Default Mode Interference in Mild Traumatic Brain Injury: Alterations in Functional Connectivity and Cerebral Blood Flow at Rest

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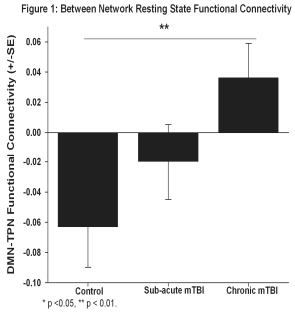
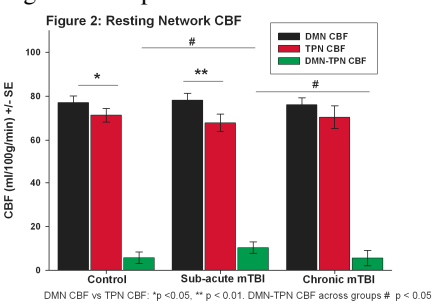
Purpose: To understand the mechanisms of recovery following mild traumatic brain injury (mTBI) and its relationship with cognitive functioning. Following mTBI, many patients exhibit post-concussive symptoms and cognitive deficits. Often clinical CT and conventional MRI are negative on such patients. Due to the diffuse nature of the injury, and especially in the absence of a focal abnormality we speculate that alterations in resting state fMRI and resting cerebral blood flow may provide better insights into the cognitive condition of the mTBI patient. Two common resting state networks are the Default Mode Network (DMN) and the Task Positive Network (TPN).[1] These networks are ideally anti-correlated, but the Default Mode Interference Hypothesis suggests that an imbalance between the DMN and TPN may result in reduced cognitive performance.[2] In addition, the DMN has increased CBF compared to the TPN at rest.[3] We hypothesize that following mTBI at rest functional connectivity between the TPN and DMN will be less anti-correlated (measured by increased functional connectivity) and that the balance in CBF between the DMN and TPN will be disrupted.

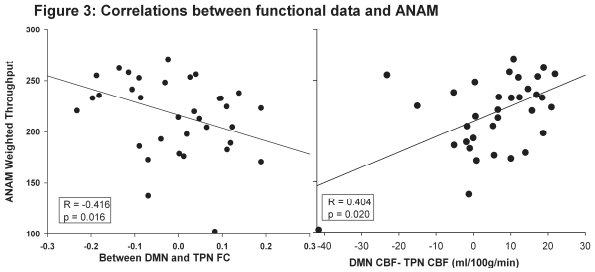
Methods: As part of the MagNeT (**Mag**netic Resonance Imaging of **Ne**uro**T**rauma) Study, mTBI patients (n=18) received an MRI evaluation in the sub-acute (1 month) and chronic (6 months) stages of injury. Participants were subject to a battery of computerized cognitive assessments using the Automated Neuropsychological Assessment Metrics (ANAM), which measures speed and accuracy of attention, memory, and thinking ability. From this assessment a weighted throughput score was computed which encompasses the accuracy and reaction time from each of the subtests of the ANAM.[4] The data from these patients was compared with data from 18 matched control subjects. A high resolution T1-weighted-MPRAGE (TE=3.44ms, TR=2250ms, TI=900ms, flip angle=9º, resolution = 256×256×96, FOV=22cm, sl. th.=1.5mm) was acquired for anatomic reference. The resting state MRI scan used a single-shot EPI sequence (TE=30ms, TR=2000ms, FOV=230mm, resolution=64×64) with 36 axial slices (sl. Th.=4mm) over 5 min 42s. The perfusion scan used the pulsed arterial spin labeling (PASL) technique based on single-shot EPI (TE=11ms, TR=2500ms, FOV=230mm, resolution 64×64) with 16 slices (sl. th.=5mm with 1mm gap) to cover the central portion of the brain. Forty-five pairs of labeled and control volumes were taken over 4 min.

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 (6mm Gaussian Kernel). Mean BOLD time series from white matter, CSF, and 6 motion correction parameters were included as regressors. Based on the control group, the DMN was extracted using a posterior cingulate cortex (PCC) seed and the TPN was extracted using bilateral dorsolateral prefrontal cortex (DLPFC) seed with coordinates based on literature.[1] ROIs were created using a 10mm sphere centered around each significantly correlated cluster for the DMN and the TPN. Resting state functional connectivity with DMN and TPN were extracted for each ROI. Average network functional connectivity within and between the DMN and TPN was calculated. ASL images were motion corrected first. CBF maps were generated using in-house MATLAB program based on [5]. ROIs from the resting state analysis were transformed from MNI space to original space and registered to the ASL data via registration to the T1-MPRAGE using AFNI. A gray matter (GM) mask from segmentation of the T1-MPRAGE was used to mask each ROI extracting CBF values from the GM of each ROI. Average CBF values for the DMN, TPN and DMN CBF-TPN CBF were calculated.





Results and Discussion: MTBI patients demonstrated increased functional connectivity between the DMN and TPN ROIs only at the chronic stage of injury at both a network level (p=0.008) and an ROI level (RDLPFC: p=0.008, L DLPFC: p=0.024, Premotor: p<0.001) (Fig1). No differences in functional connectivity within the DMN or TPN were found between the three groups. Average DMN CBF was greater than TPN CBF in controls (p=0.041), among mTBI in the sub-acute stage (p< 0.001), but not among mTBI in the chronic stage (p=0.13) (Fig2). The difference in CBF between DMS and TPN was greater in mTBI patients in the sub-acute stage compared to the control group (p=0.032), but trended towards normalization by the chronic stage (Fig 2). No differences in CBF at a network or ROI level were found between the three groups. Mild TBI patients at both time points performed just as well on the ANAM as our control subjects. However, when we constrained our analysis to the controls and chronic mTBI patients, after controlling for age we noted two significant correlations. We noted a negative correlation in between network functional connectivity and weighted throughput score (R=-0.42, p=0.02) and a positive correlation in the DMN CBF-TPN CBF and the weighted throughput score (R=0.41, p=0.01) (Fig3).



Conclusion: Our results suggest that in the sub-acute stage, mTBI may try to compensate for injury by having an increased difference between the DMN CBF and TPN CBF. In the chronic stage, while there is no longer a difference between the DMN CBF and TPN CBF, these patients have increased functional connectivity between the DMN and TPN. Furthermore, our results demonstrate that those with a reduced difference in CBF between DMN and TPN as well as increased functional connectivity between the DMN and TPN perform worse on our measure of cognitive functioning suggesting that resting state CBF changes may be associated with the interference in the DMN following mTBI.

References: [1]Fox et al, 2005. [2]Sonuga Barke et al, 2007. [3]Zou et al, 2009. [4]Kane et al, 2007. [5]Wang J et al, 2003.