Brainstem Structural Alterations Correlates with Sleep Difficulty and Pain in Gulf War Illness Veterans

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Background

- Gulf War illness (GWI) in veterans who served in the 1990-91 Persian Gulf War is manifested by multiple chronic symptoms, including pain, sleep problems, neuropsychiatric disorders, autonomic, gastrointestinal, and skin problems.
- Our previous study demonstrated brainstem structural abnormalities are specifically involved in GWI. This study aimed to provide insight into the brainstem neuro-correlates of sleep and pain syndromes that characterize GWI.

Methods

- GWI patients: n=90, Age=50 ± 5 years, 90% men, all deployed to Operation Desert Storm/Desert Shield between Aug 1990 and June 1991, all met Fukuda/CDC and Kansas criteria of GWI.
- Distribution of the Kansas GWI symptomatic domains (**Table 1**) based on self-reported Chronic Fatigue Symptom Inventory (CFS): yes = symptoms presented > 6 months.
- Sleep — assessed by the Pittsburgh Sleep Quality Index "global" scores (PSQI-GLOB) range from 0 (best) to 21 (worst).
- Pain — assessed by the Brief Pain Inventory (BPI), sum score of Items 3-6, from 0 (none) to 40 (worst).
- Fatigue — self-reports of the degree that fatigue limited daily activities in the past 6 months: 0 (none) to 4 (worst).
- Cognitive Impairment — assessed by total scores in a 26-item version of the Cognitive Difficulties Scale (CDS) questionnaire.
- MRI protocol: 3-Tesla GE scanner, 3D sagittal T1-weighted MRI (1x1x1mm^3 resolution), 2D diffusion tensor imaging (DTI) (60 directions, *b*=0, 1000. 1 x 1 x 2.5 mm^3 resolution).
- Volume Measures: Volumes of brainstem, hippocampus, total gray, white matter and total intracranial volume (TIV), extracted from FreeSufer v6.0 (**Figure 1**).
- DTI Measures: Fractional anisotropy (FA) of 10 brainstem fiber tracts, processed and measured based on our previous publication (**Figure 1**).
- Statistics: Pearson's correlation. Brainstem volumes are normalized to account for individual head size.

Table 1. Demographics and symptomatic characterizations.

No. of GWI = 90	N. of Yes	% of Yes	N. (%) of mild intensity	N. (%) of moderate intensity	N. (%) of severe intensity
Chronic Sleep Disturbance	88	98%	7 (8%)	29 (33%)	52 (59%)
Chronic Pain	89	99%	2 (2%)	32 (39%)	52 (59%)
Chronic Fatigue	76	84%	3 (4%)	39 (51%)	34 (45%)
Neurologic/Cognitive/Mood	81	90%	6 (7%)	49 (61%)	26 (32%)
Chronic G.I. Symptoms	66	73%	9 (14%)	42 (64%)	15 (22%)
Chronic Respiratory Symptoms	63	70%	21 (33%)	38 (60%)	4 (7%)

Figure 1. FA measures extracted from 10 brainstem tracts-of-interest (A-D) and regional volume measures extracted from FreeSurfer parcellations (E,F).

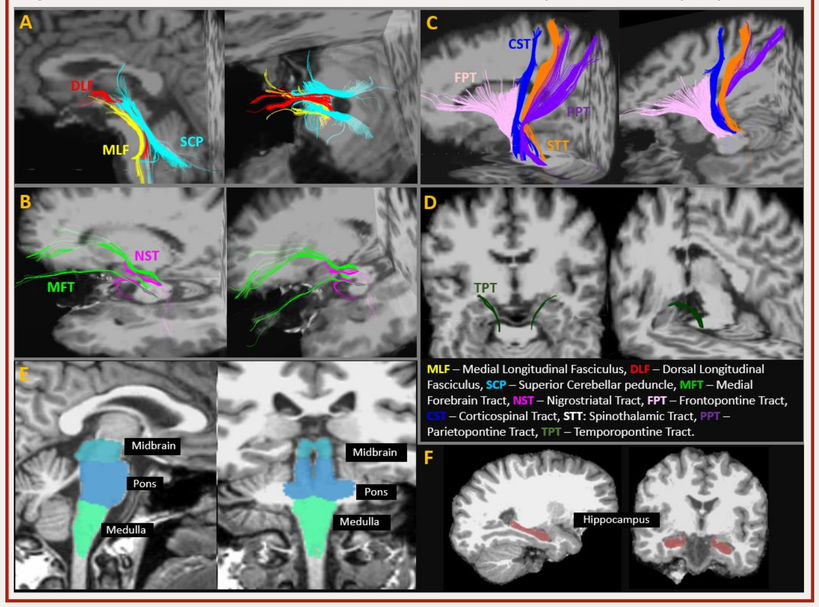
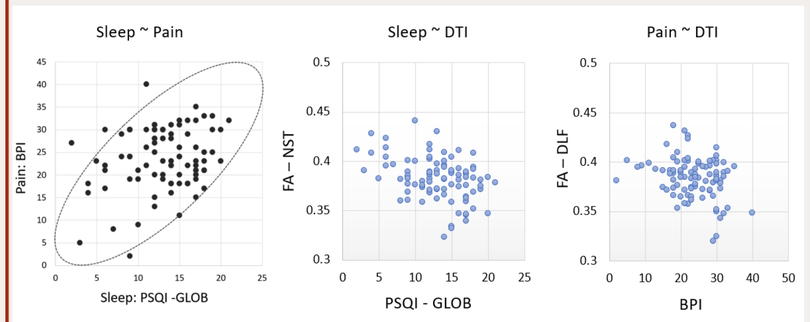


Figure 2. Relations between: pain and sleep severities, sleep and FA of the nigrostriatal tract; pain and FA of the dorsal longitudinal fasciculus.



Results

Clinical features of the GWI symptomatology:

- A majority of the GWI patients presented with pain (99%), sleep difficulties (98%), and neuropsychiatric problems (90%) as a chronic symptomatic complex (**Table 1**).
- In most patients, severities of sleep disturbance (PSQI-GLOB) and pain (BPI) were significantly correlated (r = 0.28*) (**Figure 2,** *left panel, area in circle*), except 3 patients presented pain-dominated symptom, and one presented sleep-dominated symptoms.
- PSQI-GLOB also significantly correlated with fatigue (r = 0.29*) and cognitive impairments (r = 0.52**), whereas BPI had no significant association with fatigue and cognition.

Results

Neuroimaging correlates to GWI symptomology (**Table 2**):

- PSQI-GLOB negatively correlated with overall brainstem volumes, also negatively correlated with FA of the Nigrostriatal tract (**Figure 2,** *middle panel*) – a dopaminergic pathway, Medial Forebrain tract – a mesolimbic pathway, and the Dorsal longitudinal fasciculus – a tract interconnect hypothalamus, periaqueductal gray, and locus coeruleus.
- BPI negatively correlated with FA in the Dorsal longitudinal fasciculus (**Figure 2,** *right panel*).
- Increased fatigue was associated with disrupted Nigrostriatal and Temporopontine tracts.
- Increased cognitive deficits correlated with hippocampal atrophy, diminished FA in the dopaminergic and pontine-thalamic tract.

Table 2. Pearson's correlation coefficients between brainstem volume, tract FA, and the GWI-related multiple chronic symptomatology.

Measures	PSQI-GLOB	BPI	CFS-Fatigue	CDS
Volume				
Total Brainstem	**-0.301****	-0.147	-0.066	-0.158
Medulla	**-0.245***	-0.138	-0.103	-0.097
Pons	**-0.259***	-0.095	-0.043	-0.142
Midbrain	**-0.299****	-0.228	-0.045	-0.157
Hippocampus	-0.155	-0.010	0.042	**-0.262***
Total Subcortical Vol.	-0.179	-0.152	-0.067	-0.008
Total Cortex Vol.	0.161	-0.075	0.219	0.287*
Total White Matter Vol.	-0.046	0.058	-0.089	-0.026
Total Intracranial Vol.	-0.123	-0.079	-0.220	-0.143
FA				
Dorsal Longitudinal F.	**-0.267***	**-0.270***	-0.121	-0.155
Medial Longitudinal F.	0.022	-0.072	0.054	0.165
Sup. Cerebellar Peduncle	-0.230	-0.216	-0.143	**-0.246***
Nigrostriatal Tract	**-0.390****	-0.195	**-0.272***	**-0.251***
Medial Forebrain Tract	**-0.317****	-0.125	-0.215	-0.178
Corticospinal Tract	-0.075	0.014	-0.170	-0.050
Spinothalamic Tract	-0.090	0.019	-0.139	-0.078
Frontopontine Tract	-0.213	-0.077	-0.153	-0.117
Parietopontine Tract	-0.091	0.100	-0.194	-0.077
Temporopontine Tract	-0.149	-0.026	**-0.251***	-0.171

* 0.01 < P_{FDR} ≤ 0.05; ** P_{FDR} ≤ 0.01

Conclusion

- The findings of the brainstem neuroanatomical correlates of chronic sleep disturbances and pain improve the understanding of the brainstem (neurons and circuits) damages and their pathophysiological basis underlying the chronic multi-symptoms in GWI.