EFFECTS OF MILITARY SERVICE ON THE BRAIN

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UNPUBLISHED DATA IS REMOVED FROM THIS SLIDE SET

EFFECTS OF MILITARY SERVICE ON THE BRAIN

- Military service, especially combat
  - associated with impaired health and function
- Service in the Persian Gulf War
  - associated with
    - subjective symptoms
    - neuropsychological and functional impairments
- These problems have caused great distress to soldiers, veterans and their families

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MILITARY SERVICE
EXPOSURES WHICH MAY AFFECT THE BRAIN

- Physical exposures
  - Medications
  - Pesticides
  - Vaccines
  - Sarin
- Psychological exposures
  - Stress
  - Traumatic events

IMPORTANCE OF REPLICATION

- Scientific results are usually first obtained on a small sample of the population.
- However, for a scientific finding to be robust and "generalizable"
  - Meaning, that the finding applies widely to the population
- The finding must be "replicated" (i.e. repeated)
  - In a different population of subjects
  - By different investigators
- Findings widely replicated become widely accepted

EARLY WORK AT OUR MEDICAL CENTER

- 1987: MRS of the brain
  - Stroke
  - Brain tumors
  - Epilepsy
  - Alzheimer's Disease
- 1990 : Studies of Post Traumatic Stress Disorder
  - Hippocampal volume
  - MRS: NAA

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Publications concerning PTSD

- Schuff, N., Marmar, C.R., Weiss, D.S., Neylan, T.C., Schoenfeld, F., Fein, G., and Weiner, M.W.: Reduced Hippocampal Volume and N-Acetyl Aspartate in Posttraumatic Stress Disorder. In: Annals of the New York Academy of Sciences. Supplement on Psychobiology of Posttraumatic Stress Disorders, 821:516-520, 1997.
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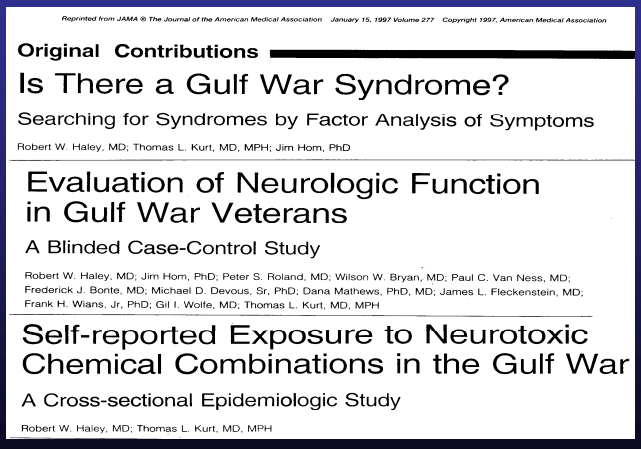
RESULTS PRESENTED TODAY
Some represent replications
Some represent new findings: need to be repeated

- NAA in basal ganglia in GWI
- Effects of Sarin exposure
  - Symptoms and neuropsychological tests
  - Brain volumes and metabolites
- Chronic multisystem illness
  - Symptoms and neuropsychological tests
  - Brain volumes and metabolites
- Post traumatic stress disorder (PTSD)
  - Symptoms and neuropsychological tests
  - Brain volumes and metabolites

Jan. 15, 1997 Issue of JAMA



Original Contributions

Is There a Gulf War Syndrome?

Searching for Syndromes by Factor Analysis of Symptoms

Robert W. Haley, MD; Thomas L. Kurt, MD, MPH; Jim Hom, PhD

Evaluation of Neurologic Function in Gulf War Veterans

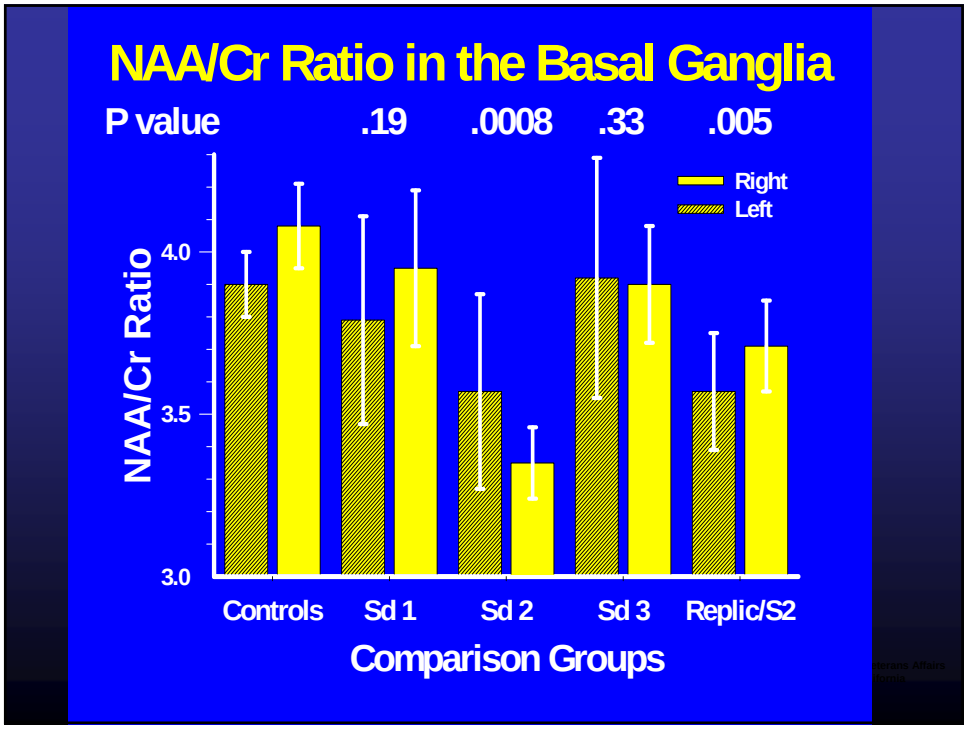
A Blinded Case-Control Study

Robert W. Haley, MD; Jim Hom, PhD; Peter S. Roland, MD; Wilson W. Bryan, MD; Paul C. Van Ness, MD; Frederick J. Bonte, MD; Michael D. Devous, Sr, PhD; Dana Mathews, PhD, MD; James L. Fleckenstein, MD; Frank H. Wians, Jr, PhD; Gil I. Wolfe, MD; Thomas L. Kurt, MD, MPH

Self-reported Exposure to Neurotoxic Chemical Combinations in the Gulf War

A Cross-sectional Epidemiologic Study

Robert W. Haley, MD; Thomas L. Kurt, MD, MPH



MRI/MRS

Pilot study for proposal: Preliminary 1H MRS measures in the right basal ganglia (n=10/group)

Measure	GWI	CONTROLS	% change	p (t-test)
NAA/Cr	3.62 ± 0.41	4.06 ± 0.72	-11	**0.05**
NAA/Cho	3.59 ± 0.92	3.90 ± 0.45	-8	0.16
Cho/Cr	1.10 ± 0.44	1.05 ± 0.22	+5	0.38
NAA [a.u.]	568 ± 160	633 ± 79	-10	0.12

a.u. = arbitrary units

GWI from our GW clinic Controls from lab staff

GWI STUDIES IN SAN FRANCISCO
Recruitment and Classification

- Any veteran of the Gulf War is eligible
- Subjects classfied after entry
- CDC criteria
  - Musculoskeletal pain
  - Fatigue
  - Neurocognitive dysfunction
- Health Questionnaires
  - 3 questionnaires on 3 separate occasions
  - 3 CDC symptoms & 6 dummy questions
- Classification
  - Gulf War Ill (GWI)
    - Endorsed two symptoms on all three questionnaires
  - Gulf War Veteran (GWV; aka Control)
    - Endorsed no single symptom more than once
  - Intermediate
    - All other combinations

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RECRUITMENT

- Referrals from GWI clinics
- Ads in veterans magazines
- 32,000 letters to Gulf War veterans (from DOD list)
- 2100 subjects telephone-screened for research
- 319 subjects enrolled in DOD 1.5T study
  - 279 completed study and had usable data.
- 162 subjects came to SFVAMC for VA 4T study
  - 158 completed study and had usable data.

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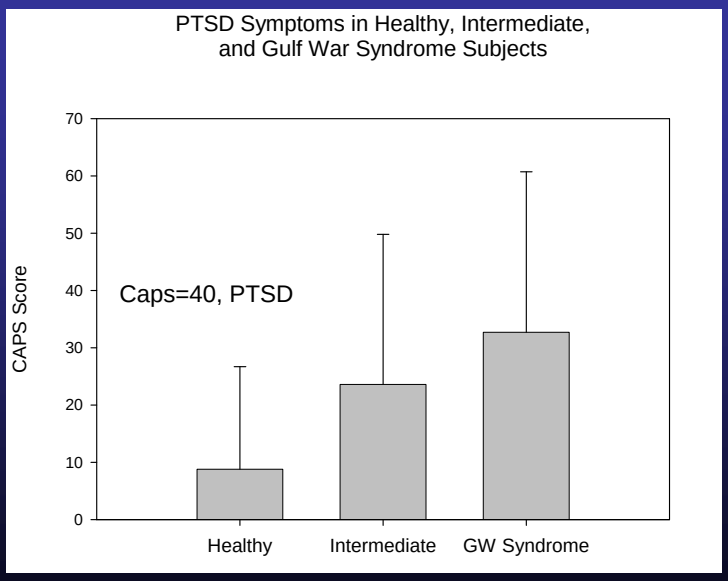
Participants 1.5 T Cohort

All Subjects:

	Controls	Intermediate	GWI	Total
Male	83	68	34	185
Female	10	4	13	27
	93	72	47	212

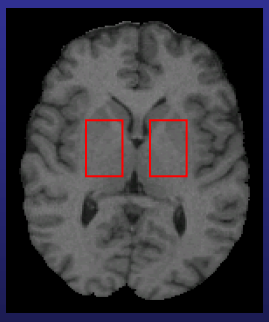
Syndrome Two Only:

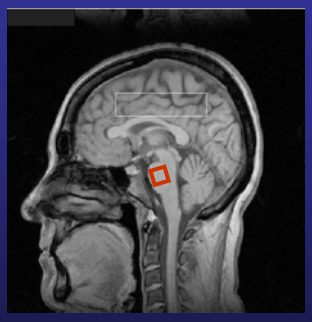
	Controls	Intermediate	GWI	Total
Male	1	7	10	18
Female	1	1	5	7
	2	8	15	25

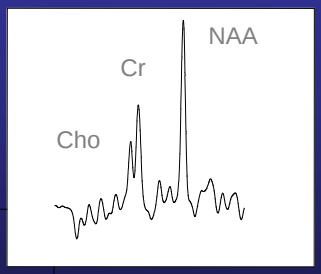


Group ANOVA: F=14.4, p< .001

MRI/MRS







20 x 40 x 15 mm^3 17 x 17 x 17 mm^3

To replicate Dr. Haley's study, 1H MR spectra are obtained from left and right basal ganglia and pons.

Three-Group Comparisons males only

Left Basal Ganglia

	n	NAA	Creatine	Choline
Vets	47	6.78 ± 0.92	4.08 ± 0.50	1.48 ± 0.20
Intermediates	37	6.78 ± 1.08	4.17 ± 0.43	1.42 ± 0.19
Illness	24	6.95 ± 0.70	4.16 ± 0.41	1.47 ± 0.19
Vets vs. Illness*		n.s.	n.s.	n.s.
Vets vs. Intermediates*		n.s	n.s.	n.s.
Intermediates vs. Illness*		n.s.	n.s.	n.s.

	n	NAA/Cre	NAA/Cho	Cho/Cre	NAA/(Cho+Cre)
Vets	47	1.66 ± 0.12	4.58 ± 0.44	0.36 ± 0.03	1.22 ± 0.09
Intermediates	37	1.62 ± 0.17	4.79 ± 0.61	0.34 ± 0.04	1.21 ± 0.12
Illness	24	1.67 ± 0.12	4.77 ± 0.51	0.35 ± 0.04	1.24 ± 0.08
Vets vs. Illness*		n.s.	0.11	n.s.	n.s.
Vets vs. Intermediates*		n.s.	n.s.	n.s.	n.s.
Intermediates vs. Illness*		n.s.	n.s.	n.s.	n.s.

*p-value = two-tail

Three-Group Comparisons males only

Pons

	n	NAA	Creatine	Choline
Vets	26	3.13 ± 0.56	1.40 ± 0.22	0.92 ± 0.15
Intermediates	27	2.91 ± 0.52	1.31 ± 0.26	0.80 ± 0.16
Illness	12	3.02 ± 0.60	1.38 ± 0.32	0.85 ± 0.19
Vets vs. Illness*		n.s.	n.s.	n.s.
Vets vs. Intermediates*		n.s.	n.s.	n.s.
Intermediates vs. Illness*		n.s.	n.s.	n.s.

	n	NAA/Cre	NAA/Cho	Cho/Cre	NAA/(Cho+Cre)
Vets	26	2.25 ± 0.39	0.66 ± 0.10	3.44 ± 0.46	1.36 ± 0.19
Intermediates	27	2.25 ± 0.32	0.62 ± 0.12	3.73 ± 0.72	1.39 ± 0.17
Illness	12	2.29 ± 0.69	0.63 ± 0.13	3.60 ± 0.63	1.39 ± 0.33
Vets vs. Illness*		n.s.	n.s.	n.s.	n.s.
Vets vs. Intermediates*		n.s.	n.s.	n.s.	n.s.
Intermediates vs. Illness*		n.s.	n.s.	n.s.	n.s.

*p-value = two-tail

Syndrome II (Ill + Int) vs. Vets males only

Left Basal Ganglia

	n	NAA	Creatine	Choline
Veterans	47	6.78 ± 0.92	4.08 ± 0.50	1.48 ± 0.20
Syndrome II	14	7.15 ± 0.69	4.29 ± 0.43	1.42 ± 0.17
Syndrome II vs. Vets*		n.s.	n.s.	n.s.

	n	NAA/Cre	NAA/Cho	Cho/Cre	NAA/(Cho+Cre)
Veterans	47	1.66 ± 0.12	4.58 ± 0.44	0.36 ± 0.03	1.22 ± 0.09
Syndrome II	14	1.67 ± 0.14	5.08 ± 0.70	0.33 ± 0.05	1.25 ± 0.10
Syndrome II vs. Vets*		n.s.	0.02	0.03	n.s.

*p-value = two-tail

Syndrome II (Ill + Int) vs. Vets males only

Pons

	n	NAA	Creatine	Choline
Veterans	26	3.13 ± 0.56	1.40 ± 0.22	0.91 ± 0.15
Syndrome II	7	3.17 ± 0.53	1.37 ± 0.36	0.83 ± 0.15
Syndrome II vs. Vets*		n.s.	n.s.	n.s.

	n	NAA/Cre	NAA/Cho	Cho/Cre	NAA/(Cho+Cre)
Veterans	26	2.25 ± 0.39	3.44 ± 0.46	0.66 ± 0.10	1.35 ± 0.19
Syndrome II	7	2.40 ± 0.56	3.85 ± 0.60	0.63 ± 0.10	1.47 ± 0.27
Syndrome II vs. Vets*		n.s.	0.06	n.s.	n.s.

*p-value = two-tail

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ARYLESTERASES
(metabolize organophosphates)

Domain	*GW Vet*	*Intermed*	*GW Ill*	*P-value Vet v Ill*
Paraoxonase	**963.1** (662.5) N=63	**867.0** (483.8) N=45	**938.3** (666.9) N=41	**0.9 ns**
Diazoxonase	**10102.6** (3633.5) N=63	**9122.5** (3278.8) N=45	**10404.4** (3701.3) N=41	**0.6 ns**

no sign of significant results between GWV and GWI.

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PARAOXONASE OR DIAZAOXONASE

- There were no paraoxonase or diazoxonase effects for either GWI (by either CDC or Syndrome II diagnosis).
- There were no results in the log transformed data.
- No PTSD effects were observed.

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

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Abstract

Background: In March 1991, a munitions storage complex at Khamisiyah, Iraq was destroyed, potentially exposing more than 100,000 US troops to low levels of the organophosphate nerve agents sarin and cyclosarin. Little is known about the neurophysiological effects of low-dose exposure to sarin/cyclosarin in humans, although some research has indicated subtle but persistent neurobehavioral and neurochemical changes in individuals exposed to sarin/cyclosarin at levels insufficient to produce obvious clinical symptoms. However, the neuroanatomical correlates of these changes are unclear. The current study examined the association between modeled estimates of sarin/cyclosarin exposure levels and volumetric measurements of gross neuroanatomical structures in 1991 Gulf War veterans with varying degrees of possible low-level sarin/cyclosarin exposure.

Methods: Twenty-six GW-deployed veterans recruited from the Devens Cohort Study participated. Magnetic resonance images of the brain were acquired and analyzed using morphometric techniques, producing volumetric measurements of white matter, gray matter, right and left lateral ventricles, and cerebrospinal fluid. Volumetric data were analyzed using exposure estimates obtained from refined models of the 1991 Khamisiyah presumed exposure hazard area.

Results: Binary comparisons of sarin/cyclosarin 'exposed' ($N = 13$) and 'unexposed' ($N = 13$) veterans revealed no differences in volumetric measurements of discrete brain tissues. However, linear trend analyses showed a significant association between higher levels of estimated sarin/cyclosarin exposure and both reduced white matter (adjusted parameter estimate = −4.64, $p < 0.0001$) and increased right lateral ventricle (adjusted parameter estimate = .11, $p = 0.0288$) and left lateral ventricle (adjusted parameter estimate = .13, $p < 0.0001$) volumes.

Conclusions: These findings suggest subtle but persistent central nervous system pathology in Gulf War veterans potentially exposed to low levels of sarin/cyclosarin and argue for further investigation of the long-term effects of low-dose sarin/cyclosarin exposures in humans.

Keywords: Magnetic resonance imaging; Morphometric analyses; Brain; Central nervous system; Chemical warfare agents; Sarin; Cyclosarin; Gulf War veterans; Khamisiyah; Iraq

1. Introduction

Sarin (GB; *o*-isopropyl methylphosphonofluoridate) and cyclosarin (GF; cyclohexyl methylphosphonofluoridate) are powerful organophosphate nerve agents that inhibit acetylcholinesterase, producing a characteristic cholinergic reaction (i.e., miosis, nausea, vomiting, weakness, respiratory paralysis, convulsions) designed to be incapacitating or lethal upon acute

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[1] The current primary affiliation for Drs. Heaton and Proctor is the US Army Research Institute of Environmental Medicine. The work described in the manuscript was performed while they both were at the VA Boston Healthcare System.

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EFFECTS OF SARIN ON THE BRAIN

- Follows up from work of Roberta White
  - Neuropsychological impairments
  - Heaton et al: Reduced WM in high-exposed compared to low exposed
    - But no differences between exposed and unexposed
- We obtained Sarin exposure information from the DOD (Larry Sipos)
- Study 1: Sarin exposure in the 1.5 T cohort
  - Retrospective analysis of existing data to replicate Heaton
- Study 2: Sarin exposure in the 4 T cohort
  - Prospective study to replicate our 1.5 T data

DEMOGRAPHICS OF SARIN EXPOSED/NON EXPOSED: 1.5T

	Exposed (N=40)	Unexposed (N=40)
Age, mean (S.D.)	44.0 (10.2)	42.7 (9.3)
No. left-handed or ambidextrous (%)	7 (18%)	5 (13%)
No. female (%)	7 (18%)	7 (18%)
No. White (%)	26 (65%)	19 (48%)
No. Married (%)	19 (48%)	25 (63%)
Years of education	14.9 (3.7)	14.5 (2.0)
No. with less than college education	5 (13%)	6 (15%)
Military status during Gulf War		
No. activity duty (%)	30 (75%)	31 (78%)
No. National Guard (%)	5 (13%)	2 (5%)
No. Reserves (%)	5 (13%)	7 (18%)
Years in the military	14.6 (9.2)	14.1 (7.8)
No. with service-connected disability (%)	18 (45%)	22 (55%)
Avg. percent VA disability (range)	38.6% (10-100%)	40.3% (5-100%)
No. currently employed (%)	26 (65%)	28 (70%)
No. with history of alcohol problem (%)	19 (48%)	22 (55%)

CMI, chronic multisymptom illness (as defined by Fukuda et al., 1998); PTSD, post-traumatic stress disorder; CAPS, Clinician Administered PTSD scale; MDD, major depression

Relationship between Sarin exposure and Haley factor analysis-derived syndromes in 1.5T Cohort

Hayley Syndromes	Exposed No affected (%)	Unexposed No affected (%)	χ^2	*p*-value
1 "impaired cognition"	3/40 (8)	3/40 (8)	0.00	1.00
2 "confusion-ataxia"	5/40 (13)	4/40 (10)	0.12	0.73
3 "arthro-myo-neuropathy"	4/40 (10)	5/40 (13)	0.12	0.73
4 "phobia-apraxia"	5/40 (13)	4/40 (10)	0.12	0.73
5 "fever-adenopathy"	2/40 (5)	2/40 (5)	0.00	1.00
6 "weakness-incontinence"	1/40 (3)	2/40 (5)	0.34	0.56

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EFFECTS OF SARIN EXPOSURE ON NEUROPSYCHOLOGICAL TEST PERFORMANCE: 1.5T Cohort (1)

	All Exposed		All Unexposed		All Exposed vs. All Unexposed		32 Exposed vs. 26 Unexposed	
	N	Mean (SD)	N	Mean (SD)	χ^2	*p*-value	χ^2	*p*-value
General Verbal Intelligence								
WAIS-III VCI	39	102.3 (12.1)	40	107.1 (13.7)	1.90	0.17	1.40	0.24
WRAT-III reading	40	47.8 (4.9)	40	48.4 (4.5)	0.17	0.68	0.21	0.65
Attention								
Continuous Performance Test[a]	28	408.5 (77.2)	32	382.0 (48.2)	1.44	0.23	1.64	0.20
TMT A, time to complete[a]	40	30.1 (10.1)	40	30.0 (11.3)	0.12	0.73	0.21	0.65
WAIS-III Digit Spans	39	16.5 (4.4)	40	16.5 (4.6)	0.08	0.78	0.02	0.88
Executive Function								
TMT B, time to complete[a]	40	66.1 (29.7)	40	67.3 (31.2)	0.00	0.99	0.01	0.91
Short Categoy Test[a]	38	28.0 (17.1)	40	25.2 (12.9)	0.33	0.57	0.40	0.53
COWAT, FAS total correct	40	40.7 (10.8)	40	38.2 (9.1)	0.96	0.33	1.53	0.22

VCI: Verbal Comprehension Index; TMT: Trail Making Test; COWAT: Controlled Oral Word Association Test; CVLT-II: California Verbal Learning Test-II, BVMT-R: Brief Visual Memory Test-R
[a]lower scores indicate better performance
[b]group difference no longer significant after the TOMM failures are excluded from analysis (χ^2=2.48, p=0.12)

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EFFECTS OF SARIN EXPOSURE ON NEUROPSYCHOLOGICAL TEST PERFORMANCE in 1.5T Cohort (2)

		EXPOSED		UNEXPOSED				
Psychomotor Function								
WAIS-III Digit Symbol, coding	40	66.7 (18.9)	40	71.4 (14.2)	1.43	0.23	0.24	0.63
Grooved Pegboard, dominant[a]	40	70.6 (15.6)	40	70.6 (12.0)	0.00	0.99	0.49	0.49
Grooved Pegboard, non-dominant[a]	40	78.9 (24.5)	40	73.6 (12.1)	0.95	0.33	0.24	0.62
Visuospatial abilities								
WAIS-III Block Design	40	41.3 (12.9)	40	45.2 (11.4)	1.87	0.17	0.43	0.51
Memory								
CVLT-II, short delay free recall	38	10.8 (3.7)	38	11.7 (3.2)	1.19	0.27	2.03	0.15
CVLT-II, long delay free recall	**38**	**10.9 (3.6)**	**38**	**12.0 (2.8)**	**1.31**	**0.25**	**4.33[b]**	**0.04[b]**
WMS-III Logical Memory, delayed Recall	40	24.4 (9.3)	40	26.0 (8.3)	0.48	0.49	0.93	0.34
BVMT-R, total recall	40	22.8 (6.1)	40	25.4 (4.5)	3.30	0.07	2.10	0.15
BVMT-R, delayed recall	40	9.2 (1.8)	40	9.4 (1.9)	0.44	0.51	0.02	0.89
Test of Memory Malingering (TOMM)								
Trial 1	38	47.0 (5.0)	40	48.4 (2.4)	0.15	0.69	0.58	0.45
Trial 2	**38**	**48.8 (3.2)**	**40**	**50.0 (0.2)**	**6.69**	**0.01**	**5.46**	**0.02**
Retention	38	48.8 (3.6)	40	49.9 (0.3)	2.67	0.10	1.44	0.23

VCI: Verbal Comprehension Index; TMT: Trail Making Test; COWAT: Controlled Oral Word Association Test; CVLT-II: California Verbal Learning Test-II, BVMT-R: Brief Visual Memory Test-R

[a]lower scores indicate better performance

[b]group difference no longer significant after the TOMM failures are excluded from analysis (χ^2=2.48, p=0.12)

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RETROSPECTIVE STUDY EFFECTS OF SARIN EXPOSURE IN BRAIN TISSUE: 1.5 T

	Exposed	Unexposed	F-value	p-value
Total GM[a]	654.14 (72.92)	675.89 (67.43)	7.68	0.007
Total WM[a]	539.28 (62.59)	521.53 (71.89)	0.70	0.95
Total CSF[a]	386.72 (131.31)	332.58 (100.48)	2.85	0.10
Hippocampus[b]	5.09 (0.67)	5.42 (0.69)	6.41	0.01
ICV[a]	1571.85 (178.37)	1530.01 (175.31)	1.39	0.24

[a]data available for 36 exposed and 40 unexposed subjects

[b]data available for 35 exposed and 40 unexposed subjects

FAILED TO REPLICATE WM CHANGES: HEATON ET AL.

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CORRELATIONS BETWEEN BRAIN TISSUE VOLUME AND NEUROPSYCOLOGICAL TESTS: 1.5T Cohort

	Hippocampal volume		Total GM volume		Total WM volume	
	Unexposed (N=40)	Exposed (N=32)	Unexposed (N=40)	Exposed (N=32)	Unexposed (N=40)	Exposed (N=32)
WAIS-III VCI	**0.28**	**0.48****	**0.13**	**0.27**	**0.38***	**0.22**
TMT A[a]	**-0.18**	**0.12**	**-0.38***	**-0.35***	**-0.10**	**-0.21**
COWAT, FAS	**-0.17**	**0.18**	**0.02**	**0.61****	**0.20**	**0.43****
WAIS-III Block Design	**0.14**	**0.29**	**0.36***	**0.42****	**-0.08**	**0.34***
Grooved Pegboard, non-dominant hand[a]	**-0.02**	**-0.25**	**-0.14**	**-0.36***	**0.21**	**-0.12**

**$p<0.01$, *$p<0.05$

[a]lower scores indicate better performance

MRI volumes as a function of Arylesterase in sarin-exposed GW veterans

	QQ	QR	RR	F-value	p-value
N	10	10	10		
ICV	1680.51 (224.28)	1617.71 (305.50)	1544.40 (1256.79)	0.68	0.41
Total GM	664.63 (74.17)	697.35 (67.58)	644.01 (78.32)	1.79	0.19[a]
Total WM	543.24 (46.16)	639.78 (27.16)	523.00 (65.14)	2.52	0.04[a,b]
Hippocampus	5.01 (0.45)	5.28 (0.54)	4.91 (0.89)	0.96	0.40[a]

[a] ANCOVA with ICV as covariate
[b]planned contrasts: QQ and QR significantly different, p=0.03

planned contrasts shows that QR subjects have more WM volume than QQ subjects, which goes against the argument that the R allele is somehow protective.

• Haley et al. (1999) showed that ill GW veterans with the neurologic symptom complexes were more likely to have the R allele (heterozygous QR or homozygous R) than to be homozygous Q for the PON1 gene.

CHRONIC MULTISYSTEM ILLNESS

CHRONIC MULTISYSTEM ILLNESS (CMI)

Self-reported symptoms	Clusters
Not enough energy to complete daily tasks	→ Fatigability Cluster
Joint or muscle pain for no apparent reason	→ Musculoskeletal Cluster
Feeling irritable or Difficulty remembering or Difficulty concentrating or Feeling worried, tense, or anxious or Problems getting to sleep or Feeling depressed	→ Mood and Cognition Cluster

CMSI: DEMOGRAPHICS AND PTSD

	Severe CMSI (N=107)	Mild-mod CMSI (N=91)	Sx but not CMSI (N=89)	No Sx (N=92)	F or χ^2	*p*-value
Age, mean (S.D.)	44.7 (9.3)	47.4 (8.1)	46.5 (9.8)	47.8 (10.5)	2.24	0.08
No. left-handed or ambidextrous (%)	21 (20%)	8 (9%)	10 (11%)	10 (11%)	6.20	0.10
No. female (%)	23 (22%)	5 (6%)	8 (9%)	12 (13%)	12.81	0.005
No. White (%)	63 (59%)	63 (69%)	57 (64%)	69 (75%)	6.30	0.10
No. Married (%)	65 (61%)	60 (66%)	51 (57%)	55 (60%)	1.32	0.72
Years of education[1]	14.4 (2.0)	14.9 (2.0)	14.7 (2.0)	15.7 (2.4)	7.33	<0.0001
No. with less than college education	24 (22%)	12 (13%)	14 (17%)	8 (9%)	5.80	0.12
Current CAPS[2]	28.8 (29.2)	13.0 (18.3)	10.0 (18.9)	2.9 (9.7)	28.17	<0.0001
Lifetime CAPS[3]	49.8 (39.2)	31.6 (32.4)	19.6 (26.6)	9.2 (20.6)	31.50	<0.0001
No. with PTSD*	39 (36%)	9 (10%)	7 (8%)	1 (1%)	58.55	<0.0001
HAMD[4]	11.9 (6.6)	6.7 (4.7)	4.7 (4.2)	1.5 (2.2)	82.61	<0.0001
No. with MDD Dx	67 (63%)	47 (52%)	27 (30%)	8 (9%)	69.13	<0.0001
SCID Global Assessment of Function[4]	64.7 (12.4)	73.8 (11.4)	78.8 (10.7)	84.7 (8.2)	60.62	<0.0001
No. with history of alcohol problem (%)	64 (60%)	47 (52%)	40 (45%)	36 (39%)	9.39	0.025
Military status during Gulf War						
No. activity duty (%)	82 (77%)	65 (71%)	63 (71%)	72 (78%)		
No. National Guard (%)	5 (5%)	10 (11%)	8 (9%)	6 (7%)		
No. Reserves (%)	19 (18%)	16 (18%)	18 (20%)	14 (15%)		

[1]Tukey's post-hoc: No Sx different from all others, p≤0.03
[2]Tukey's post-hoc: Severe CMSI different from all others, p<0.0001; No Sx different from mild-mod CMSI, p=0.006
[3]Tukey's post-hoc: Severe CMSI different from all others, p<0.0001; mild-mod CMSI different from all others, p<0.05
[4]Tukey's post-hoc: all groups different from each other, p<0.05
[5]Tukey's post-hoc: no Sx different from severe CMSI, p<0.0001
[6]Tukey's post-hoc: all groups different from each other except for mild-mod CMSI and NOT CMSI
[7]Tukey's post-hoc: severe CMSI different from all others, p<0.0001

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CMI :NEUROPSYCHOLOGICAL TESTS:1.5T Cohort

	Healthy Controls	CMI	Severe CMI	Ctrls vs. CMI		Ctrls vs. severe CMI	
				F-value	*p*-value	F-value	*p*-value
N	59	152	129				
Age	45.0 (9.4)	45.3 (9.0)	44.6 (9.1)	0.03	0.86	0.10	0.75
Education	17.7 (1.8)	14.5 (2.5)	14.4 (2.6)	0.41	0.53	0.74	0.40
Current CAPS	4.4 (11.9)	23.9 (27.1)	25.0 (27.7)	28.22	<0.0001	29.85	<0.0001
Female:male	10:49	24:128	23:106				
ATTENTION							
TMT, A[1]	28.0 (9.2)	31.4 (10.2)	31.6 (10.7)	6.72	0.01[a]	6.27	0.013[a]
WAIS 3, digit span	17.0 (4.0)	16.6 (4.0)	16.4 (4.0)	0.48	0.50[a]	1.61	0.21[a]
EXECUTIVE FUNCTION							
TMT, B[1]	**60.6 (25.1)**	**68.1 (27.6)**	**69.4 (28.8)**	**3.38**	**0.067[a]**	**4.64**	**0.033[a]**
Short Category[1]	25.4 (16.2)	29.0 (14.0)	29.4 (14.2)	1.10	0.30[a]	1.38	0.24[a]
PSYCHOMOTOR FUNCTION							
Grooved Pegboard, dom[1]	68.9 (11.9)	71.5 (12.3)	71.8 (12.4)	0.40	0.53[a]	0.57	0.45[a]
Grooved Pegboard, Non-dom[1]	76.0 (18.6)	754 (13.6)	75.8 (13.8)	0.34	0.56[a]	0.10	0.76[a]
WAIS 3, digit symbol, coding	73.6 (15.8)	67.8 (14.5)	67.4 (14.3)	4.41	0.037[a]	5.57	0.019[a]
WAIS 3, digit symbol, pairing	**14.3 (4.0)**	**13.0 (4.1)**	**13.0 (4.1)**	**4.29**	**0.040[a]**	**4.13**	**0.043[a]**
SHORT-TERM MEMORY							
CVLT, total learning	53.3 (9.6)	50.1 (9.9)	50.2 (9.9)	2.46	0.12[a]	1.79	0.18[a]
CVLT, short delay free recall	12.0 (2.8)	10.4 (3.2)	10.5 (3.2)	6.11	0.014[a]	5.07	0.026[a]
CVLT, long delay free recall	12.2 (2.8)	10.8 (3.4)	10.8 (3.4)	3.14	0.078[a]	2.80	0.10[a]
CVLT, total hits	14.8 (1.6)	14.7 (1.5)	14.7 (1.5)	0.05	0.83[a]	0.14	0.71[a]
GENUINE EFFORT							
TOMM, trial 1	48.8 (2.1)	47.6 (3.4)	47.3 (3.6)	5.22	0.023[a]	7.16	0.008[a]
TOMM, trial 2	49.9 (0.3)	49.7 (1.2)	49.7 (1.3)	1.57	0.21[a]	2.22	0.14[a]
TOMM, retention	49.9 (0.4)	49.6 (4.7)	49.5 (1.8)	1.94	0.17[a]	2.56	0.11[a]

[a]ANCOVA with current CAPS as covariate
[1]lower score indicates better function

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CMSI AND NAA/CHO

Region/Metabolite	Severe CMSI (N=44)	Mild-mod CMSI (N=34)	Sx but Not CMSI (N=35)	No Sx (N=41)	F-value	*p*-value
Left Basal Ganglia NAA/Cho*	4.9 (0.6)	4.5 (0.5)	4.4 (0.8)	4.6 (0.5)	2.72	0.047

ANCOVA with scanner strength as covariate; there were significant group differences in education, current CAPS and HAMD however those variables did not contribute significantly to overall model

*planned contrasts showed that Sx but not CMSI (p=0.01) and mild-mod CMSI (p=0.04) were significantly different from severe CMSI; No Sx moderately (p=0.06) different from Sx but not CMSI

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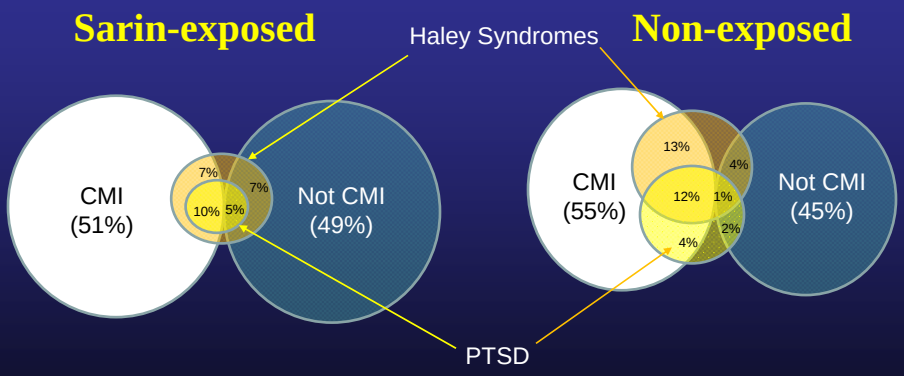
CMI AND HALEY SYNDROMES IN SARIN EXPOSED/NON EXPOSED :1.5 T Cohort (% of sarin exposed and non-exposed)



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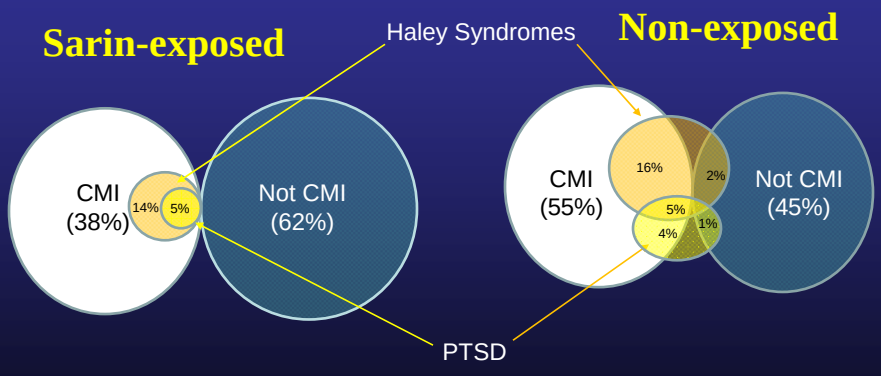
CMI AND HALEY SYNDROMES IN SARIN EXPOSED/NON EXPOSED :4 T (% of sarin exposed and non-exposed)



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SUMMARY OF CMI ANALYSES

- CMI symptoms strongly overlap with PTSD and Haley Syndromes
- CMI symptoms associated with few NP changes
- CMI symptoms not associated with Sarin exposure
- CMI symptoms not associated with imaging changes

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RELATIONSHIP OF PTSD TO CHANGES IN THE BRAIN

Feb-09 N. Schiff

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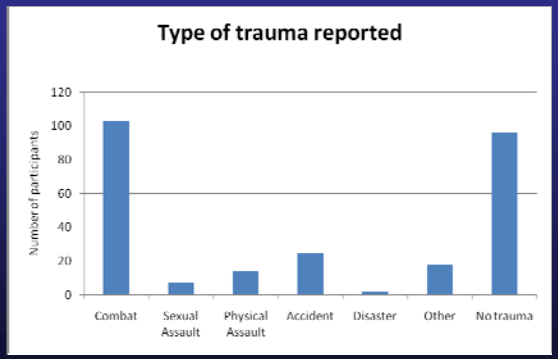
TRAUMA IN 244 GULF WAR VETERANS 1.5 T COHORT



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PTSD Symptoms from the CAPS

Re-experiencing Symptoms

- Intrusive recollections
- Distressing dreams
- Acting or feeling as if event were recurring
- Psychological distress at exposure to cues
- Physiological reactivity on exposure to cues

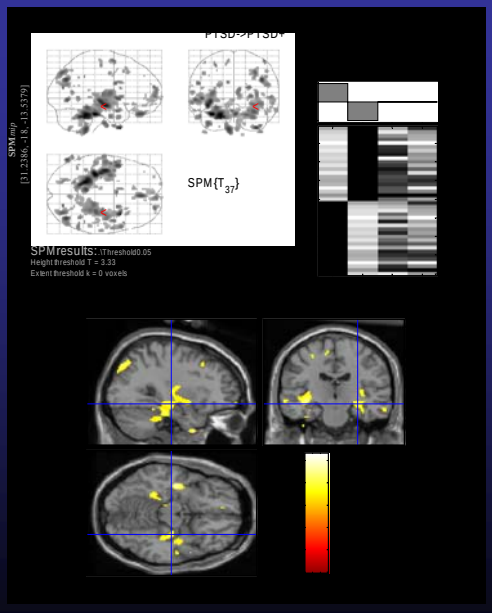
Avoidance and Numbing Symptoms

- Avoidance of thoughts, feelings, conversations
- Avoidance of activities, places, people
- Inability to recall aspects of trauma
- Diminished interest or participation in activities
- Detachment or estrangement
- Restricted range of affect
- Sense of foreshortened future

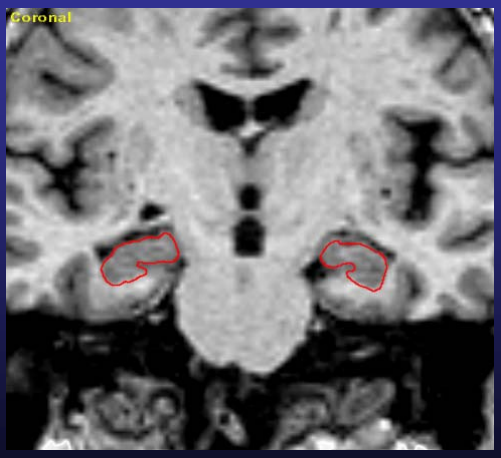
Hyperarousal Symptoms

- Difficulty falling or staying asleep
- Irritability or outbursts of anger
- Difficulty concentrating
- Hypervigilance
- Exaggerated startle response

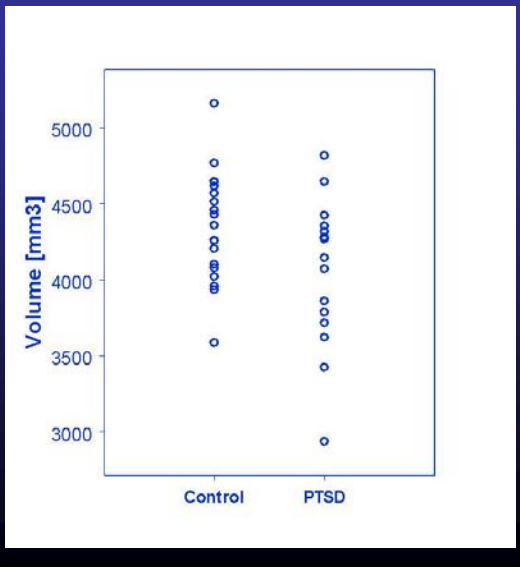
EFFECTS OF PTSD ON BRAIN STRUCTURE



HIPPOCAMPUS

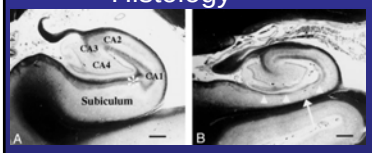


Hippocampal Volume in PTSD (N= 20 in each group (p<0.05))



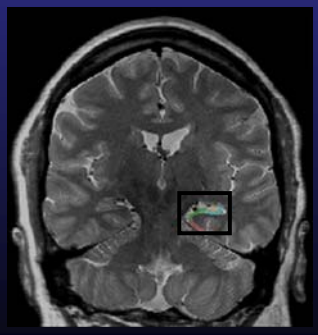
High-Field MRI of Hippocampal Subfields (Susanne Mueller)

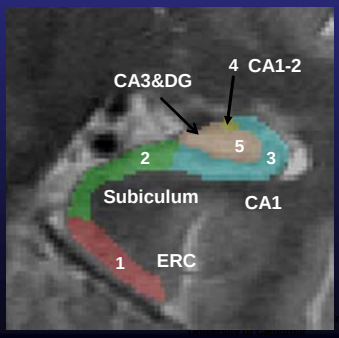
Histology



4 Tesla MRI

Resolution
0.4 x 0.5 x 2mm³





ORIGINAL ARTICLE

Magnetic Resonance Imaging of Hippocampal Subfields in Posttraumatic Stress Disorder

Zhen Wang, MD; Thomas C. Neylan, MD; Susanne G. Mueller, MD; Maryann Lenoci, MA; Diana Truran, MS; Charles R. Marmar, MD; Michael W. Weiner, MD; Norbert Schuff, PhD

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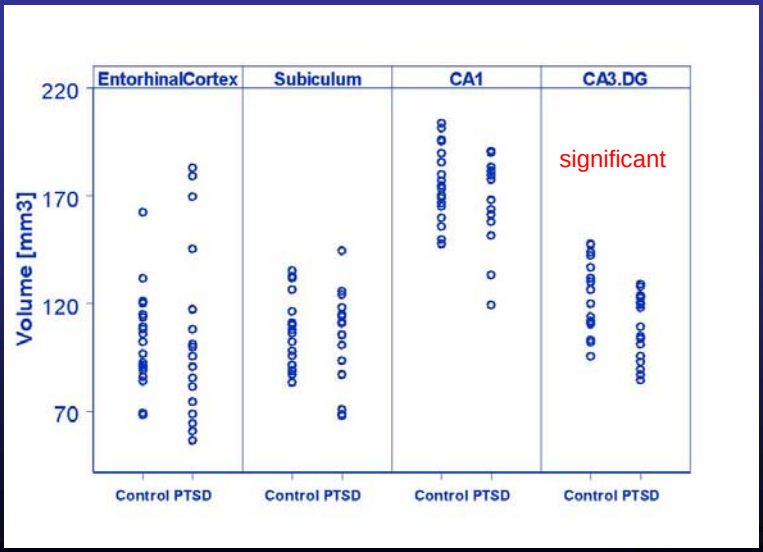
Subfield Volumes In PTSD

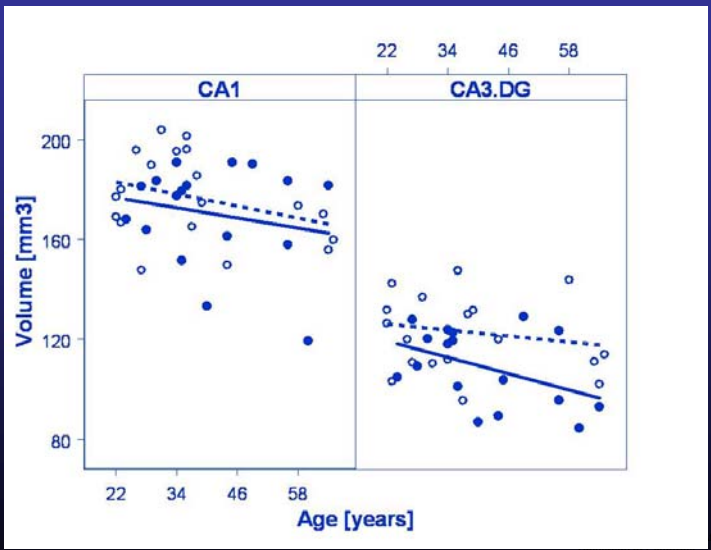
17 PTSD +
CAPS: 61 ± 14

19 Control
CAPS: 8 ± 7



Differential Effects Of PTSD And Age

PTSD
Control



Subfields In Other Conditions

By Susanne Mueller et al. Neuroimage. 2008;42(1):42-8

Table 1. Subfield and Total Hippocampal Volumes in mm3

	Control N = 47	MCI N = 14	AD N = 14
ERC	202.4 ± 54.0	168.4 ± 48.0	145.0 ± 53.4*
Subiculum	200.2 ± 36.1	184.7 ± 38.1	154.2 ± 44.9*
CA1	331.4 ± 47.0	285.1 ± 42.5*	264.4 ± 63.1*
CA1-2 transition	20.5 ± 5.5	15.1 ± 3.4 *	14.1 ± 3.8*
CA3&DG	224.4 ± 37.7	227.2 ± 24.3	230.3 ± 54.7
Total Hippocampus	5520.6 ± 770.4	5154.9 ± 817.7	4450.8± 1285.2*

* p<0.05 compared to controls

ERC, entorhinal cortex; CA1-2 transition, CA1-CA2 transition zone (definition see text); CA3&DG, CA3 and CA4 together with dentate gyrus

AD : Alzheimer's disease
MCI: Mild cognitive impairment, a transitional condition to AD

OVERALL SUMMARY

- Did not replicate NAA changes in BG in GWI
  - Didn't replicate arylesterase findings
- No changes of brain volumes or metabolites in GWI or multisystem illness
- Concerning effects of sarin exposure
  - Reduced GM in 1.5 T cohort: not replicated at 4T
  - Reduced WM high exposed at 4T, not seen at 1.5 T
  - No effects on Haley syndromes, neuropsychological tests, multisystem illness or PTSD: No clinical effects!
- No relationship of arylesterase to any symptom, impairment, or MRI/MRS data

SUMMARY (CONTINUED)

- PTSD symptomatology
  - Commonly occurs with GWI
  - Commonly occurs with MSI
- PTSD is associated with
  - Hippocampal atrophy
    - Longitudinal atrophy in ongoing severe PTSD
  - CA3-dentate subfield atrophy
  - Reduced GABA
  - Other changes (DTI perfusion)
  - Neuropsychological impairments
  - Risk for dementia (Yaffe et al)

CONCLUSION AND FUTURE DIRECTIONS

- There appears to be a biological basis for some of the symptomatology and impairments associated with military service and physical/psychological exposures
- Much more investigation is needed in order to
  - Understand the pathophysiology of symptoms/impairments
  - Develop improved methods for diagnosis
  - Develop improved treatments
- Future directions
  - Using improved MRI/MRS methods to detect changes
  - Using MRI/MRS to guide treatment

FUTURE DIRECTIONS

- Use MRI/MRS to identify changes in the brain
  - Traumatic brain injury
  - PTSD
  - Anxiety/depression and other symptoms: suicide risk
- Develop "personalized" indicators for optimum treatment response
- Determine effects of aging in Gulf War veterans
  - Increased risk for ALS, Parkinsons's or Alzheimer's disease?
  - Detect progressive brain atrophy, amyloid, cognitive decline

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