Metabolite Changes in Anatomical Substructures of the Brain Following Traumatic Brain Injury

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INTRODUCTION: Cognitive deficits are commonly observed in as many as one third of subjects with mild traumatic brain injury (TBI; [1]). The underlying causes of the observed cognitive deficits common to this group of subjects might be presence of tissue microstructural and/or metabolite alterations in brain anatomical substructures that mediate cognitive function. Conventional neuroimaging methods are, however, not helpful in identifying neuropathological correlates for the cognitive deficits. Our previous whole-brain MRSI study [2], in which data analyses were performed by brain lobes, indicated widespread and diffuse proton metabolite alterations in subjects with mild-to-moderate TBI. It has been reported recently that changes in tissue volume/structure or metabolite abnormalities in the hippocampus, anterior cingulate, prefrontal cortex, middle frontal gyrus, superior parietal cortex, basal ganglia and thalamus in subjects with TBI correlated with cognitive fatigue [3], depression [4], and memory functioning [5]. In this study, metabolite data from 28 bilateral brain anatomical substructures were extracted from whole-brain MRSI data to evaluate alterations in N-acetyl aspartate (NAA), total-choline (Cho) and total-creatine (Cr) in subjects with TBI by comparing with a group of controls.

METHODS: MRI and MRSI data were obtained at 3T from 39 subjects with mild-to-moderate TBI (Glasgow coma scale score: 8-15, mean age: 25.3 years, age range: 18-42 years; scanned between 1 and 15 weeks after injury) and 88 age-range matched controls (mean age: 28.5 years). The MRSI data were obtained from the whole-brain using a volumetric EPSI sequence (TR/TE=1710/70 ms, 135 mm slab, T_{acq}= 26 min.; details in [2]). Data were processed using the MIDAS package [6, 7]. After 3D spatial smoothing, the processed MRSI data were interpolated to 64x64x32 mm^3, and then spatially registered with the MNI T1-MRI template at 2 mm isotropic resolution. For identifying anatomical substructures, a brain atlas in MNI space with 45 3D-anatomical volumes in each hemisphere was used [8]. The 14 volumes selected for this study include cingulum, hippocampus, caudate, putamen, thalamus, and some of the volumes were obtained by combining contiguous volumes in the same lobe. In each of the volumes, spectral quality was controlled by including only spectra from voxels with fitted linewidths of ≤ 12 Hz and tissue volume ≥70% of the voxel volume. The NAA and Cho values (in institutional units) and Cho/NAA ratio were compared between the groups using the 2-tailed t-test, and a p-value of ≤0.05 was considered significant. For brevity, only data from 5 volumes are shown.

RESULTS AND CONCLUSIONS: In the table, the mean metabolite values or Cho/NAA ratio in 5 volumes in the left hemisphere of the control and TBI groups are listed and the results from the right hemisphere volumes are similar. The observations from the table, in the TBI group as compared to the control group, are: 1) significantly decreased NAA in all the anatomical structures, with % of decrease ranging from 5.3% in the cingulum to10.3% in the hippocampus, 2) there was no difference in Cho and Cr (not shown), and 3) significantly increased Cho/NAA in all the volumes but the putamen. The results indicate that significant metabolite alterations, specifically in NAA, occurred in these anatomical substructures of the brain after TBI. The absence of significant change in Cr and Cho indicates that the neurons in these structures may be dysfunctional or partially recovered from injury. In addition, the results suggest that there are primary or secondary microscopic injuries in these structures undetectable on conventional MRI. Metabolite changes observed in these structures can be correlated with neuropsychological test scores obtained from the group of subjects with TBI to evaluate associations between the metabolite changes and compromised cognitive function. This study shows the advantage of acquiring whole-brain MRSI data and the flexibility it provides for analysis using lobar and anatomical substructural brain atlases.

Table: Metabolite values (in inst. units) and ratio in 5 anatomical regions in the left hemisphere for the TBI and control groups. Mean ± SD and p-values (*p≤0.05, **≤0.01) are provided.

Metabolite	Group	Cingulum	Hippocam.	Caudate	Putamen	Thalamus
NAA	TBI	2516 ±397*	2285±328**	2344±356**	2503±361*	2524±388**
	Control	2666±239	2547±271	2518±281	2650±238	2734±257
Cho	TBI	426±70	526±79	472±84	456±82	529±96
	Control	429±56	537±77	484±76	466±75	535±74
Cho/NAA	TBI	0.17±0.02*	0.23±0.03**	0.20±0.03**	0.18±0.02	0.21±0.03**
	Control	0.16±0.02	0.21±0.03	0.19±0.02	0.18±0.02	0.20±0.02

ACKNOWLEDGEMENTS: This work is supported by NIH grants R01NS055107 and R01EB000822.

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