Presentation 4 – Kristin Heaton

Neuropsychological and Neuroanatomical Findings in 1991 GW Veterans with Estimated Low-level Exposures to Sarin and Cyclosarin

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The opinions or assertions contained herein are the private views of the author(s) and are not to be construed as official or reflecting the views of the Army or the Department of Defense.

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Overview

- **Background**
- **Study 1** – Neurobehavioral Outcomes
  Proctor et al. (2006)
- **Study 2** – Neuroanatomical Outcomes
  Heaton et al. (in press)
- **Summary and Conclusions**
- **Discussion**

Exposure: Sarin/Cyclosarin

Sarin/Cyclosarin

- Organophosphate compounds
- Military Designations (G agents)
  - Sarin (GB)
  - Cyclosarin (GF)
- Absorbed via …
  - Skin, mucus membranes, lungs, gastrointestinal system
- Lipophilic - readily cross blood-brain barrier

Sarin/Cyclosarin (2)

- Bind and inhibit acetylcholinesterase (AChE)
- Accumulation of acetylcholine (ACh) at receptor sites (nicotinic and muscarinic) throughout peripheral and central nervous system
- Overstimulation of ACh targets

Sarin/Cyclosarin (3)

Symptom Profile

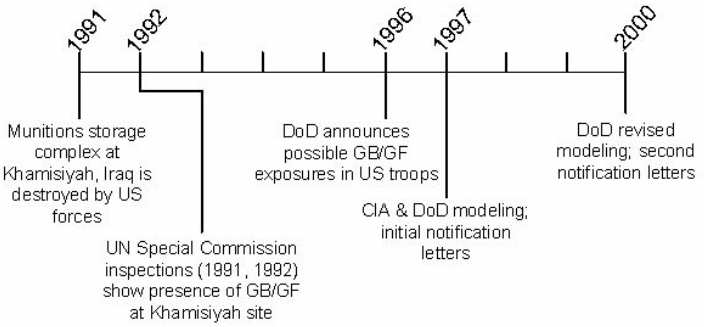
- miosis (pupil constriction)
- eye irritation/vision changes/lacrimation
- headache
- gastrointestinal distress (diarrhea/vomiting)
- respiratory distress
- tachycardia (heart rate > 100 bpm)
- weakness/fatigue
- tremor/fasciculation

Exposure Scenario: Khamisiyah, Iraq

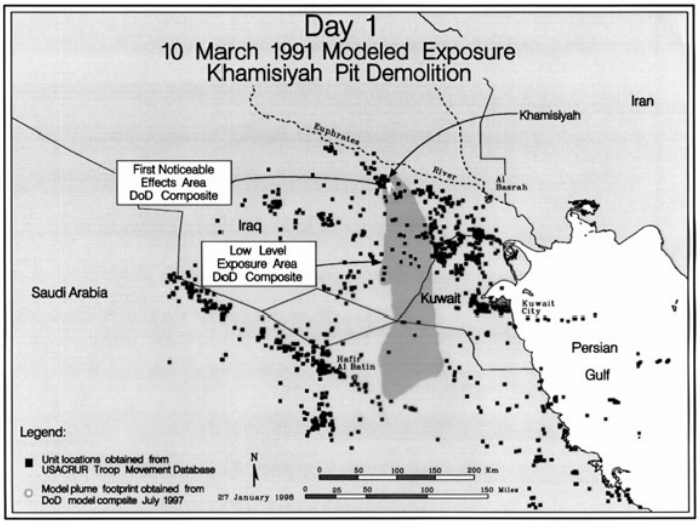
Khamisiyah, Iraq

- Large munitions storage facility
- Destroyed by US Army demolition teams (March 1991)
- No on-site monitoring of nerve agent levels
- Munitions at site later found to have contained sarin/cyclosarin
- DoD directs modeling of Khamisiyah plume: 1996; 2000

Khamisiyah Timeline



Khamisiyah Exposure Area



Low-level Sarin Exposure

Low-level Exposures

- Animal research (low dose exposure)
  - neurobehavioral decrements (motor, visual-spatial function, spatial memory)
  - changes in EEG activity (increased beta activity)
  - changes in receptor function and densities
- Tokyo research (mostly moderate-high exposure)
  - subtle neurobehavioral decrements (attention, motor function, postural control)
  - neurophysiological changes (evoked potentials, structural changes)
- GW research (estimated low-level exposure)
  - subtle neurobehavioral decrements (short term memory, attention, visual-spatial and motor function, mood)
  - changes in neuronal function (MRS studies)

Low-level Exposures (2)

- Exposure analyses
  - categorical comparisons
  - trend analyses of exposure level – health outcome relationships

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- **Study 2** – Heaton et al. (in press)
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Effects of Sarin and Cyclosarin Exposure During the 1991 Gulf War on Neurobehavioral Functioning in US Army Veterans

SP Proctor, KJ Heaton, T Heeren, RF White

NeuroToxicology 2006;27:931–939

Grant support for this study provided by Department of Veterans Affairs (DVA) Office of Research and Development (1994–2000)

Objective

To examine neurobehavioral task performances, 4-6 years post-deployment, in GW veterans presumed to have received varying degrees of low-level sarin/cyclosarin exposure at Khamisiyah, Iraq.

Ft. Devens Cohort

- Approximately 3000 GW veterans who returned home through Ft. Devens, MA
- Roughly 100 different Army units
- Time 1: Spring of 1991 (physical/psychological effects)
- Time 3: 1994-1996
  - Stratified, random subset of Devens Cohort (N = 320)
  - Comprehensive Evaluation:
    - Occupational/environmental exposures
    - neurobehavioral function
    - psychological and physical health status
  - 95% of participants evaluated prior to 1996 announcement by DoD of possible nerve agent exposure

Study Sample

- 140 GW-deployed veterans from Time 3 subset of the Devens cohort
- Veterans represented 28 different Army units during deployment
- Veterans were:

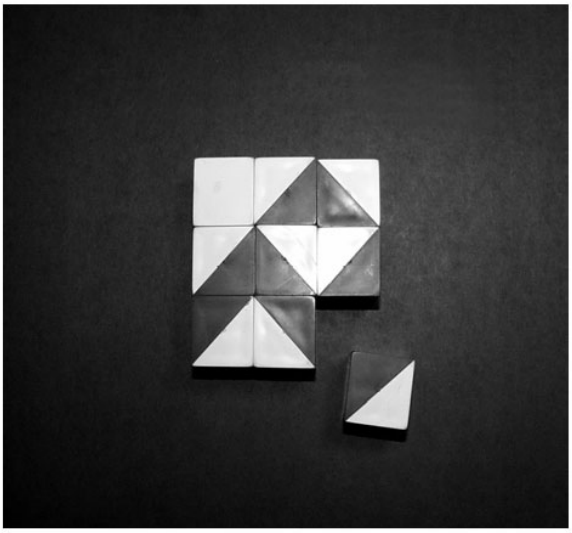
35 years old (SD = 9 years)	44% Female
14 years education (SD = 2 years)	92% Caucasian
14% left handed/ambidextrous	89% Enlisted

Outcome Measures

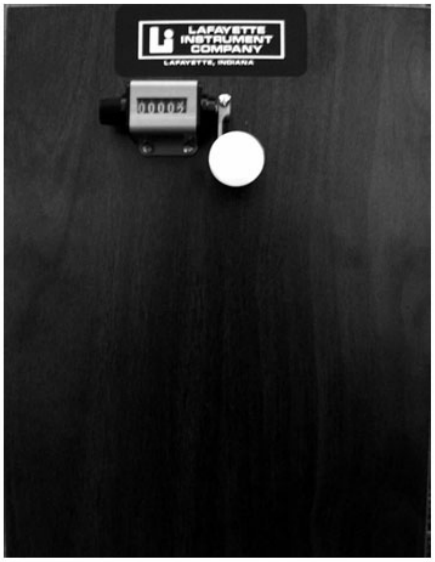
Neurobehavioral Test Battery

- Executive function
- Psychomotor function ← *Anticipated effects*
- Visual-spatial abilities ←
- Short-term memory
- Mood

WAIS-R Block Designs



Finger Tapping Test



Analyses

- Categorical comparisons
  - Comparison of neuropsychological performance across exposure groups
  - Analyses controlled for unit affiliation, age, PTSD symptoms, and other factors
- Linear Trend analyses
  - Examine relationship between unit-level exposure estimates and neuropsychological performances
  - Analyses controlled for unit affiliation, age, PTSD symptoms, and other factors

Exposure Groups

For categorical comparisons:

- **Low-to-no Exposure**
  < 0.01296 mg min/m^3 (GPL)
- **Moderate Exposure**
  > 0.01296 mg min/m^3 (GPL); <0.072 mg min/m^3
- **Higher Exposure**
  > 0.072 mg min/m^3

Results

- Greater decrements in visual-spatial (Block Designs) and psychomotor functions (Purdue Pegboard) associated with higher levels of estimated sarin/cyclosarin exposure.

Outcomes	Adj. parameter est. for 0.1 mg min/m^3	95 % CI	p-value
Purdue Pegboard dominant hand	-0.93	-1.6, -0.28	0.005
Purdue Pegboard non-dominant hand	-0.48	-0.92, -0.04	0.03
WAIS-R Block Designs raw score	-4.0	-5.8, -2.2	<0.0001

Results

- Better performance on a gross motor task (finger tapping) associated with higher levels of estimated sarin/cyclosarin exposure

Outcomes	Adj. parameter est. for 0.1 mg min/m^3	95 % CI	p-value
Finger Tapping dominant hand	2.4	0.96, 3.8	0.001
Finger Tapping non-dominant hand	2.2	0.83, 3.6	0.002

Conclusions

- Less proficient neuropsychological performance 4-6 years post-exposure associated with presumed low-level sarin/cyclosarin exposure.
- Results consistent (in terms of domains affected) with effects seen following low-dose organophosphate pesticide exposure and those reported for people exposed to sarin in the 1995 terrorist attacks on the Tokyo Subway system

Overview

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Quantitative Magnetic Resonance Brain Imaging in US Army Veterans of the 1991 Gulf War Potentially Exposed to Sarin and Cyclosarin

KJ Heaton, CL Palumbo, SP Proctor, RJ Killiany, DA Yurgelun-Todd, RF White

NeuroToxicology (in press)

Funding support provided by cooperative agreement with the Boston University School of Public Health (Department of Environmental Health) from the National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA (Grant number: cooperative agreement U50/CCU114464-01). Research Carried out at the Boston Environmental Hazards Center, under grant support from the Department of Veterans Affairs (DVA) Office of Research and Development (1994-2000).

Objective

To examine gross neuroanatomical outcomes, 8-10 years post-deployment, in GW veterans presumed to have received varying degrees of low-level sarin/cyclosarin exposure at Khamisiyah, Iraq.

Study Sample

- 26 GW-deployed veterans recruited from the Time 3 subset of the Devens Cohort
- Veterans represented 14 different Army units during deployment
- Veterans were:

41 years old (SD = 9 years)	42% Female
14 years education (SD = 2 years)	100% Caucasian
16% left handed/ambidextrous	88.5% Enlisted

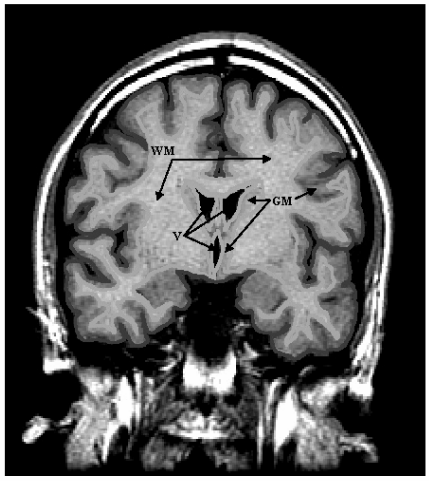
Methods

- MRI study conducted in 1999-2001 (8-10 years post-deployment)
- MR images acquired using 1.5 T, GE scanner (McLean Hospital)
- Coronal brain images segmented and analyzed using semi-automated MRX software program (Kikinis et al., 1992)

Methods (2)

- MRX analyses yielded volumetric measurements of
  - white matter
  - gray matter
  - cerebrospinal fluid
  - right and left lateral ventricles

MRX segmentation



Analyses

- Binary comparisons
  - Comparison of gross brain tissue volumes across exposure groups (ANOVA)
  - Analyses controlled for age and PTSD symptoms
- Linear Trend analyses
  - Examine relationship between unit-level exposure estimates and brain tissue volumes
  - Analyses controlled for unit affiliation, age, and PTSD symptoms

Exposure Groups

For Binary Comparisons:

- **'Exposed' (N = 13)**
  > 0.01296 mg min/m^3 (GPL)
- **'Unexposed' (N = 13)**
  < 0.01296 mg min/m^3 (GPL)

Results

- Binary comparisons ('exposed' vs 'unexposed') yielded no differences in any of the volumetric measurements.

Results

- Smaller white matter and larger lateral ventricle volumes associated with higher levels of estimated sarin/cyclosarin exposure.

	Adjusted Parameter est. for 0.1 mg min/m^3	95% CI	p-value
% White matter per cranial volume *GW unit-level exposure estimates*	-4.64	-4.79, -4.49	<0.0001
% Gray matter per cranial volume *GW unit-level exposure estimates*	0.83	-1.62, 3.28	0.5052
% CSF per cranial volume *GW unit-level exposure estimates*	0.22	-0.29, 0.73	0.3934
% right lateral ventricle per cranial volume *GW unit-level exposure estimates*	0.11	0.01, 0.22	0.0288
% left lateral ventricle per cranial volume *GW unit-level exposure estimates*	0.13	0.07, 0.19	<0.0001

Conclusions

Results suggest that exposure to low levels of sarin/cyclosarin might contribute to *subtle* white matter degradation that can be detected 8-10 post-exposure.

Findings add to earlier studies documenting possible neurophysiological and structural brain changes in sarin exposed animals and humans.

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- **Study 2** – Heaton et al. (in press)
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Overall Conclusions

Overall, results of these two studies suggest that exposure to sarin/cyclosarin at levels insufficient to produce obvious clinical symptoms may contribute to both functional and structural brain changes in GW veterans, including:

- decrements in visual-spatial and motor system functioning, and
- white matter degradation.

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Overall Conclusions (2)

These findings are consistent with prior research involving human and animal models suggesting neurobehavioral and neurophysiological effects following both low-level sarin exposures and low-dose exposure to organophosphate pesticides.

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Recommendations

Further research is needed to examine this question…

- in a larger group of veterans,
- using a a more holistic approach (functional, neurophysiological, biochemical, neuroanatomical), and
- with a longitudinal focus.

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Thank You!