Transverse Relaxation Measurements of Brain Metabolites in Gulf War Illness

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Introduction
Relaxation times are often an assumed value in spectroscopy studies, despite their potential diagnostic value and usefulness in quantifying metabolite concentrations. The purpose of this study was to measure the transverse (T_2) relaxation times of the major brain metabolites (NAA, Cr_t, and Cho_t) in left and right basal ganglia of veterans with Gulf War Illness (GWI) and age-matched veteran controls to determine if the T_2 values differ between ill veterans and controls or among the three syndrome variants of GWI.

Methods
Gulf War veteran subjects consisted of 49 male participants (44-76 years old, mean age 59±7.2), from the Twenty-fourth Reserve Naval Mobile Construction Battalion (Seabees), the same group from earlier studies on GWI *(1-4)*. The age- and education-matched groups consisted of 14 normal veterans, 10 Syndrome 1 ("impaired cognition"), 14 Syndrome 2 ("confusion-ataxia"), and 11 Syndrome 3 ("central pain") subjects. T_2 relaxation times of N-acetylaspartate (NAA), creatine (Cr_t), and choline (Cho_t) were measured with a 3T Trio TIM system (Siemens AG, Erlangen, Germany) using a 12-channel head coil and single-voxel spectroscopy (SVS) PRESS with varying echo delay (TE) values of 60, 90, 135, 195, and 270 ms (32 averages at TE ≤ 135 ms, 64 averages at TE ≥195 ms, to compensate for decreasing SNR at higher TE values) at a TR of 2500 ms. The voxel (20mm x 30mm x 20mm) was placed reproducibly in the basal ganglia for each measurement (Fig. 2) by using the Siemens AutoAlign feature with high-resolution localizers. For each measurement on individual subjects, the water line width was approximately 18 Hz or less. Post-acquisition analysis consisted of HLSVD filtering of the remaining water signal, apodization of 5 Hz, quantification of metabolite signals by the non-linear AMARES algorithm of the jMRUI software package *(5)*, and an unweighted least-squares fit of the logarithm of the peak areas vs. echo time.

Results
The Syndrome 2 group had significantly ($p<0.05$) longer T_2 values than the veteran controls in left basal ganglia NAA (11.4% longer, $p = 0.019$) (Fig. 1) and Cr_t (6.4% longer, $p = 0.044$) and in right basal ganglia Cho_t (9.55% longer, $p = 0.021$). Syndrome 2 subjects also had significantly ($p<0.05$) longer T_2 values than Syndrome 1 veterans (Fig. 1) in left basal ganglia NAA (11.35% longer, $p = 0.007$). NAA T_2 values for Syndrome 1 subjects were quite similar to those for normal control subjects in both mean and distribution.

Discussion
Significant differences between groups (GWI Syndromes 1-3 and controls) in metabolite T_2 values in the basal ganglia were measured in several instances. The molecular mechanisms underlying the longer NAA and Cr_t T_2 in left basal ganglia and Cho_t T_2 in right basal ganglia of Syndrome 2 subjects compared to normal controls (and Syndrome 1 subjects in left basal ganglia NAA) are unknown, but reflect a similar trend observed in NAA T_2 relaxation in patients with Alzheimer's disease *(6)*. These relaxation time differences could contribute to group differences in metabolite concentrations measured with long echo times, but are insignificant factors (a 10% difference in NAA T_2 values would result in <2% correction in concentration values at TE=30ms) in short echo time spectroscopy. Further statistical analysis (e.g. non-parametric testing) might be necessary for better outlier assessment. Expansion of the subject population beyond the original cohort is in progress.

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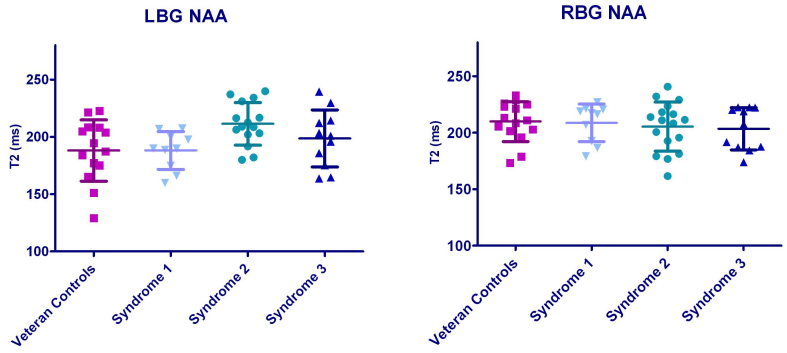

Fig 1. Left and right basal ganglia NAA T_2 relaxation data (in ms) for Gulf War veteran subjects

Metabolite (Area)	Control T_2 (ms)	Syn 1 T_2 (ms)	Syn 2 T_2 (ms)	Syn 3 T_2 (ms)
NAA (LBG)	188 ± 27	188 ± 16	211 ± 18	199 ± 25
NAA (RBG)	210 ± 18	209 ± 16	205 ± 22	203 ± 19
Cr_t (LBG)	117 ± 10	117 ± 10	124 ± 8	120 ± 12
Cr_t (RBG)	128 ± 13	129 ± 10	128 ± 15	122 ± 8
Cho_t (LBG)	156 ± 32	153 ± 18	164 ± 18	157 ± 20
Cho_t (RBG)	158 ± 15	165 ± 31	174 ± 19	165 ± 13

Table 1. NAA T_2 relaxation data (in ms) for left and right basal ganglia in Gulf War veteran subjects.

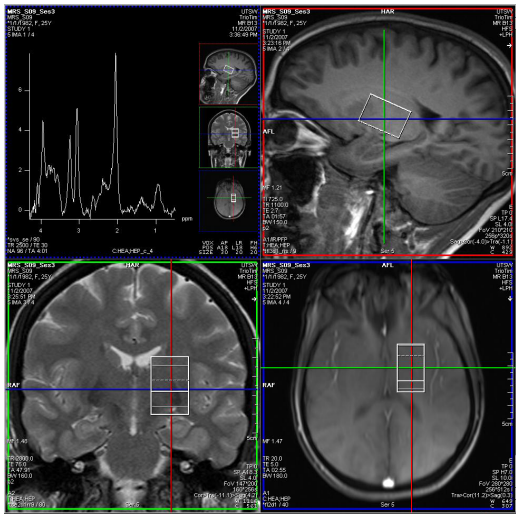

Fig 2. Location of the left basal ganglia voxel and a sample spectrum

References
1. Haley RW, Marshall WW, McDonald GG, Daugherty MA, Petty F, Fleckenstein, JL. *Radiology* 2000; 215: 807-817.
2. Haley RW, Fleckenstein, JL, Marshall WW, McDonald GG, Kramer, GL, Petty F. *Arch. Neurol.* 2000; 57: 1280-1285.
3. Hom J, Haley RW, Kurt TL. *Arch Clin Neuropsychol* 1997; 12: 531-544.
4. Haley RW, Kurt TL, Hom J. *JAMA* 1997; 277: 215-222.
5. Naressi A, Couturier C, Devos JM, Janssen M, Mangeat C, de Beer R, Graveron-Demilly D. *MAGMA* 2001; 12: 141-152.
6. Christiansen P, Schlosser A, Henriksen O. *Magn. Reson. Imaging* 1995; 13: 457-462.