Reduced NAA and Glutamate in Healthy Military Subjects Compared to Civilian Controls

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TARGET AUDIENCE: Researchers and clinicians with interest in brain metabolism in military medicine

PURPOSE: Many studies have examined traumatic brain injury and post-traumatic stress disorder among other neurological disorders in military subjects. A few of these research studies had used healthy civilian subjects as a control group and found significant differences between patients and controls. However, comparing civilian controls alone with military patients might introduce flaws to data analysis since there may be inherent differences between military and civilian subjects. To our knowledge, there has not been a systematic study that challenges the assumptions that the cohorts are the same. In this ^{1}H MRS study, the main objective was to investigate the validity of this assumption by detecting the significant difference in MRS quantifiable metabolites between healthy military subjects and civilian subjects.

METHODS: *Participants.* 9 healthy military subjects (including service members and veterans, mean age 32.1±9.7, 3 female, 6 male) and 9 age- and gender-matched healthy civilian controls (mean age 32.7±11.6) were recruited and consented under local IRB approval. Both healthy military and civilian subjects had no history of neurological disorders, psychological disorders or drug addiction by self-report. All subjects also underwent neuropsychological evaluation including Rivermead Post-Concussive Symptoms Questionnaire, Post Traumatic Stress Disorder (PTSD) Checklist – Civilian Version, Beck Depression Inventory II, Automated Neuropsychological Assessment Metrics – version 4- TBI Battery, Wechsler Memory Scale – III Spatial Span Test, Rey Auditory Verbal Learning Test, Test of Memory Malingering, Trail Making Test - A&B, Wechsler Adult Intelligence Scale III, Processing Speed Index.

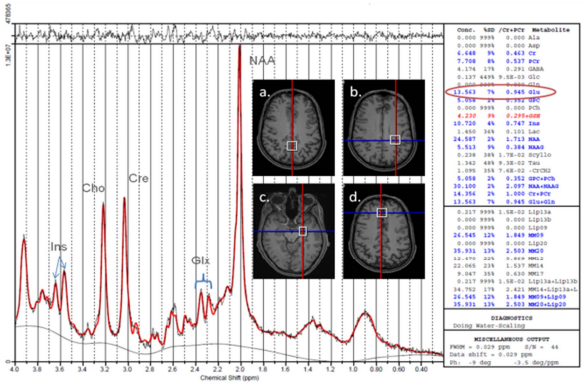

Figure 1. An example of LCmodel processed spectrum acquired from PWM in a healthy military subject. Inset: the four different MRS voxel locations studied: a. PCG, b.PWM c. Left-temp, d. ACG.

MRS data acquisition and analysis. This study was performed in a Siemens 3T MAGNETOM Skyra scanner and using 32-channel head coil. Single Voxel MRS was acquired using conventional PRESS in four different brain regions shown in Figure 1: Posterior Cingulate Gyrus (PCG; 20x20x20mm), Posterior White Matter (PWM; 20x20x20mm), Anterior Cingulate Gyrus (ACG; 20x20x20mm) and Left-temporal Lobe (hippocampus area, Left-temp; 20x15x15mm). All voxels were acquired using TE = 30 ms, TR = 2 s, bandwidth = 1.2 kHz, 1024 complex data points, water saturation, and 128 averaged acquisitions. Unsuppressed water spectrum with the same parameters but without water suppression and 16 averages. Total scan time: 5.13 minutes per voxel. PRESS data was analyzed using LCmodel. Metabolite concentrations were expressed in institutional units as well as a ratio of metabolite to total creatine (Cr+PCr).

RESULTS: Figure 1 shows an example of a 3T spectrum acquired in a healthy military control. Among all LC-model quantifiable metabolites, glutamate and NAA concentration showed significant differences between healthy military and civilian subjects. Compared to civilian subjects, lower Glu/Cr+PCr ratios were observed in military subjects in all four voxel locations (Figure 2a) and significantly in PCG ($p<0.05$) and PWM ($p<0.001$). In addition, reduced NAA+NAAG/Cr+PCr ratios were also observed in military subjects across all four voxel locations (Figure 2b) and significantly lower in PCG ($p<0.05$) and, PWM ($p<0.001$). Cr+PCr was not found to be significantly different. All healthy civilian and military subjects were negative for post-concussive symptoms, PTSD, and depression. There were no significant differences between the two groups in their performance on neuropsychological testing.

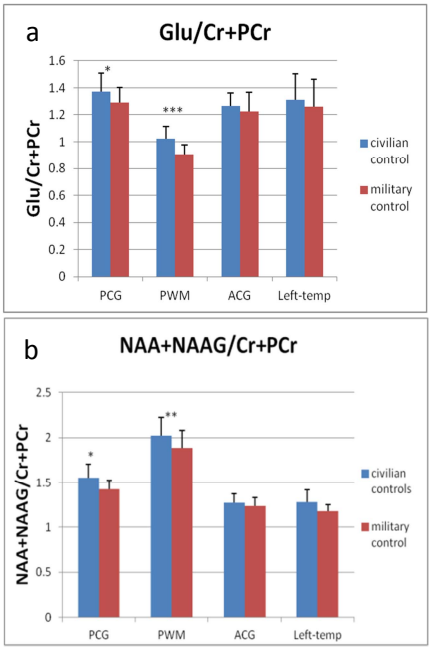

Figure 2. a.Regional Glu/Cr+PCr ratio.
b Regional NAA+NAAG/Cr+PCr ratio.
* $p<0.05$, ** $p<0.01$, *** $p<0.001$

DISCUSSION: Glutamate and NAA showed similar trends which both had lower mean ratios in the military group across all four voxel locations and the most significant reduced mean ratios in PWM. Even though similar findings were shown in glutamate and NAA, they were not highly correlated with each other with R^2=0.54 in PWM. Reduced Glu and NAA have been found in depression[1] however both cohorts did not show depression as evaluated by BDI. Regarding lower NAA, a study showed that changes of NAA may be due to different education levels[2], but we did not find significant difference in years of education between civilian and military group in this study. Therefore, the reason for lower Glutamate and NAA in healthy military subjects than civilian subjects in this study is still unclear. Future studies will include a larger cohort and additional measures to compare the two groups.

CONCLUSION: Lower Glutamate and NAA concentration in healthy military group compared to healthy civilian group indicates a difference between the two and the assumption that the two groups are the same is not true. Military studies should utilize healthy controls with similar military background.

REFERENCES: 1. Merugumala et al. MRI in Psychiatry. (2014) 2.Glodzik L et al. Psychiatry Research: Neuroimaging. 204 (1) 49–54 (2012)

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