Accelerated Brain Aging in Gulf War Illness: Deep Learning–Derived Brain Age in Gulf War Veterans

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Introduction & Objectives

- Gulf War veterans were exposed to neurotoxicants including organophosphate pesticides and chemical weapons during the 1990–1991 Gulf War.
- Approximately 35% continue to experience Gulf War Illness (GWI), characterized by chronic fatigue, pain, and cognitive dysfunction (Steele, 2000).
- Whether wartime neurotoxicant exposures are linked to biologically accelerated brain aging remains unknown.
- Brain age deviation provides a single, interpretable metric of how much "older" a brain appears relative to chronological age (He et al., 2021 & 2022).

Objective:

Test whether veterans with GWI show accelerated brain aging using two independent pretrained deep learning brain age prediction models and evaluate whether brain age deviation is associated with neuropsychological, inflammatory, and symptom outcomes.

Methods

Participants & Methods

- Cohort: 228 veterans with GWI and 76 GW veteran controls from the BBRAIN
- MRI: multi-site 3T T1-weighted structural scans.
- Models: 2D ResNet-101 and 3D SFCN, trained on 8,859 lifespan T1 MRI scans.
- Brain age deviation is defined as the difference between the predicted brain age and the chronological age.
- Analyses: generalized linear regression adjusted for age, sex, and education; FDR correction applied for multiple comparisons correction.

Table 1. Participant characteristics

Group	N	% Female (N)	Mean age ± SD
GWI	228	19.74% (45)	52.52 ± 6.48
GW controls	76	13.16% (10)	55.52 ± 7.23
Total	304	18.09% (55)	53.27 ± 6.79

Results

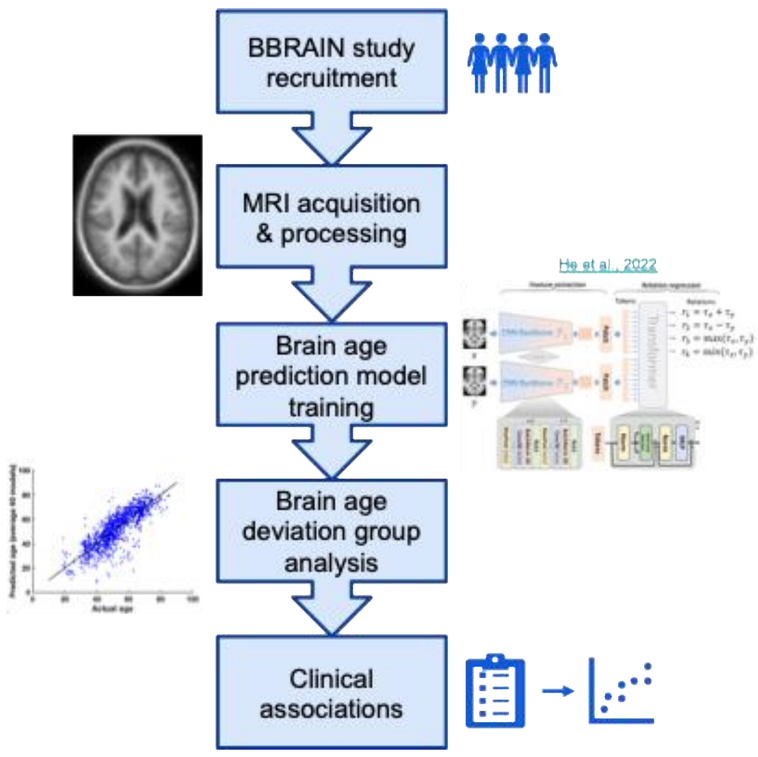

Figure 1. Overview of study workflow. The Boston Biorepository, Recruitment and Integrative Network (BBRAIN) is a multi-site collaboration for retrospective and prospective research on GWI . From the BBRAIN, we included 166 GW veterans originally recruited as part of the Gulf War illness Consortium (GWIC) study, and 138 GW veterans from the University of California, San Francisco (UCSF) (Steele, 2000).

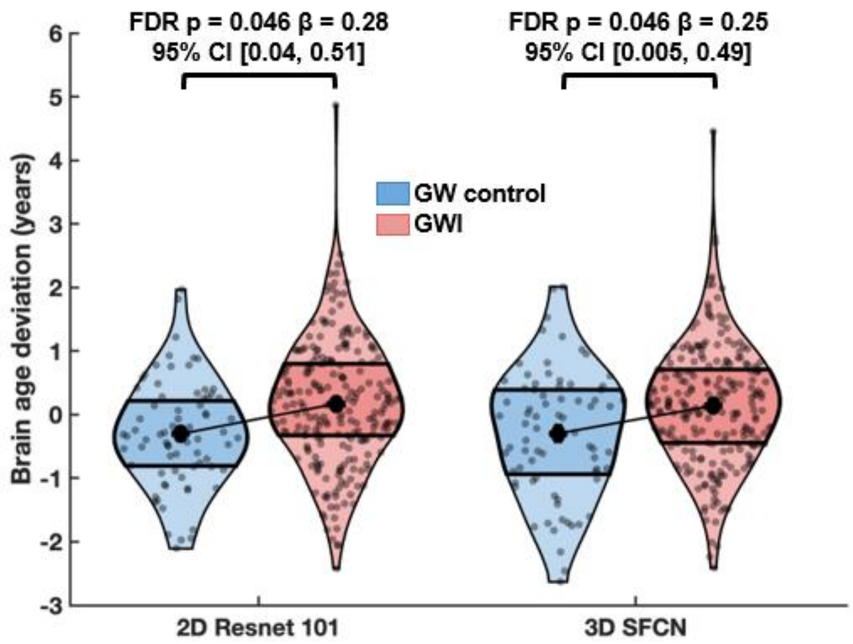

Figure 2. Group differences in brain age deviation. Veterans with GWI showed higher brain age deviations in the whole group sample from the 2D ResNet 101 and 3D SFCN models. Standardized β estimates and 95% confidence intervals were derived from z-scaled measures analyzed with generalized linear regression models adjusted for age, sex, and education level.

- Two independent pretrained models detected greater brain age deviation in GWI.
- The use of independent 2D and 3D architectures strengthens confidence that the effect is not model-specific.

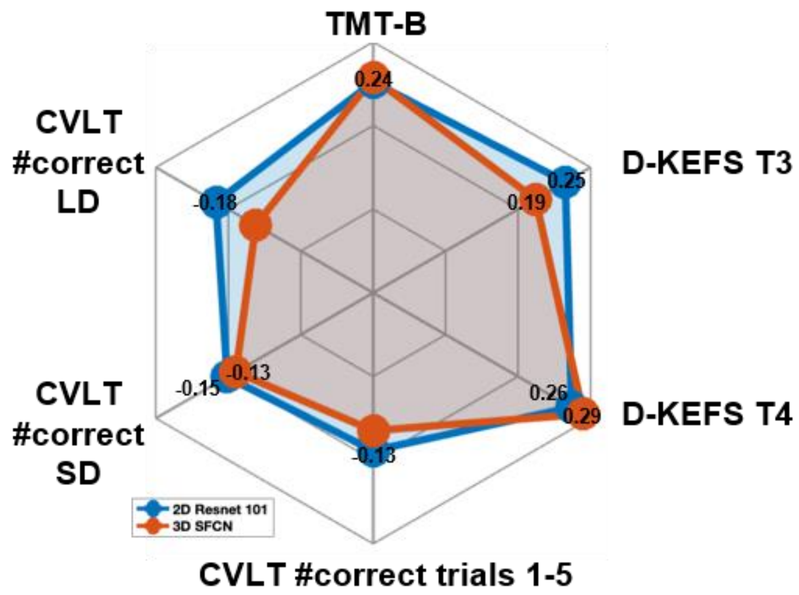

Figure 3. Associations between brain aging measures and health outcome measures. Higher brain age deviations were associated with a number of cognitive and symptom outcome measures. Significant ($p<0.05$) associations were denoted with standardized β estimates at each measure across the spider plot axes. Associations between baseline brain age deviations and cognitive outcomes were adjusted for age, sex, and education level.

- Executive function: Brain age deviation was associated with the Trail Making Test (TMT-B) and the Delis Kaplan Executive Function System (D-KEFS) Color-Word Interference Test, with strongest effects observed for executive function measures (**Figure 3**).
- Memory: Higher brain age deviation was associated with poorer California Verbal Learning Test – Second edition for learning and memory (CVLT-II) in the learning and delayed recall performance.
- Psychomotor speed: Brain age deviation was related to Grooved Pegboard performance (**Table 2**).

Table 2. Associations between baseline brain age deviation measures and follow-up cognitive and health outcomes

		2D ResNet 101		3D SFCN	
Follow-up Outcomes	Sample size	standardized b (95% CI)	FDR P (Raw P)	standardized b (95% CI)	FDR P (Raw P)
Cognitive outcomes					
D-KEFS Trial 3	64	0.43 (0.15, 0.72)	0.007 (0.004)	0.31 (0.02, 0.60)	0.038 (0.038)
D-KEFS Trial 4	64	0.23 (-0.07, 0.52)	0.266 (0.133)	0.08 (-0.21, 0.38)	0.573 (0.573)
CVLT # of correct responses in trials 1-5	64	-0.03 (-0.33, 0.28)	0.848 (0.848)	-0.075 (-0.37, 0.22)	0.848 (0.615)
CVLT # of correct responses in short delay recall	64	-0.10 (-0.40, 0.20)	0.686 (0.499)	-0.06 (-0.35, 0.23)	0.686 (0.686)
CVLT # of correct responses in long delay recall	64	-0.13 (-0.44, 0.17)	0.435 (0.378)	-0.12 (-0.41, 0.18)	0.435 (0.435)
CVLT # of correct responses in List B recall	64	-0.32 (-0.61, -0.03)	0.067 (0.034)	-0.23 (-0.52, 0.06)	0.113 (0.113)
CPT3 Detectability (T-score)	64	0.34 (0.03, 0.65)	0.066 (0.033)	0.27 (-0.04, 0.58)	0.082 (0.082)
CPT3 Commission errors (T-score)	64	0.40 (0.09, 0.70)	0.023 (0.011)	0.23 (-0.08, 0.54)	0.145 (0.145)
CPT3 Perseveration (T-score)	64	0.42 (0.10, 0.72)	0.019 (0.010)	0.23 (-0.09, 0.54)	0.155 (0.155)
Other outcomes					
POMS Fatigue (T-score)	65	0.02 (-0.25, 0.30)	0.866 (0.866)	0.19 (-0.08, 0.46)	0.319 (0.160)
POMS Confusion (T-score)	65	0.15 (-0.13, 0.42)	0.294 (0.294)	0.27 (-0.001, 0.53)	0.101 (0.051)

Summary of Key Findings:

- Veterans with GWI showed significantly greater brain age deviation than GW controls on both ResNet and SFCN.
- Associations were strongest and most consistent for executive functioning measures.
- Brain age deviation was also related to memory, psychomotor speed, systemic inflammation, and pain severity.
- Convergent findings across two models support brain age as a candidate biomarker for long-term neurobiological consequences of GWI.

Conclusions

- Deep learning models trained on brain MRIs show that compared to GW controls, veterans with GWI appear to be 1.4 years older (0.28 standard deviations higher) by the 2D ResNet model, and 1.2 years older (0.25 standard deviations higher) by the 3D Simple Fully Convolutional Network (SFCN) model.
- Brain age deviation correlated with executive, memory, psychomotor, inflammatory, and fatigue measures relevant to GWI.
- These findings support brain age as a promising biomarker for monitoring long-term neurobiological risk and prioritizing early intervention.

References & Acknowledgements

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Conflicts of interest:
None