

Persistent basal ganglia NAA/Cr ratio differences in Gulf War Illness

S. Cheshkov^{1,2}, A. Chang¹, H-M. Baek¹, S. Ganji¹, E. Babcock¹, R. Briggs^{1,2}, and R. Haley²

¹Radiology, UT Southwestern Medical Center, Dallas, TX, United States, ²Internal Medicine, UT Southwestern Medical Center, Dallas, TX, United States

Introduction

Abnormalities in ratios of brain metabolites, namely decrease in the N-acetylaspartate to creatine ratio (NAA/Cr), were previously measured via magnetic resonance spectroscopy (MRS) at 1.5T in bilateral basal ganglia and pons [1,2] and in left hippocampus [3] of Gulf War Illness patients. The original veterans of the Seabees cohort studied in 1997-1998 [1] recently participated in a follow-up study at 3T. A part of the protocol used single voxel spectroscopy (SVS) ¹H MR to study metabolite concentrations in the left and right basal ganglia of control veterans and three illness variants called Syndromes 1 (“impaired cognition”), 2 (“confusion-ataxia”), and 3 (“central pain”) [4]. The group comparison of this new 3T data indicates lower NAA/Cr ratio in all three Syndrome groups compared to the control (Ctl) group, the decrease is significant in the left basal ganglia and nearly significant in the right basal ganglia. This study advances the understanding of the chemical changes in the brain in Gulf War Illness and indicates possible neuronal damage in the affected population.

Methods

Fifty-five Gulf War veterans (16 control subjects, 11 Syndrome 1 veterans, 16 Syndrome 2 veterans, and 12 Syndrome 3 veterans), matched by age, sex, and education, were studied with the same SVS left and right basal ganglia protocol. A single voxel spectroscopy sequence (SVS PRESS) was used on a Siemens 3T Trio TIM with the following parameters: TR/TE/NS = 2500ms/30ms/96, voxel (centered in the basal ganglia, bilaterally) volume = 12.0 mL (20 mm x 30 mm x 20 mm), spectral width = 2000 Hz, water suppression bandwidth = 50 Hz, data points = 1024, acquisition time = 4:10 min. An unsuppressed water spectrum was also acquired for eddy current compensation and quantitation. High-resolution, high-contrast localizer images were used to ensure accurate and reproducible voxel positioning. Post-processing of the MRS data was performed using LCModel [5]. Group and hemispheric differences were studied using two-tailed parametric (t test) and nonparametric (Kruskal-Wallis) tests and unbalanced 2-way ANOVA.

Results and Discussion

Manual adjustment of the shim currents produced metabolite half-height line widths of 9-14 Hz in most sessions. An example of the basal ganglia spectrum processed with LCModel is shown in Figure 1. The average Cramer-Rao lower bounds were in the range of 3-4% for creatine (Cr), N-acetyl aspartate (NAA), and total choline. Although a water reference spectrum was collected for metabolite quantitation, the NAA/Cr ratio is reported for comparison with the original [1] study and because it is less sensitive to individual shim variations and possible metabolite relaxation time differences [6]. The mean NAA/Cr ratio in the left basal ganglia (LBG) was approximately 12% lower in Syndrome 1, 7% lower in Syndrome 2, and 14% lower in Syndrome 3 than in the control group. The same ratio in the right basal ganglia (RBG) was 6% lower in Syndrome 1, 4% lower in Syndrome 2, and 5% lower in Syndrome 3 than in the control group (see Table 1 for pair-wise two-tailed t test data and significance levels). With a relatively small number of subjects in each group, non-parametric testing (Kruskal-Wallis) typically provides greater statistical power and better control for outliers, as illustrated in Table 1 and Figure 2. In a 2-way ANOVA, $p = 0.0002$ for the group factor significance. Additionally, the NAA/Cr ratio is significantly lower in the right basal ganglia than in the left, with an overall hemispheric effect significance of $p < 0.0001$. In the original Haley et al. study [1], Syndrome 2 patients had significantly lower NAA/Cr in the right basal ganglia than did controls (18% difference, $p < 0.001$, single tail tests) and a less significant group difference in the same direction in the left basal ganglia (9% difference, $p < 0.09$). Preliminary data from a subset of the controls and Syndrome 2 subjects in this study showed similar results [7]. Similarly, Meyerhoff et al. [2] reported that NAA/Cr was reduced by 11% in right basal ganglia of GW Illness veterans compared to controls ($p = 0.05$).

Conclusion

N-acetylaspartate is widely regarded as an objective marker of neuronal health or viability, and any statistically significant reductions in NAA are potentially important indicators of organic brain disease. The observed trends in the current Gulf War Illness study are consistent with previous work done a decade ago [1,2]; the differences in the magnitude of the NAA/Cr reductions between [1] and the present work may be due to differences in methods used in the two studies or changes in the disease process with time. Metabolite relaxation time measurements were also performed in the current study; these results will be reported separately.

Acknowledgments

This study was supported by IDIQ contract VA549-P-0027, awarded and administered by the Department of Veterans Affairs Medical Center, Dallas, TX, and by NIH (NCR) 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 acknowledge Drs. Kaundinya Gopinath, Jeffrey Spence and Mette Posamentier for useful discussions.

References

- [1] Haley, R. et al., Radiology 2000; 215: 807-817.
- [2] Meyerhoff, D.J. et al., Proc Intl Soc Magn Reson Med 2001; 9: 994.
- [3] Menon et al., Brain Res. 2004; 1009: 189-194.
- [4] Haley R. et al., JAMA 1997; 277: 215-222.
- [5] Provencher, S., Magn Reson Med 1993; 30: 672-679.
- [6] Traber, F. et al., J Magn Reson 2004; 19: 537-545.
- [7] Cheshkov, S et al. Proc. Intl Soc Magn Reson Med 2009; 17: 1126.

Table 1. Mean basal ganglia NAA/Cr ratio (and group standard deviation) by group and hemisphere. P-values are for parametric and non-parametric comparisons to the control group.

	LBG NAA/Cr (SD)	p-value, param/non-param	RBG NAA/Cr (SD)	p-value, param/non-param
Ctl	1.38(0.17)		1.18(0.10)	
Syn 1	1.21(0.10)	0.006/0.003	1.11(0.12)	0.09/0.06
Syn 2	1.28(0.11)	0.06/0.013	1.13(0.09)	0.12/0.16
Syn 3	1.19(0.10)	0.002/0.001	1.12(0.09)	0.09/0.08

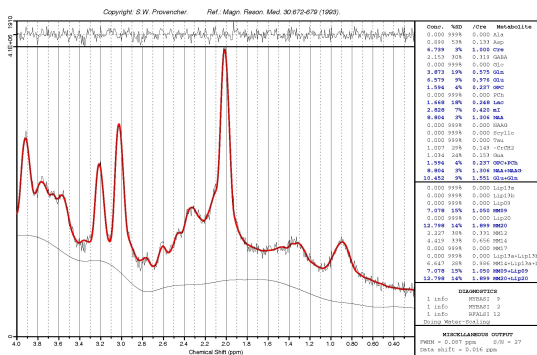


Figure 1. 3T ¹H MR spectrum of the left basal ganglia of a representative subject processed using LCModel. Metabolites detected with acceptable reliability are shown in blue.

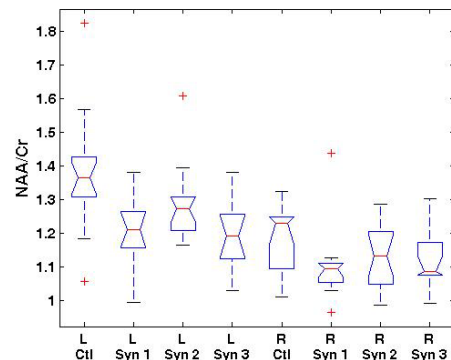


Figure 2. Group and hemispheric differences in the basal ganglia NAA/Cr ratio. Red lines represent median values. Non-intersecting notches indicate significance (here in median values, $p < 0.05$). Plus signs represent outliers (outside of 1.5 inter-quartile range).