White Matter Damage in Gulf War Illness Patients: A Quantitative MRI Relaxometry Study

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Introduction: Gulf War Illness (GWI) is a multi-symptom disorder characterized by cognition (e.g. attention, memory), emotion and somatosensory deficits [1-2]. One of the hypothesized causes of GWI is exposure to organophosphates [3-4], which are known to cause demyelination as well as axonal degeneration [5], which can lead to changes in white matter (WM) \( T_2 \) [6-7]. Reductions in regional and global WM volumes have been observed in GWI and other studies of organophosphate exposure [3-4, 8]. Quantitative \( T_2 \) mapping has been employed to examine WM damage in a number of disease models [6, 9-11]. WM \( T_2 \) changes with disease can manifest as lesions, e.g., as in multiple sclerosis (MS) [6], or as \( T_2 \) increases in normal appearing white matter (NAWM) that correlate significantly with cognitive deficits, e.g., Alzheimer’s disease (AD) [9], aging [10] and MS [11]. In this study, WM integrity was examined with a multi-slice multi-echo (MSME) \( T_2 \)-mapping sequence, and differences between three groups of ill Gulf War veterans with Syndromes 1 (Syn1), 2 (Syn2), 3 (Syn3) [2, 12], and a healthy control veteran group were assessed.

Methods: Seventy Gulf-War Veterans (16 Syn1 (mild cognitive impairment: ages 38-69 yrs; mean 49.2 yrs), 18 Syn2 (severe confusion-ataxia: ages 38-65 yrs; mean 49.4 yrs), 12 Syn3 (central pain: ages 40-67 yrs; mean 49.9 yrs), and 24 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 [2, 12], were studied. Written informed consent was obtained from all subjects in the protocol approved by the local Institutional Review Board. Data were acquired with a T2-mapping MSME sequence with the following parameters: TR = 3000 ms, 32 echoes with TEs from 10-320 ms in steps of 10 ms; FOV = 220 mm, 1.7 mm x 1.7 mm in-plane resolution, eleven 7 mm axial slices extending from pons to centrum semiovale. A whole brain high-resolution (1 mm x 1 mm x 1 mm) \( T_2 \)-weighted anatomical scan using a MPRAGE sequence was also acquired. Quantitative \( T_2 \) maps were obtained from the MSME data without nonmonoeponential fitting [13]. The \( T_2 \) maps were spatially normalized to the Talairach template. Average \( T_2 \) maps for each group were calculated and compared in \( T_2 \) between groups were obtained with 2-way (Group X Subjects) mixed-effects ANOVA. The ANOVA t-contrast maps were clustered and multiple comparison corrected significance was assessed with Monte-Carlo modeling [14]. Data analysis was conducted with AFNI, FSL and Matlab.

Results & Discussion: \( T_2 \) relaxation time values in the control group were similar to those reported in normal control populations [13]. Syn2 exhibited significantly (cluster \( p < 0.05 \)) increased \( T_2 \) values (ranging from 2.3-3.5 ms) compared to controls (Figure 1; Table 1) in WM areas of left hemisphere lateral cholinergic pathway [15]: internal and external capsule and corona radiata, in addition to left fornix. Syn3 had significantly (cluster \( p < 0.05 \)) increased WM \( T_2 \) values (ranging from 2.3-3.5 ms) compared to controls (Figure 1; Table 1) bilaterally in parts of the lateral cholinergic pathway, in addition to fornix and brainstem. The Syn2/Syn3 patients did not exhibit WM lesions such as those seen in multiple sclerosis [6] but showed increases in \( T_2 \) in NAWM similar in magnitude to those seen in some MS, AD and aging studies [9-11]. Both Syn2 and Syn3 exhibited decreased \( T_2 \) in a few gray matter areas (e.g. cuneus for Syn2 and anterior cingulate and superior temporal gyrus for Syn3). There were no significant differences between the \( T_2 \) maps of Syn1 and controls.

Increased \( T_2 \) values in cholinergic pathways of Syn2 and Syn3 indicates white matter impairment which could reflect demyelination, axonal degeneration and/or neuroinflammation [6-7]. Reduced WM integrity in cholinergic pathways complements findings of abnormal cerebral blood flow response to cholinergic challenge that have been reported in the same group of patients [16-17]. The increased \( T_2 \) values in WM neighboring insula and hippocampus also corresponds to the areas exhibiting reduced WM volume correlating with serum cholinesterase levels after exposure to sarin [8].

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<td>Left hemisphere lateral cholinergic pathway: internal/external capsule, corona radiate, fornix</td>
<td>Cuneus, occipital gurus</td>
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Table 1: Areas with significant between-group differences in \( T_2 \) relaxation times


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