Gulf War Illness-Associated Multiple Toxic Exposures in Predicting Current Brainstem Atrophy

Yu Zhang [1], Yashar Rahimpour [1,2] Rayma Williams [1], Gladys Marina Veltkamp [1], Xiaojian Kang [1], J. Wesson Ashford [1,2], Peter J. Bayley [1,2], Ansgar J. Furst [1,2,3,4]

[1] War Related Illness and Injury Study Center (WRIISC), VA Palo Alto Health Care System; [2] Psychiatry and Behavioral Sciences, and [3] Neurology and Neurological Sciences, Stanford University;
[4] Polytrauma System of Care (PSC), VA Palo Alto Health Care System

Background

- Chronic multisymptom illness/Gulf War illness (CMI/GWI) is characterized by persistent, multiple chronic symptoms, and affects a growing number of veterans who served in the Southwest Asia theater of military operations during 1990s.
- Research suggested that CMI/GWI symptoms, including cognitive and neurobehavioral changes, are linked to the GW deployment-related toxic exposures [1]. Our previous study [2] found that CMI/GWI symptoms are associated with brainstem atrophy, indicating damage to the central nervous system.
- The objective of this study was to explore the relationship of specific exposures with CMI/GWI symptoms and brainstem atrophy.

Methods

- Demographic information
  - 147 Veterans: Age = 54±7.5 years old; 86% Male
  - Deployment: 125 deployed to ODS/DS (8/1990 – 2/1991), 22 deployed to other conflicts during 1990 – 1999.
  - Race: 110 White, 12 Black, 9 Asian, 6 Other, 10 Mixed
  - Service Branch: 66 Army, 30 Navy, 23 Air Force, 28 Marine Corps
  - Years of Education: 14.7±2.3 years; Years of service: 9.8±9 years
- Exposure assessments
  - Categories: Exposed / Unexposed to 34 military exposure items.
  - Exposure Frequency Index (Table 1): a 0 – 4 score for frequency/duration of each exposure item during deployment.
- CMI/GWI symptom assessments
  - Kansas symptom criteria [3]: the veterans met the moderate or multiple symptom criteria in at least three of the six domains.
  - Symptom Severity Index (Table 1): a 0 – 3 score of 18 chronic symptom items that are included in the CDC Chronic Fatigue Syndrome Inventory.
- Brain MRI volumetry
  - MRI protocols: 3-Tesla GE scanners, 3D sagittal T1-weighted (T1WI).
  - FreeSurfer segmentation + parcellation for volume measures of head size, total cortex, subcortex, and 16 subcortical regions.
  - FreeSurfer brainstem segments for volume measures of the whole brainstem, midbrain, pons, and medulla.
- Statistics:
  - Step-1. Odds ratio for comparing the prevalence of meeting Kansas symptom criteria in exposed *vs.* unexposed groups.
  - Step-2. Partial correlation (controlling for demographic variables) / Spearman's correlation between the individual exposure index and symptom index. Since some exposure indices were intercorrelated, multiple regression was used to rank the top relevant exposure factors among multiple coexisting exposures.
  - Step-3. Partial / Spearman's correlation between individual exposure index and brainstem volume. Multiple regression ranks key exposure factors.
  - Step-4. Partial / Spearman's correlations and ANCOVA for multiple key exposures in association with brainstem atrophy.

Table 1. Item-level scoring for the exposure frequency and symptom severity indices.

Exposure Frequency Index	
0	Not exposed or, no noticeable health effects
1	Seldom to few days while deployed
2	Occasionally to about half of deployment
3	Majority of days during deployment
4	Every day while deployed
Symptom Severity Index	
0	No symptoms (present for 6 months or more)
1	Mild symptom
2	Moderate symptom
3	Severe Symptom

Figure 1. Age-adjust Odds Ratio (aOR) comparing percentages of veterans meeting the Kansas criteria in exposed vs. unexposed groups.

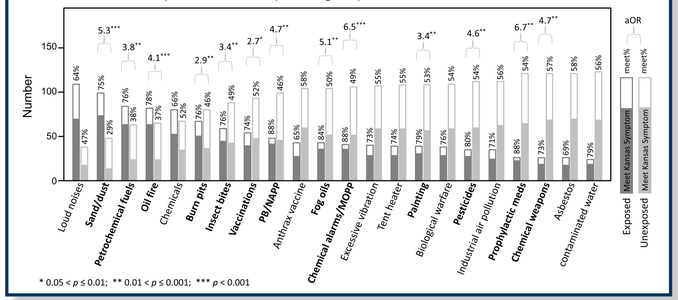

Figure 2. *Left*: Correlation between brainstem volume and exposure frequency index. *Right*: Differences in brainstem volumes between unexposed / single exposure and multiple key exposures.

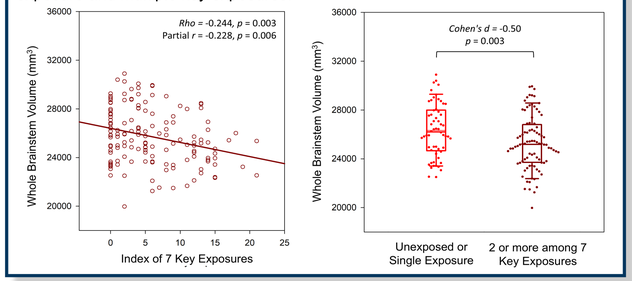

Table 2. Partial and Spearman correlations between exposure and symptom severity indices. Multiple regression ranked the most important variables contributing to the relationship between exposure and symptom severity.

Exposure Frequency Index	Asso. w/ Symptom Severity Index				Multiple Regression			
	Partial Corr.	*p* values	*Rho*	*p* values	*Beta*	*t* values	*p* values	Rank
Chemical alarms/ MOPP4	**0.415**	**<0.001**	**0.450**	**<0.001**	**2.37**	**2.27**	**0.03**	**[1]**
Sand/dust	**0.395**	**<0.001**	**0.494**	**<0.001**	1.32	1.83	0.07	**[2]**
PB/NAPP	**0.362**	**<0.001**	**0.410**	**<0.001**	1.19	1.51	0.13	**[3]**
Painting	**0.194**	**0.02**	**0.189**	**0.02**	1.15	1.47	0.15	**[4]**
Oil fire	**0.366**	**<0.001**	**0.430**	**<0.001**	1.13	1.62	0.11	**[5]**
Chemical weapons	**0.291**	**<0.001**	**0.221**	**0.007**	0.95	0.67	0.51	**[6]**
Pesticides	**0.308**	**<0.001**	**0.270**	**0.001**	0.93	1.28	0.20	**[7]**
Fog oils	**0.276**	**0.001**	**0.324**	**<0.001**	0.62	0.77	0.44	**[8]**
Loud noises	**0.181**	**0.03**	**0.231**	**0.005**	0.37	0.62	0.54	**[9]**
Prophylactic meds	**0.262**	**0.001**	**0.301**	**<0.001**	0.36	0.37	0.71	**[10]**
Insect bites	**0.278**	**0.001**	**0.286**	**<0.001**	0.02	0.03	0.98	**[11]**
Tent heater	**0.230**	**0.005**	**0.233**	**0.005**	-0.18	-0.23	0.82	[12]
Burn pits	**0.272**	**0.001**	**0.351**	**<0.001**	-0.41	-0.56	0.58	[13]
Petrochemical fuels	**0.258**	**0.002**	**0.352**	**<0.001**	-0.57	-0.93	0.35	[14]
Chemicals	0.159	0.06	**0.187**	**0.02**	-0.83	-1.29	0.20	[15]
Biological warfare agents	**0.223**	**0.007**	**0.255**	**0.002**	-1.10	-1.10	0.27	[16]
Excessive vibration	0.142	0.09	0.172	0.04				
Vaccinations	0.131	0.12	0.155	0.06	Items were not included in the multiple regression model if their individual correlations were not significant			
Anthrax vaccine	0.095	0.26	0.097	0.24				
Industrial air pollution	0.155	0.06	0.145	0.08				
Asbestos	**0.203**	**0.01**	0.139	0.09				
Ingestion of contaminated water	0.154	0.07	0.141	0.09				

Table 3. Partial and Spearman correlations between exposure index and brainstem volume. Multiple regression ranked the most important variables contributing to the relationship between exposure and brainstem volume.

Exposure Frequency Index	Asso. w/ Brainstem Atrophy				Multiple Regression			
	Partial Corr.	*p* values	*Rho*	*p* values	*Beta*	*t* values	*p* values	Rank
Pesticides	**-0.234**	**0.005**	**-0.244**	**0.003**	**-380.2**	**-2.27**	**0.03**	**[1]**
Painting	-0.118	0.159	-0.171	0.038	-215.8	-1.23	0.22	**[2]**
Chemical alarms/ MOPP4	-0.152	0.070	**-0.207**	**0.012**	-193.1	-0.83	0.41	**[3]**
Oil fire	-0.123	0.143	-0.128	0.122	-173.7	-1.09	0.28	**[4]**
Insect bites	-0.107	0.204	-0.168	0.041	-106.7	-0.64	0.52	**[5]**
PB/NAPP	-0.067	0.429	-0.148	0.074	-96.7	-0.53	0.60	**[6]**
Fog oils	-0.081	0.335	-0.097	0.242	-86.1	-0.46	0.65	**[7]**
Chemical weapons	-0.122	0.148	-0.129	0.119	-59.3	-0.18	0.86	[8]
Prophylactic meds	-0.127	0.131	-0.171	0.038	-27.5	-0.12	0.90	[9]
Loud noises	-0.024	0.778	-0.105	0.207	5.5	0.04	0.97	[10]
Sand/dust	-0.001	0.990	-0.058	0.484	181.2	1.18	0.24	[11]

Results

- Step-1 analysis (Figure 1):
  - Top 22 (out of 34) military exposures (listed in the X axis) were considered relevant to the GW deployment (>15% exposed).
  - Age-adjusted Odds Ratios (aOR) highlighted 13 (out of 22) exposures had a greater percentage that met the Kansas symptom definition for CMI/GWI.
- Step-2 analysis (Table 2):
  - Exposure to 16 (out of 22) individual items was correlated with the symptom severity index. These exposure items overlapped with the 13 items highlighted in the Step-1 analysis.
  - Multiple regression (including 16 top exposures as multiple independent variables) ranked 11 exposure items that predominantly contribute to the positive relationships between the exposure and symptom indices.
- Step-3 analysis (Table 3):
  - Exposure to pesticides was negatively correlated with the brainstem volume.
  - Multiple regression (including 11 top exposures from step-2 analyses as multiple independent variables) identified 7 key exposures that predominantly contributed to the negative correlations between the exposure index and brainstem volume.
- Step-4 analysis (Figure 2):
  - Combined index of the 7 key exposures was significantly correlated with reduced brainstem volume.
  - Veterans with multiple toxic exposures (at least 2 out of the 7 key exposures, N=88) had smaller brainstem volume compared to the unexposed veterans (none or single exposure, N=59).

Conclusion

- The results suggested that a longer duration of multiple deployment-related exposures is associated with a more severe level of GWI symptoms nearly 30 years after the GW.
- Seven key exposures predicted brainstem atrophy, suggesting a combination of specific toxic exposures may have caused brainstem damage leading to downstream GWI symptoms.

Reference

[1] Keating et al. Environ Health. 2003. [2] Zhang et al. Neurotoxicology. 2020. [3] Gifford et al. Life Sci. 2021.