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

Kaundinya Gopinath[1,2], Saurabh Vaidya[2], Sandeepkumar Ganji[2], Sergey Cheshkov[2], Robert Haley[3], and Richard Briggs[2,3]

[1]*Department of Radiology & Imaging Sciences, Emory University, Atlanta, GA, United States,* [2]*Department of Radiology, UT Southwestern Medical Center, Dallas, TX, United States,* [3]*Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, United States*

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., Alzheimers'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 T_2-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 x1 mm x 1 mm) T_1-weighted anatomical scan using a MPRAGE sequence was also acquired. Quantitative T_2 maps were obtained from the MSME data with monoexponential fitting [13]. The T_2-maps were spatially normalized to the Talairach template. Average T_2 maps for each group were calculated and differences 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 controlled 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].

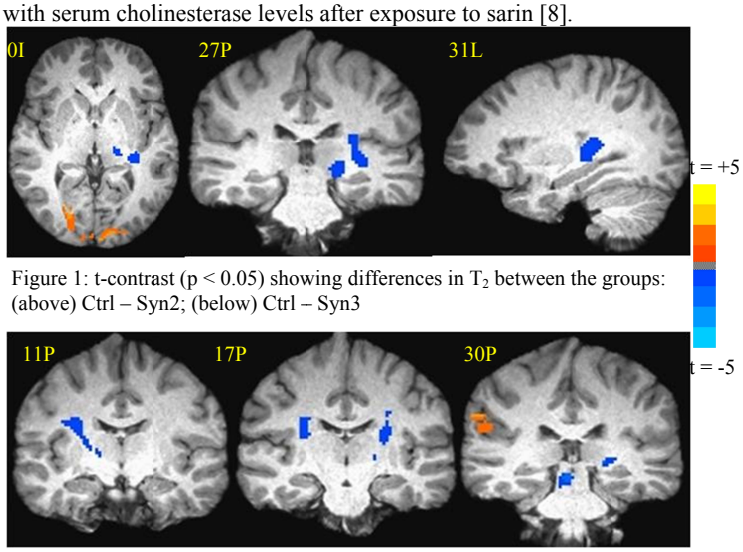

Figure 1: t-contrast ($p < 0.05$) showing differences in T_2 between the groups: (above) Ctrl – Syn2; (below) Ctrl – Syn3

Syn2 > Control ($p < 0.05$)	Left hemisphere lateral cholinergic pathway: internal/external capsule, corona radiate; fornix
Control > Syn2 ($p < 0.05$)	Cuneus, occipital gurus
Syn3 > Control ($p < 0.05$)	Bilateral lateral cholinergic pathway: internal/external capsule, corona radiate; fornix extending to hippocampus, centrum semiovale; brainstem, posterior WM
Control > Syn3 ($p < 0.05$)	Bilateral anterior cingulate, superior temporal gyrus at BA42 and BA40, S1

Table 1: Areas with significant between-group differences in T_2 relaxation times

References: [1] Binns J., et al., GWVI-RAC report, 2004 [2] Haley R., et al., JAMA 277:231-7, 2000; [3] Heaton K., et al.,Neurotox., 28:76-769, 2007; [4] Chao L., et al., Neurotox., 32:814-822, 2011; [5] Chang P-A., et al., Chem. Bio. Interac., 180:127-130, 2009; [6] MacKay A., et al., Neuroim. Clin N Am., 19:1-26, 2009; [7] Deoni S., et al., Top. Magn. Reson. Imag., 21:101-113, 2010; [8] Yamasue H. et al., Ann Neurol 61:37-46, 2007; [9] House M., et al., Am J Neuroradiol., 27:430-439, 2006; [10] Bartzokis G., et al., Neurobiol. Aging, 31:1554–1562, 2010; [1] Whittall K., et al., Mag. Reson. Med., 47:403-409, 2002; [12] Iannacchione V., et al., Neuroepidemiol., 37:129-140, 2011; [13] Wasnapura J., et al., J Mag. Reson. Imag., 9:531–538, 1999; [14] Forman S., et al., Mag. Reson. Med., 33:636-47, 1995; [15] Selden N., et al., Brain, 121:2249-2257, 1998; [16] Liu P., et al., Neurotox., 32:242-246, 2011; [17] Li X. et al. Radiology, 261:218-225, 2011.

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. The authors would like to acknowledge Dr. Thomas Mareci, PhD., University of Florida, for useful discussions.