Quantitative Sensory Testing fMRI: Differences between Gulf War Illness Patients and Deployed Controls

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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warming thresholds (in hands) in veterans suffering from Gulf War Illness were also found in another previous study [unpublished]. In this study, brain activation in response to warm sensation stimuli and painfully hot stimuli was measured with a QST fMRI paradigm, and differences between four groups of Gulf War veterans with Syndromes 1 (Syn1), 2 (Syn2), 3 (Syn3) [2], and control group were assessed.

Methods: Fifty-three right–handed male Gulf-War Veterans: 11 Syn1 (ages 40-60 yrs; mean 51.3 yrs), 16 Syn2 (ages 53-73 yrs; mean 62.8 yrs), 12 Syn3 (ages 47-66 yrs; mean 56.7 yrs), and 14 controls (ages 51-76 yrs; mean 60.5 yrs), were studied with a QST fMRI paradigm. Written informed consent was obtained from all subjects. Warm sensation and hot-pain temperature thresholds for all subjects were first determined outside the scanner with a Medoc Pathway with ATS 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 warm sensation and hot-pain sensation) 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/sec. 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 3.5-4 mm). A high-resolution T_1-weighted anatomical scan using a MPRAGE sequence was also acquired. The 3 hot-pain temperature functional scans were separated in time (by 4 – 5 min) by doing the anatomical scans between them to avoid any confounds that might arise because of subject sensitization to repeated high temperature stimuli.

The voxel time series data from each condition were motion corrected, smoothed with a FWHM = 5 mm isotropic gaussian filter and concatenated. Hemodynamic response (HDR) to the warm and pain stimuli were estimated with GLM-based deconvolution analysis. The estimated HDR maps were spatially normalized to the Talairach template. Individual group activation maps and between-group differences in warm sensation and hot pain activation were assessed with Student's t-tests on the HDR amplitudes. These t-maps were clustered and significance of cluster-level activation was assessed with Monte-Carlo modeling [5].

Results and Discussion: No significant differences were noticed in the warm sensation threshold ($p > 0.5$) assessed outside the scanner between the 4 groups, and in the hot pain threshold ($p > 0.5$) between control group and Syn2 & Syn3. Syn1 had significantly higher hot pain threshold ($p < 0.05$) than the other groups. FMRI activation to warm sensation in the control group was similar to what is seen in age-matched controls [6]. The control group showed significantly higher activation ($p < 0.01$) to warm sensation compared to Syn1 and Syn2 (Figure 1, Table 1). No significant difference between the warm sensation activation patterns of the control groups and Syn3 was noted.

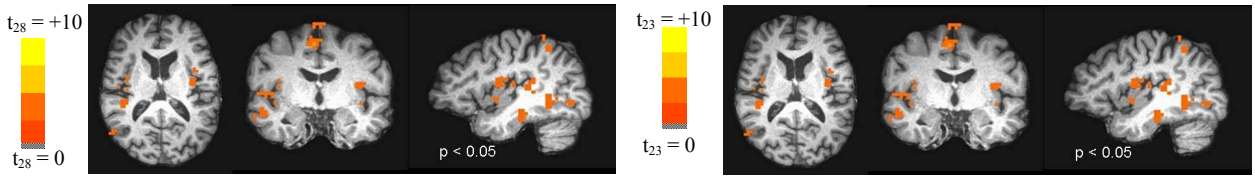

Figure 1: Between group differences in fMRI activation to warm sensation: (left) Control – Syn2, and (right) Control – Syn1

Control > Syn2 ($p < 0.05$)	Bilateral: insular cortex, primary and secondary somatosensory cortices (SI, SII), cingulate gyrus, posterior parietal cortex (PPC), precentral gyrus, supplementary motor area (SMA), superior temporal gyrus (STG), basal ganglia, thalamus
Control > Syn1 ($p < 0.05$)	Bilateral: insular cortex, SI & SII, PPC, cingulate gyrus
Control ($p < 0.01$)	Bilateral: insular cortex, SI & SII, cingulate gyrus, PPC, precentral gyrus, SMA, STG, basal ganglia, thalamus

Table 1: Brain activation to warm sensation

For the hot pain stimuli, the control group exhibited focused activation in sensorimotor, insular cortex and other pain areas reported in literature [7]. Syn2 ($p < 0.01$) and to a lesser extent Syn1 ($p < 0.05$) exhibited higher activation to hot pain compared to controls in a number of areas associated with pain processing (Figure 2, Table 2). The Syn3 group's hot pain activation map was similar to that of the control group.

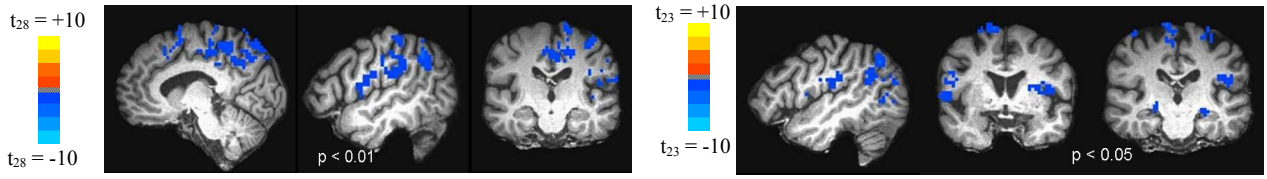

Figure 2: Between-group differences in fMRI activation to hot pain: (left) Control – Syn2, and (right) Control – Syn1

Syn2 > Control ($p < 0.05$)	Left: SI & SII, insular cortex, STG, cerebellum Bilateral: cingulate gyrus, SMA, medial frontal cortex, and brainstem
Syn1 > Control ($p < 0.05$)	Left: SII, PPC, insular cortex, cingulate, STG
Control ($p < 0.00001$)	Left >> Right: SI & SII, PPC, insular cortex, pre-motor cortex, cerebellum, thalamus and basal ganglia

Table 2: Brain activation to hot pain

The greater fMRI activation to warm sensation in the control group compared to Syn1 and Syn2 groups is consistent with prior findings of increased warm sensation detection thresholds in QST of GWS patients [3]. This suggests a neurological abnormality of small-fiber peripheral nerves or central sensory processing in ill Syn1 and Syn2 Gulf War veterans. Increased fMRI activation to pain in Syn1 and Syn2 compared to controls indicates hyper-reactivity of these two syndromes to thermal pain. Taken in conjunction with the lack of differences in pain threshold, this indicates that GWI sensory and pain perception abnormalities are inconsistent with a fibromyalgia model of the disease [8].

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