

## **Nerve agent exposure and physiological stress alter brain microstructure and immune profiles after inflammatory challenge in a long-term animal model of Gulf War Illness Dataset**

Gulf War Illness (GWI) is a disorder experienced by one-third of the veterans of the 1990-91 Gulf War, with symptoms including fatigue, chronic pain, respiratory and memory problems. Exposure to toxic chemicals during the war, such as oil well fire smoke, pesticides, physiological stress, and nerve agents, is thought to have triggered abnormal neuroinflammatory responses that contribute to GWI. Previous studies using animal models have indicated that combined exposure to high physiological stress and GW-relevant organophosphates, such as sarin nerve agent and chlorpyrifos and dichlorvos, produces neuroinflammation and changes in diffusion magnetic resonance imaging (MRI) measures, suggesting a neuroimmune basis for GWI. In the current study, we examined brain structure and immune function of a chronic rat model of GWI and showed that a combination of long-term corticosterone treatment (CORT, to mimic high physiological stress) and diisopropyl fluorophosphate exposure (DFP, to mimic sarin exposure) resulted in elevations of multiple inflammatory cytokines, an increased activated microglial population, and disrupted brain microstructure in the hippocampal regions. Moreover, prior exposures to these agents modeling the “in-theater,” initiating exposure conditions experienced by veterans with GWI can induce long-term alterations in neuroimmune signaling, resulting in an exacerbated neuroinflammatory response to future immune challenges. The goal of the study was to establish a long-term model of GWI in rats that would be more relevant to the current state of ill veterans. As such, rats were initially exposed to the stress hormone corticosterone (CORT) for 1 week followed by a single exposure to the sarin surrogate diisopropyl fluorophosphate, to mimic “in-theater” conditions of high physiological stress and nerve agent exposure. This initial exposure was followed up with 4 weeks of intermittent re-exposure to week-long bouts of CORT and a final exposure to the prototypical inflammagen, lipopolysaccharide (LPS) to mimic a systemic inflammatory challenge.

### **Data Collection Methods**

Adult male Sprague-Dawley rats received CORT (200 mg/L in 0.6% ethanol) in the drinking water (or regular drinking water) for 7 days followed by a single injection of DFP (1.5 mg/kg, i.p.) or saline (control) on Day 8.

Rats were then given 7 day bouts of CORT exposure (or regular drinking water) every other week for an additional 4 weeks with a single injection of LPS (0.25 mg/kg, s.c.) or saline (control) on the day after the removal of the final week of CORT. Experimental groups included: Saline (control), CORT alone, CORT+DFP, CORT+LPS, CORT+DFP+LPS. Inflammatory cytokine mRNA expression was measured in the brain by quantitative real time PCR at 6 hours post-LPS or saline.

### **Publications using this dataset**

Chia-Hsin Cheng, Yi Guan, Vidhi P. Chiplunkar, Farzad Mortazavi, Maria L. Medalla, Kimberly Sullivan, James P. O’Callaghan, Bang-Bon Koo, Kimberly A. Kelly, Lindsay T. Michalovicz (2024) Nerve agent exposure and physiological stress alter brain microstructure and immune profiles after inflammatory challenge in a long-term rat model of Gulf War Illness. *Brain Behav Immun. – Health*. 42: 100878.

### **Acknowledgement**

The work that generated this dataset was supported by Intramural funding from the Centers for Disease Control and Prevention – National Institute for Occupational Safety and Health and Congressionally-Directed Medical Research Program, Gulf War Illness Research Program grants: W81XWH-17-1-0440 and W81XWH-22-10488 (B-B. Koo, PI).

When a publication makes use of this dataset, acknowledgement of the development of the dataset should be attributed to Michalovicz LT, Kelly KA, O’Callaghan JP.

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