FMRI Reveals Abnormal Central Sensory Processing in Gulf War Illness

K. Gopinath[1,2], L. Butler[1], B. Thapa-Chhetry[1], A. Goyal[1], P. Gandhi[1], Y. Fang[1], L. Ouyang[1], S. Ganji[1], L. Jiang[1], S. Vaidya[1], D. Buhner[2], W. Ringe[3], R. Briggs[1,2], and R. Haley[2]

[1]Department of Radiology, UT Southwestern Medical Center, Dallas, TX, United States, [2]Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, United States, [3]Department of Psychiatry, UT Southwestern Medical Center, Dallas, TX, United States

Introduction: Central pain is a widespread symptom of ill Gulf War veterans [1,2]. A previous study [3] reported a two-fold increase in cooling detection threshold during Quantitative Sensory Testing (QST) of right foot in GW Illness veterans. Higher cooling thresholds (in all extremities) and higher warming thresholds (in hands) in veterans suffering from Gulf War Illness were also found in another previous study (Haley et al., personal communication). In this study, brain activation in response to innocuous and noxious heat stimuli was measured with a QST fMRI paradigm, and differences between three groups of ill Gulf War veterans with Syndromes 1 (Syn1), 2 (Syn2), 3 (Syn3) [2], and a healthy control veteran group were assessed.

Methods: Eighty-eight right–handed Gulf-War Veterans (19 Syn1 (mild cognitive impairment: ages 38-69 yrs; mean 49.2 yrs), 20 Syn2 (severe confusion-ataxia: ages 38-65 yrs; mean 49.4 yrs), 20 Syn3 (central pain: ages 40-67 yrs; mean 49.9 yrs), and 29 controls (ages 39-66 yrs; mean 49.8 yrs)), statistically sampled from a national survey of over 8,000 veterans of the 1991 Gulf War, were studied with a QST fMRI paradigm. Written informed consent was obtained from all subjects in the protocol approved by the local Institutional Review Board. Warming and heat pain temperature thresholds for all subjects were first determined outside the scanner with a Medoc Pathway with CHEPS thermode (Medoc, Ramat Yishai, Israel), using the method of limits [4]. The thermode was placed on the right inner forearm of the subjects. MR scans were performed with a Siemens 3T TIM Trio scanner using a 12-channel array receive-only head coil. During each of the six fMRI scans (3 each for innocuous and noxious heat stimulation) 10 thermal stimuli were applied. For each stimulus, the temperature ramped up to the threshold temperature at a rate of 8°C/sec and stayed at that temperature for 3 sec before ramping down to the baseline temperature of 32°C. ISIs of 14, 16 and 18 seconds in duration were pseudo-randomized. FMRI scans were obtained with a whole-brain sagittal gradient echo EPI sequence (TR/TE = 2000/24 ms, FA = 90^0, in-plane resolution = 3 mm x 3 mm, 40 slices with thickness 4 mm). A high-resolution T_1-weighted anatomical scan using a MPRAGE sequence was also acquired. The voxel time series data from each condition were motion corrected, smoothed with a FWHM = 5 mm isotropic gaussian filter and concatenated. Hemodynamic responses (HDR) to the innocuous and noxious heat stimuli were estimated with GLM-based deconvolution analysis. The estimated HDR-amplitude maps were spatially normalized to the Talairach template. Individual group activation (to innocuous and noxious heat) and between-group differences were assessed with 2-way (Group X Runs) mixed effects ANOVA on the HDR amplitudes. These activation maps were clustered and significance of cluster-level activation was assessed with Monte-Carlo modeling [5].

Results & Discussion: There were no significant differences ($p > 0.3$) among the 4 groups in either the warming or heat pain threshold assessed outside the scanner. FMRI activation to innocuous heat (Table 1) and noxious heat (Table 2) in the control group was similar to what is seen in age-matched controls [6,7]. The Syn3 group and to a lesser extent the Syn1 group exhibited significantly less activation ($p < 0.05$) to innocuous heat compared to the controls (Figure 1, Table 1). No significant difference between the innocuous heat activation patterns of the control groups and Syn2 was noted. All three syndrome groups, Syn1 (Figure 2), Syn2 and Syn3 exhibited significantly ($p < 0.05$) decreased noxious heat activation compared to controls in a number of areas associated with pain processing (Figure 2, Table 2). The decreased brain activation to innocuous and noxious heat in ill Gulf War veterans, in conjunction with similar QST thresholds, suggests a neurological abnormality of small-fiber peripheral nerves or central sensory processing, maybe arising from damage of the spinothalamic tract [8]. Abnormalities in thalamus and thalamocortical processing have also been observed in structural and functional neuroimaging studies conducted on the same group of GW Illness patients (unpublished results).

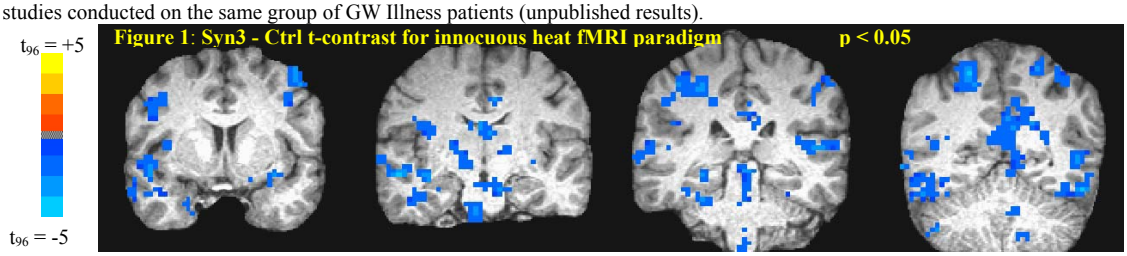

Table 1: Brain activation to innocuous heat

Syn1 < Ctrl ($p < 0.05$)	Left: dorsolateral prefrontal cortex (DLPFC), inferior parietal lobule (IPL), lateral parietal cortex (LPC) Bilateral: primary (S1) and secondary (S2) sensorimotor cortex
Syn3 < Ctrl ($p < 0.05$)	Bilateral: DLPFC, ventrolateral prefrontal cortex (VLPFC), superior temporal gyrus (STG), insular cortex (IC), S1, S2, precentral gyrus (PrecenG), cingulate gyrus (CG), posterior cingulate (PCC), paracentral lobule (PCL), thalamus, basal ganglia, IPL, Brodmann area 7 (BA7), LPC, cerebellum
Control ($p < 0.01$)	Bilateral: dorsal anterior cingulate (DACC), DLPFC, VLPFC, STG, IC, S1, S2, precentral gyrus, cingulate gyrus, PCC, PCL, thalamus, basal ganglia, IPL, BA7, LPC, cerebellum

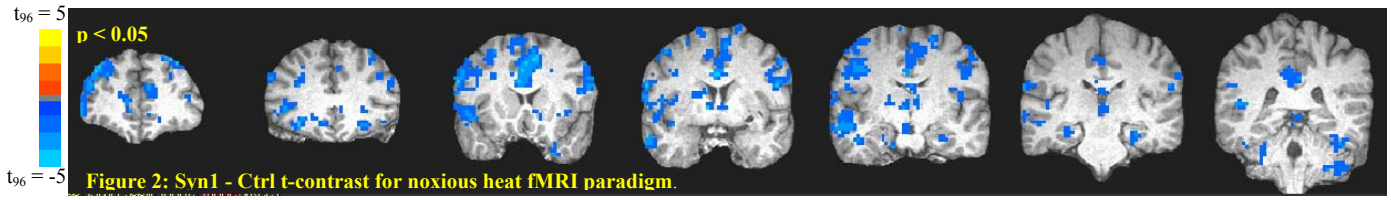

Table 2: Brain activation to noxious heat

Syn1 < Control ($p < 0.05$)	Bilateral: DACC, ventral anterior cingulate (VACC), DLPFC, VLPFC, IC, S1, S2, CG, supplementary motor area (SMA), PCC, IPL, BA7, PrecenG, PCL, amygdala, hippocampus, basal ganglia, thalamus, cerebellum, brainstem
Syn2 < Control ($p < 0.05$)	Bilateral: DACC, DLPFC, IC, S1, S2, CG, SMA, basal ganglia, thalamus, cerebellum, brainstem
Syn3 < Control ($p < 0.05$)	Bilateral: DACC, DLPFC, IC, S1, S2, CG, SMA, PCC, basal ganglia, thalamus, cerebellum, brainstem
Control ($p < 0.00001$)	Bilateral: DACC, VACC, DLPFC, VLPFC, STG, IC, S1, S2, PrecenG, CG, PCC, PCL, thalamus, basal ganglia, amygdala, hippocampus, brainstem, IPL, BA7, LPC, cerebellum

References: [1] Binns J., et al., GWVI-RAC report, 2004 [2] Haley R. et al., JAMA 277:231-7, 2000; [3] Jamal G., et al., J Neurol Neurosurg Psychiatr., 60:449-451, 1996; [4] Forman S., et al.,33:636-47, 1995; [5] Kelly H., et al., Muscle Nerve., 32:179-184, 2005;[6] Sung E., et al., Int J Neurosci., 117:1011-27, 2007; [7] Apkarian A., et al., European Journal of Pain 9:463–484, 2005; [8] Vartiainen N., et al., Pain, 144:200-208, 2009.

Acknowledgments: This study was supported by IDIQ contract VA549-P-0027, awarded and administered by the Department of Veterans Affairs Medical Center, Dallas, TX, by DoD grant DAMD 17-01-1-0741, and by NIH (NCRR) Grant Number UL1RR024982. The content does not necessarily reflect the position or the policy of the Federal government or the sponsoring agencies, and no official endorsement should be inferred.