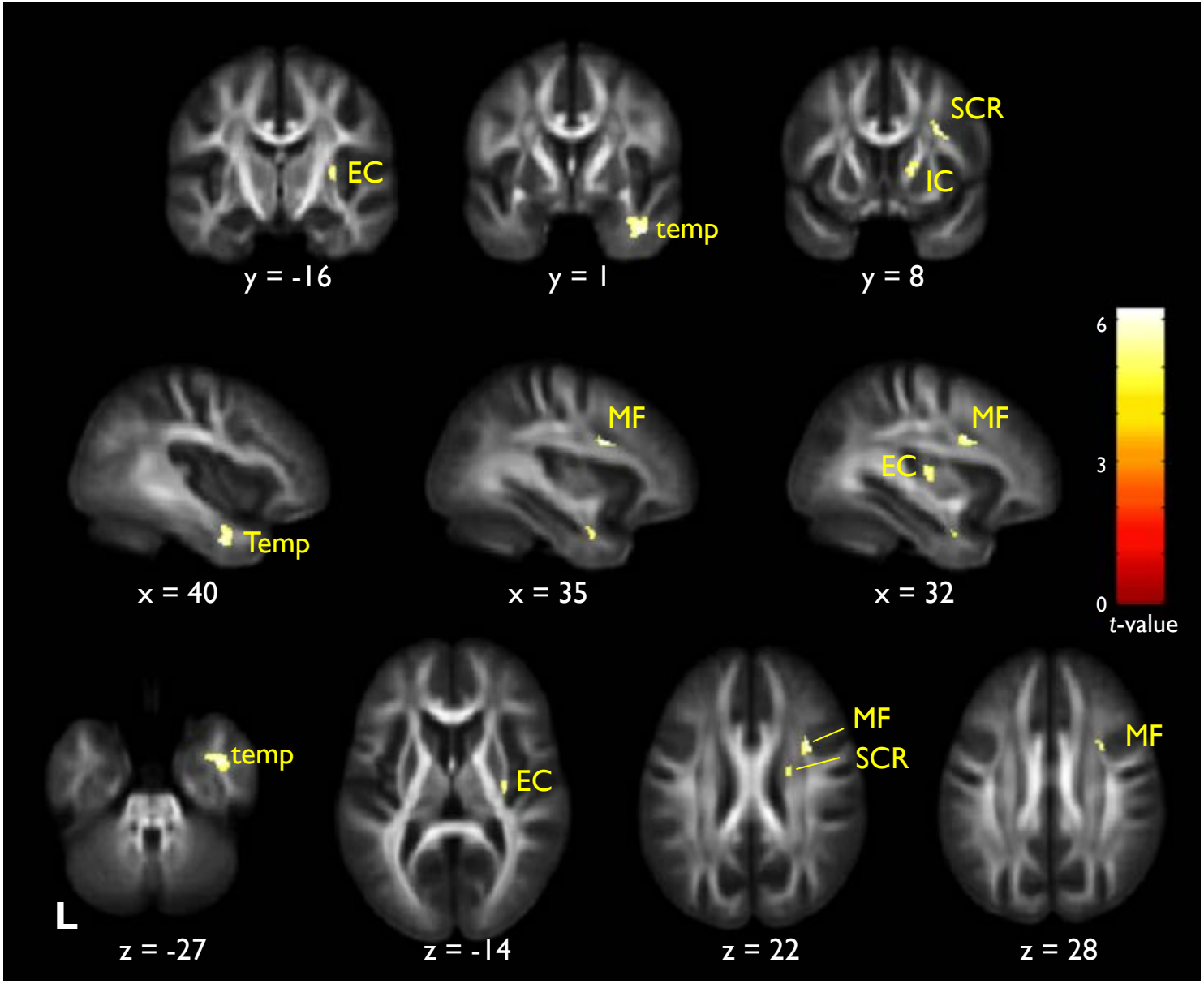




$T \geq 2.46, P_{FDR} = 0.05$

$T \geq 4.72, P_{FWE} = 0.05$

Effects of GB/GF exposure on Radial Diffusivity



Summary

Low-level GB/GF exposure has an effect on:

- GM volume (including HP)
- WM volume
- WM integrity

Summary

Low-level GB/GF exposure has an effect on:

- GM volume (including HP)
- WM volume
- WM integrity

neurobehavioral function ?????

J Physiology (Paris) (1998) 92, 317–323
© Elsevier, Paris

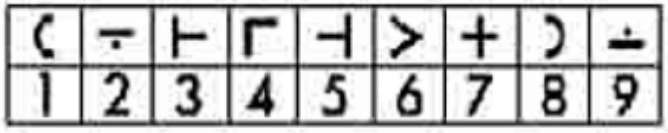
Chronic neurobehavioral and central and autonomic nervous system effects of Tokyo subway sarin poisoning

Kazuhito Yokoyama[a], Shunichi Araki[a], Katsuyuki Murata[a], Mariko Nishikitani[a], Tetsu Okumura[b], Shinichi Ishimatsu[b], Nobukatsu Takasu[b]

[a]*Department of Public Health and Occupational Medicine, Graduate School of Medicine, University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113-0033, Japan*
[b]*Emergency Department, St. Luke's International Hospital, 9-1 Akashi-cho, Chuo-ku, Tokyo 104-0044, Japan*

Abstract — To evaluate delayed (prolonged) neurobehavioral and neurophysiological effects of acute sarin poisoning, nine male and nine female patients of the Tokyo subway sarin poisoning in Japan were examined by neurobehavioral tests, posttraumatic stress disorder (PTSD) checklist, brain evoked potentials, computerized static posturography, and electrocardiographic R-R interval variability, 6–8 months after the poisoning. Their serum cholinesterase activities on the day of the poisoning (March 20, 1995) were 13–131 (mean 72.1) IU/L. The results suggested delayed effects on psychomotor performance, the higher and visual nervous system and the vestibulo-cerebellar system with psychiatric symptoms resulting from PTSD. (©Elsevier, Paris)

- Impaired psychomotor speed (digit symbol)



Environmental Health Perspectives, 2001 109(11):1169-73

Effects of Sarin on the Nervous System in Rescue Team Staff Members and Police Officers 3 Years after the Tokyo Subway Sarin Attack

Yuji Nishiwaki,[1] Kazuhiko Maekawa,[2] Yasutaka Ogawa,[3] Nozomu Asukai,[4] Masayasu Minami,[5] Kazuyuki Omae,[1] and the Sarin Health Effects Study Group

[1]Department of Preventive Medicine and Public Health, School of Medicine, Keio University, Tokyo, Japan; [2]Department of Traumatology and Critical Care, Graduate School of Medicine, University of Tokyo, Tokyo, Japan; [3]National Institute of Industrial Health, Kawasaki, Japan; [4]Department of Social Psychiatry, Tokyo Institute of Psychiatry, Tokyo, Japan; [5]Department of Hygiene and Public Health, Nippon Medical School, Tokyo, Japan

- Impaired memory (backward digit span)

WMS – backwards digit span

J Occup Health 2005; 47: 299–304

Journal of Occupational Health

Effects of Sarin on the Nervous System of Subway Workers Seven Years after the Tokyo Subway Sarin Attack

Koichi MIYAKI[1], Yuji NISHIWAKI[1], Kazuhiko MAEKAWA[2], Yasutaka OGAWA[3], Nozomu ASUKAI[4], Kimio YOSHIMURA[5], Norihito ETOH[1], Yukio MATSUMOTO[1], Yuriko KIKUCHI[1], Nami KUMAGAI[1] and Kazuyuki OMAE[1]

[1]Department of Preventive Medicine and Public Health, School of Medicine, Keio University, [2]Kanto Central Hospital, [3]National Institute of Industrial Health, [4]Tokyo Institute of Psychiatry and [5]Cancer Information and Epidemiology Division, Research Institute, National Cancer Center, Japan

- Impaired memory (backward digit span)
- Impaired psychomotor function (finger tapping)

Effects of GB exposure

	Memory	Psychomotor function
TSSA victims	✓	✓

TSSA = Tokyo Subway Sarin Attack

Neuropsychological Function in Gulf War Veterans: Relationships to Self-Reported Toxicant Exposures

Roberta F. White, PhD,[1,2,3,4,5,6,*] Susan P. Proctor, DSc,[1,3,4] Timothy Heeren, PhD,[1,7] Jessica Wolfe, PhD,[1,2,4,5,8] Maxine Krengel, PhD,[1,2,4] Jennifer Vasterling, PhD,[9,10] Karen Lindem, PhD,[2,4] Kristin J. Heaton, MS,[1] Patricia Sutker, PhD,[9] and David M. Ozonoff, MD, MPH,[1,3,11]

Background *The present study was aimed at (1) exploring evidence of central nervous system (CNS) dysfunction among Gulf War (GW) veterans on neuropsychological tests and (2) examining whether performance on neuropsychological tests was related to specific neurotoxicant exposures experienced in the Gulf.*

Methods *The GW-deployed groups were selected using stratified random sampling methods from two distinct cohorts of GW veterans. A comparison group that had been called up for GW service but deployed to Germany rather than the Gulf also was examined. Neuropsychological function was assessed using a pre-determined battery chosen to include tests known to be highly sensitive to the behavioral effects of the neurotoxicants thought to have been present in the Gulf.*

Results *Self-reported exposures were related to neuropsychological test performance controlling for post-traumatic stress disorder, major depression, and other known covariates of neuropsychological test performance. Results showed that GW-deployed veterans performed more poorly than the Germany-deployed veterans on several specific neuropsychological tests, but after adjustment for multiple comparisons, only the differences in mood complaints remained significant. Within the GW-deployed group, self-reported exposure to chemical warfare agents was associated with poorer performance on cognitive tests involving specific functional domains.*

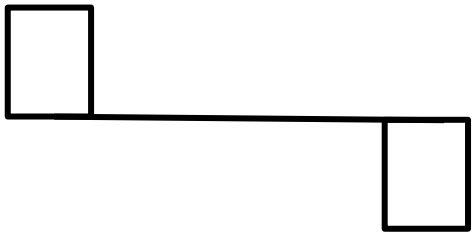
Conclusions *Results provide evidence that there are subtle differences in CNS function among GW-deployed veterans who report chemical warfare agent exposure while in the GW theater.* Am. J. Ind. Med. 40:42–54, 2001.

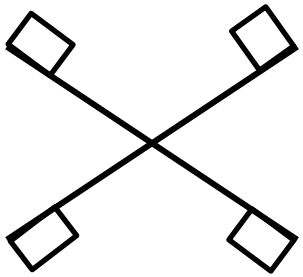
KEY WORDS: neuropsychology, Gulf War veterans, cognitive function, environmental exposures

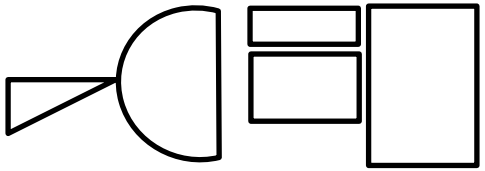
Neuropsychological Function in Gulf War Veterans: Relationships to Self-Reported Toxicant Exposures

Roberta F. White, PhD,[1,2,3,4,5,6,*] Susan P. Proctor, DSc,[1,3,4] Timothy Heeren, PhD,[1,7] Jessica Wolfe, PhD,[1,2,4,5,8] Maxine Krengel, PhD,[1,2,4] Jennifer Vasterling, PhD,[9,10] Karen Lindem, PhD,[2,4] Kristin J. Heaton, MS,[1] Patricia Sutker, PhD,[9] and David M. Ozonoff, MD, MPH,[1,3,11]

- **Impaired memory**
  - backward digit span
  - CVLT – learning Trial 2 & short delayed recall
  - Delayed visual reproduction







Effects of GB/GF exposure

	Memory	Psychomotor function	Visuospatial function
TSSA victims	✓	✓	
GW vets with self-reported exposure	✓		✓

TSSA = Tokyo Subway Sarin Attack

Available online at www.sciencedirect.com
ScienceDirect
NeuroToxicology 27 (2006) 931–939

NeuroToxicology

Effects of sarin and cyclosarin exposure during the 1991 Gulf War on neurobehavioral functioning in US army veterans☆

Susan P. Proctor [a,b,c,d,*,1], Kristin J. Heaton [a,b,d,1], Tim Heeren [a,e], Roberta F. White [a,b,f]

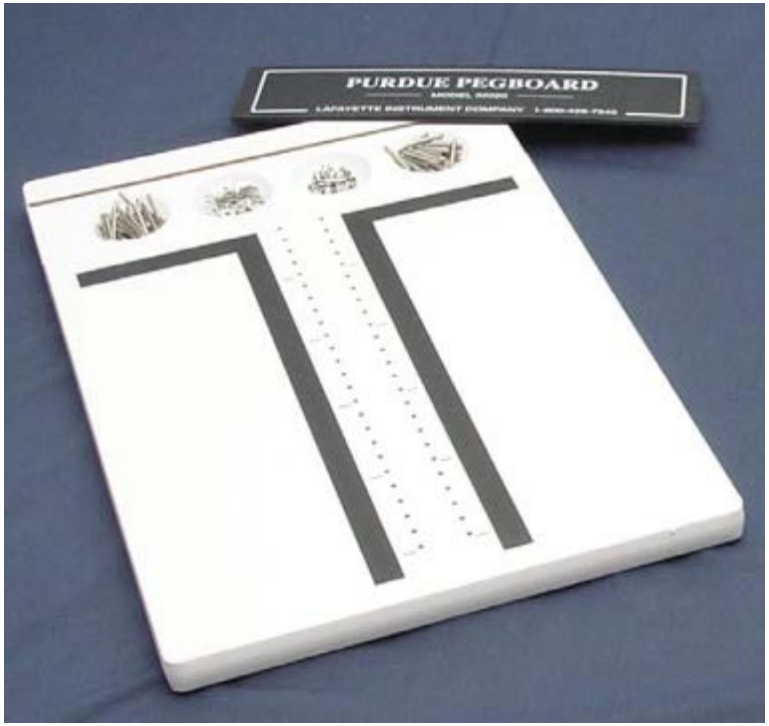
[a] Boston Environmental Hazards Center, VA Boston Healthcare System, Boston, MA, United States
[b] Boston University School of Public Health (Environmental Health), Boston, MA, United States
[c] National Center for PTSD, VA Boston Healthcare System, Boston, MA, United States
[d] Military Performance Division, US Army Research Institute of Environmental Medicine, Natick, MA, United States
[e] Boston University School of Public Health (Biostatistics), Boston, MA, United States
[f] Boston University School of Medicine (Neurology), Boston, MA, United States

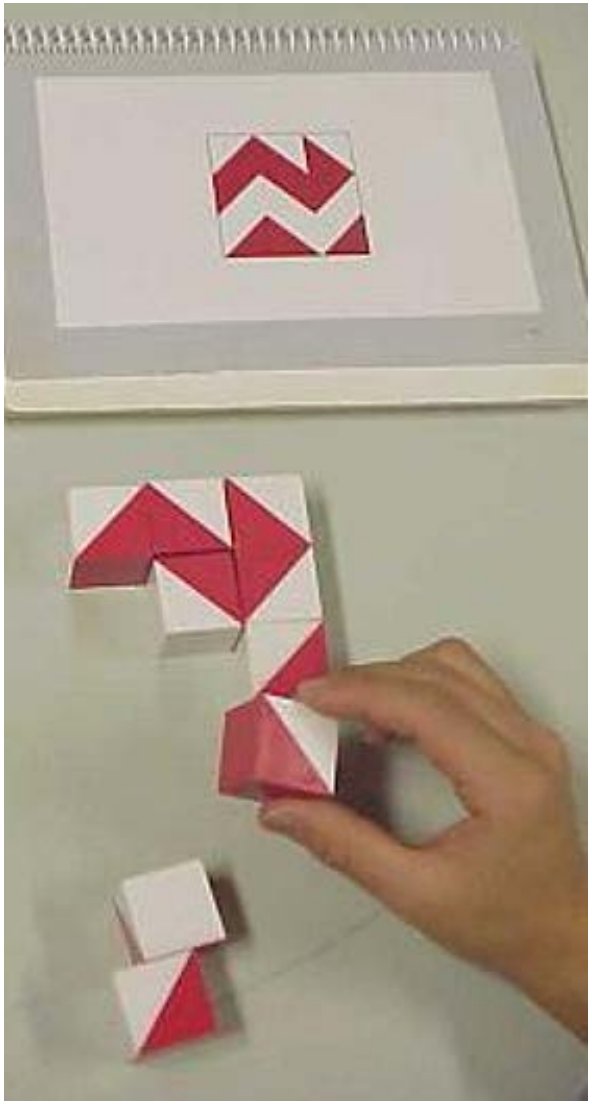
Received 26 May 2006; accepted 2 August 2006
Available online 7 August 2006

Abstract

Background: During the Gulf War (GW), in early March 1991, a munitions dump at Khamisiyah, Iraq, was destroyed. Later, in 1996, the dump was found to have contained the organophosphate chemical warfare agents, sarin and cyclosarin.
Methods: Data collected in a study conducted between 1994 and 1996, before the Khamisiyah incident was publicly disclosed, were used to examine neurobehavioral task performances of GW veterans ($n = 140$) categorized as having received high, moderate, or low-to-no exposure dose levels to sarin and cyclosarin at Khamisiyah, Iraq. Exposure levels were based on modeled estimates of the exposure plume and on troop location information at the time of the Khamisiyah event. Based on recent findings observed in follow-up studies of persons exposed to sarin during the 1995 terrorist attacks in Japan, we hypothesized that exposure to sarin and cyclosarin would be associated with poorer performances on objective neurobehavioral tasks in specific functional domains (particularly in visuospatial abilities and psychomotor functioning) in a dose-dependent manner.
Results: Sarin and cyclosarin exposure was significantly associated with less proficient neurobehavioral functioning on tasks involving fine psychomotor dexterity and visuospatial abilities 4–5 years after exposure.
Conclusions: Findings suggest a dose–response association between low-level exposure to sarin and cyclosarin and specific functional central nervous system effects 4–5 years after exposure.

Keywords: Sarin; Neurobehavioral functioning; Central nervous system effects; Exposure assessment; Gulf War veterans


PURDUE PEGBOARD



Effects of GB/GF exposure

	Memory	Psychomotor function	Visuospatial function
TSSA victims	✓	✓	
GW vets with self-reported exposure	✓		✓
GW vets with predicted exposure		✓	✓

TSSA = Tokyo Subway Sarin Attack

California Verbal Learning Test

	Exposed	Unexposed
N	107	317
No. Female (%)	11 (10%)	36 (11%)
Age, years	46.4 ± 8.5	46.3 ± 9.5
Education, years	14.8 ± 2.2	14.9 ± 2.1
No. current PTSD diagnosis (%)	10 (9%)	42 (13%)
No. CMI cases (%)	68 (64%)	217(69%)

PTSD: Posttraumatic Stress Disorder
CMI: Chronic Multisymptom Illness as defined by Fukuda et al. (1998)

California Verbal Learning Test

	Exposed	Unexposed
Trial 1	5.9 (1.9)	6.2 (1.8)
Trials 1-5	47.5 (11.0)	49.8 (10.2)
Free Recall		
Short delay	10.1 (3.5)	10.5 (3.3)
Long delay	10.7 (3.3)	11.0 (3.4)
Cued Recall		
Short delay	11.4 (2.8)	11.7 (2.9)
Long delay	11.5 (3.1)	11.8 (3.0)
Recognition Memory	0.72 (0.25)	0.75 (0.25)

California Verbal Learning Test

MANCOVA accounting for age, sex, education, PTSD, CMI

age:	$F_{8,410}=4.56$, $p<0.001$
sex:	$F_{8,410}=2.28$, $p=0.02$
education:	$F_{8,410}=2.53$, $p=0.01$
PTSD:	$F_{8,410}=2.51$, $p=0.01$
CMI:	$F_{8,410}=2.51$, $p=0.01$

No overall effect of GB/GF exposure: $F_{8,410}=0.97$, $p=0.46$

California Verbal Learning Test

	Exposed	Unexposed
Trial 1	5.9 (1.9)	6.2 (1.8)
Trials 1-5*	47.5 (11.0)	49.8 (10.2)
Free Recall		
Short delay	10.1 (3.5)	10.5 (3.3)
Long delay	10.7 (3.3)	11.0 (3.4)
Cued Recall		
Short delay	11.4 (2.8)	11.7 (2.9)
Long delay	11.5 (3.1)	11.8 (3.0)
Recognition Memory	0.72 (0.25)	0.75 (0.25)

*$F_{1,417}$= 4.51, p=0.03

Continuous Performance Test

	Exposed	Unexposed
N	88	261
No. Female (%)	9 (10%)	30 (12%)
Age, years	46.2 ± 8.4	46.3 ± 9.9
Education, years	14.9 ± 2.3	14.9 ± 2.2
No. current PTSD diagnosis (%)	9 (10%)	35(13%)
No. CMI cases (%)	56 (64%)	168 (64%)

PTSD: Posttraumatic Stress Disorder
CMI: Chronic Multisymptom Illness as defined by Fukuda et al. (1998)

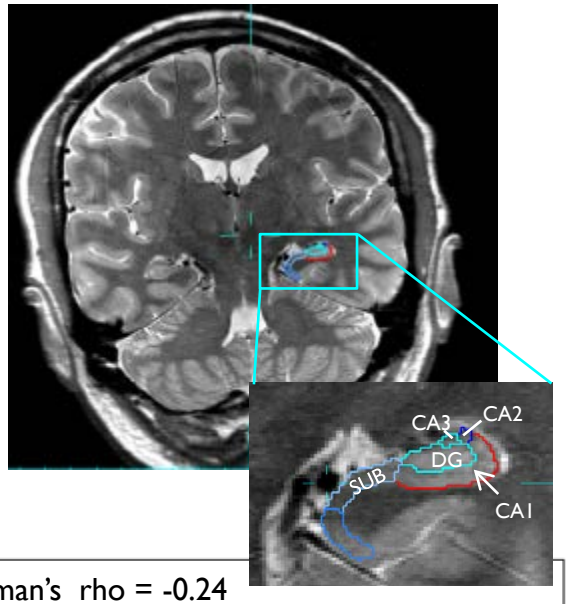
Continuous Performance Test

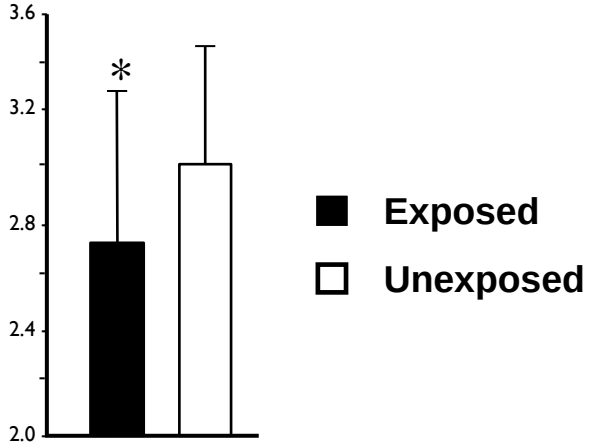
	Exposed	Unexposed
# Omissions†	3.1 (7.5)	2.0 (5.1)
# Commissions	11.7 (6.3)	11.7 (7.4)
Hit RT (ms)*	430.8 (73.9)	402.3 (62.2)

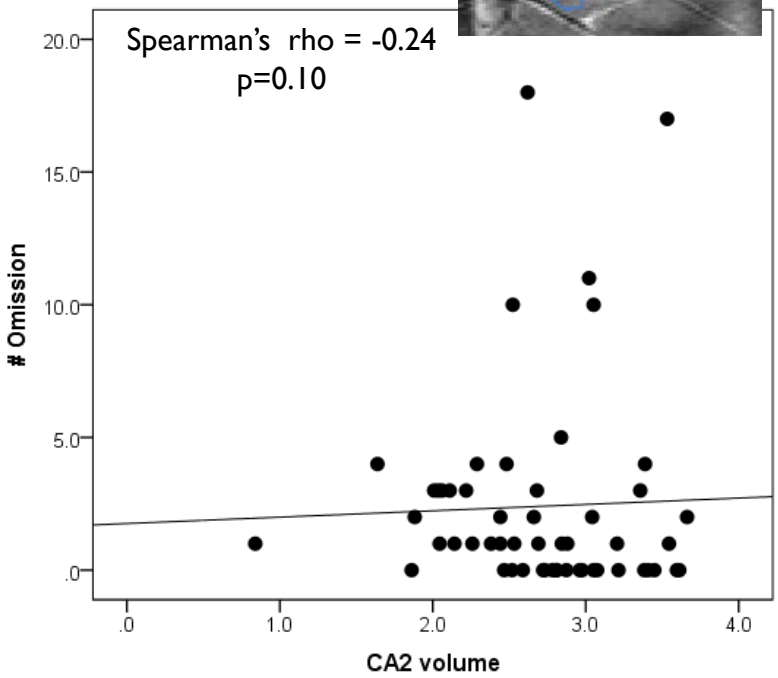
*$F_{1,342}$= 13.16, p<0.001
† $F_{1,342}$= 2.41, p=0.12

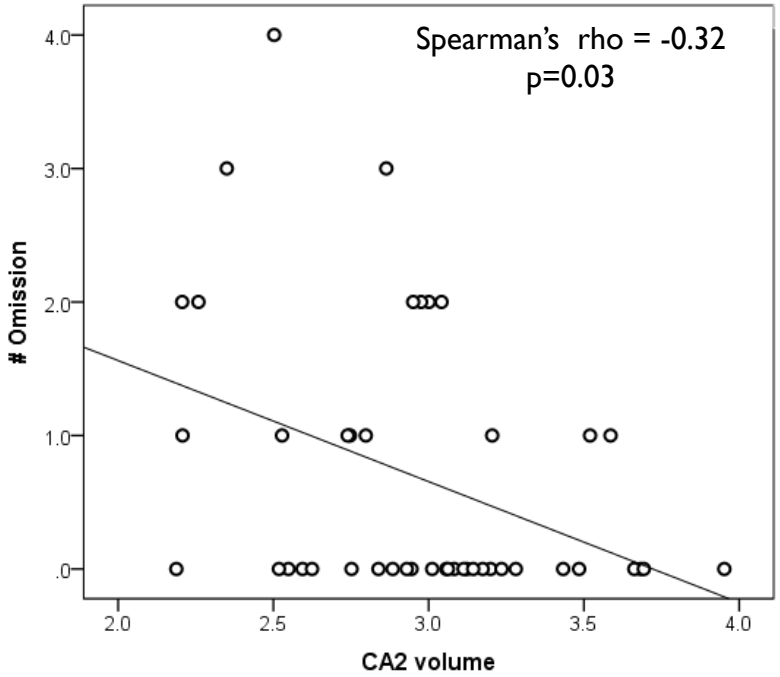
Overall effect of GB/GF exposure in MANCOVA: $F_{3,340}$=6.35, p<0.001

Relationship between CA2 and attention









Effects of GB/GF exposure

	Memory	Psycho-motor	Visuo-spatial	Attention
TSSA victims	✓	✓		
GW vets with self-reported exposure	✓		✓	
GW vets with predicted exposure	✓	✓	✓	✓

TSSA = Tokyo Subway Sarin Attack

Summary

Low-level GB/GF exposure has an effect on:

- GM volume (including HP)
- WM volume
- WM integrity
- neurobehavioral/cognitive function
  - memory
  - psychomotor function
  - visuospatial ability
  - attention

Future Avenues of Research

1) Is there on-going GM and WM atrophy and insult to WM integrity?

2) Are GB/GF exposed veterans at risk for accelerated aging and neurodegenerative diseases?

3) Are there therapies that might slow or reverse these effects?

Acknowledgements

GW Veteran participants
Mike Weiner
Stephen Kriger
Daniel Stevens
Peter Ng
Shannon Buckley
Linda Abadjian
Jennifer Hlavin and her staff at CIND
Diana Truran Sacrey and her staff at CIND
Scott Seggerman and Andrew Ricci at DMDC
Larry Sippos and his staff at Force Readiness and Health Assurance Force Health Protection & Readiness Defense Health Agency Office of the Assistant Secretary of Defense (Health Affairs) Defense Health Headquarters

Continuous Performance Test

MANCOVA accounting for age, sex, education, PTSD, CMI

age:	$F_{5,338}=4.27$, $p=0.001$
sex:	$F_{5,338}=1.80$, $p=0.11$
education:	$F_{5,338}=0.86$, $p=0.51$
PTSD:	$F_{5,338}=1.17$, $p=0.32$
CMI:	$F_{5,338}=3.61$, $p=0.003$

Overall effect of GB/GF exposure: $F_{5,338}=4.73$, $p<0.0001$