Multimodal Imaging of Functional Alterations of the Thalamus Following Mild Traumatic Brain Injury

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Purpose: The aim of this study is to investigate the acute functional alterations in the thalamus following mild traumatic brain injury (mTBI) using resting state fMRI (rs-fMRI) and magnetic resonance spectroscopy imaging (MRSI). Following injury, mTBI patients experience a wide array of somatic and cognitive symptoms. Since the thalamus acts as a relay center between sensory inputs and cortical processing and includes multiple nuclei with projections to cortical areas associated with sensory and cognitive processing. Since mTBI is a diffuse injury it is likely that these connections will be functionally disrupted following injury.

Methods: Participants included 77 mTBI patients (44.0±17.0 yrs; 59M/18F) who received a rs-fMRI scan at the acute stage (within 10 days of injury) and 35 controls (HC) (37.2±17.3 yrs; 19M:16F). A subset of these mTBI patients (n=47) and HCs (n=28) received an MRS scan. In addition, a subset of mTBI patients (n=49) and HCs (n=34) completed the Automated Neuropsychological Assessment Metrics (ANAM) [1], a computerized cognitive assessment.

Imaging was performed on a Siemens Tim-Trio 3T MRI scanner using a 12-channel receive only head coil. A high resolution T1-weighted-MPRAGE was acquired for anatomic reference. For the resting state fMRI scan, T2*-weighted images were acquired using a single-shot EPI sequence (TE = 30 ms, TR =2000 ms, FOV = 220 mm, resolution = 64 × 64) with 36 axial slices (sl. thick. = 4 mm) over 5 min 42 s that yielded 171 volumes. The CONN-fMRI Functional Connectivity toolbox v13.h was used to process the resting state data, and included slice time correction, realignment, coregistration to structural image, spatial normalization to MNI template and spatial smoothing (5mm Gaussian Kernel). Mean BOLD time series from white matter, CSF, and 6 motion correction parameters were included as regressors. Seed based resting state functional connectivity (rs-FC) analysis was completed using the 7 sub-thalamic regions from Oxford thalamic connectivity Atlas to create group rs-FC maps for the mTBI and HC groups. Sub-thalamic regions include those with projections to primary motor (M1), primary sensory (S1), occipital lobe (OCC), premotor cortex (PM), prefrontal cortex (PFC), posterior parietal cortex (PP) and temporal lobe (TEMP). To determine the rs-FC between the sub-thalamic regions and cortical areas, two sets of correlation matrices were created using the 7 sub-thalamic ROIs and cortical regions associated with (1) Default Mode Network (DMN) and (2) Sensory areas including Broadman's Areas (BA) 1, 2, 3, 4, 6, 17, 41, 42, 46.

MRS was acquired using 3D phase-encoded point-resolved spectroscopy (3D-PRESS) MRSI sequence (TE/TR = 135/1300ms; FOV = 160x160x106mm^3; VOI = 106x106x48mm^3; acquired resolution = 12x12x8; interpolated resolution = 16x16x8; total acquisition time = 7min 40sec). Quantification of the MRSI data was carried out offline using LCModel. [2] The NAA/Cr and Cho/Cr ratios were calculated for the average of two voxels in the right and left thalamus as well as in a voxel located in the posterior cingulate cortex (PCC).

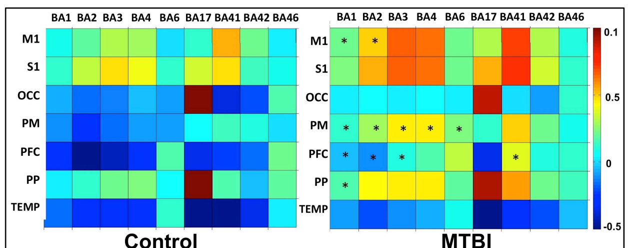

Figure 1: Correlation matrices between sub-thalamic ROIs and cortical areas associated with sensory processing. Brodmann's areas (BA) 1, 2, 3, 4, 6, 17, 41, 42, 46. *p <0.05 (unc) based on t-test between HC and mTBI.

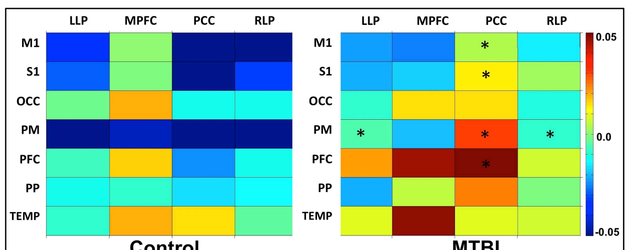

Figure 2: Correlation matrices between sub-thalamic ROIs and DMN regions. Posterior cingulate cortex (PCC), left and right lateral parietal (LLP, RLP), medial prefrontal cortex (MPFC). *p <0.05 (unc) based on t-test between HC and mTBI.

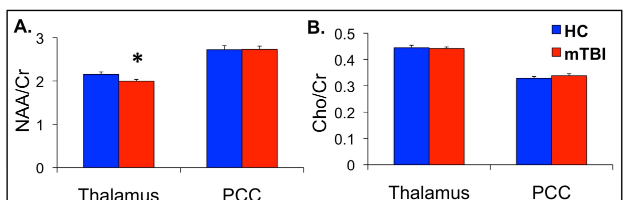

Figure 3: MRS Results: A. NAA/Cr Ratio B. Cho/Cr Ratio * p < 0.05

Results and Discussion: Acute mTBI patients demonstrated reduced cognitive performance compared to HCs on the weighted throughput score of the ANAM (p=0.001) as well as multiple subtests including code substitution, code substitution delayed, match to sample, mathematical processing, and procedural reaction time (p-values < 0.05). Rs-fMRI data suggests increased thalamo-cortical connectivity in acute mTBI patients. Specifically, compared to the HC group, acute mTBI patients have increased rs-FC between multiple sub-thalamic seed regions and cortical areas associated with primary motor and somatosensory processing (BA1-4), premotor (BA6) and primary auditory processing (BA41) (Figure 1). Compared to the HC group, mTBI patients have increased rs-FC between multiple sub-thalamic seed regions and the PCC node of the DMN as well as increased rs-FC between the PM sub-thalamic region and the LLP and RLP (Figure 2). Acute mTBI patients have a reduced NAA/Cr ratio in the thalamus, but not in the PCC. No differences in Cho/Cr ratio were noted in either the thalamus of PCC (Figure 3). Numerous correlations between rs-FC between the thalamus and cortical areas and Cho/Cr ration were noted in the HC group that are absent from the acute mTBI group suggestive of an association between altered rs-FC and metabolic changes in the thalamus.

Conclusion: Our results suggest that during the acute stage of mTBI there is increased thalamo-cortical connectivity, including both increased connectivity between the thalamus and cortical areas associated with primary sensory processing as well as the DMN as well as an altered metabolic profiles with reduced NAA/Cr in the thalamus. These results provide evidence for a functionally damaged thalamus in the initial days following mTBI and may be associated with common post concussive symptoms experienced by these patients including sensitivity to sensory stimuli and cognitive deficits.

References: [1] Kane et al., 2005. [2]Provencher, 2001