# Interhemispheric functional connectivity in the thalamus and dorsolateral prefrontal cortex of mild TBI patients with and without Post-Concussive Syndrome

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**Purpose:** To investigate the mechanisms underlying cognitive impairments following mild traumatic brain injury (mTBI). Many mTBI patients report persistent symptoms and demonstrate reduced cognitive functioning, often in the absence of clinical CT or MRI findings. Studies using alternative MR techniques such as MR spectroscopy, diffusion tensor imaging, and functional MRI (fMRI) have noted metabolic and structural alterations in the corpus callosum following mTBI.[1,2,3] Damage to the corpus callosum will reduce interhemispheric functional connectivity (IH-FC), possibly contributing to the cognitive impairments noted in mTBI patients. Disruptions in thalamic resting state functional networks have been noted in mTBI patients,[4] and activation and diffusion changes in the dorsolateral prefrontal cortex (DLPFC) of mTBI patients have been related to post-concussive symptoms and cognitive impairments.[5,6] We hypothesize that mTBI patients will demonstrate reduced resting state IH-FC in both the thalamus and the DLPFC, and will show decreased neuropsychological performance. Furthermore, we expect patients reporting Post-Concussive Syndrome[7] (PCS) will have more severely reduced IH-FC and neuropsychological functioning than those without PCS.

**Methods:** As part of the MagNeT (**Mag**netic Resonance Imaging of **Ne**uro**T**rauma) Study, mTBI patients (Glasgow Coma Scale score=13-15) received an MRI evaluation in the acute (≤10 days) and sub-acute (1 month) stages of injury. Patients also completed the Automated Neuropsychological Assessment Metrics (ANAM), a battery of computerized cognitive assessments which measure speed and accuracy of attention, memory, and cognition. A throughput score was computed for each of 7 ANAM subtests based on reaction time and accuracy, as was a weighted throughput score summarizing overall performance.[8] PCS was determined at the sub-acute stage by the presence of ≥3 of following symptoms as reported on the Rivermead Post-Concussion Symptoms Questionnaire[9]: headaches, dizziness, sleep, trouble concentrating, fatigue, memory problems, and irritability[10]. Twenty-two patients with functional connectivity and ANAM data at the sub-acute visit were age and gender matched to 22 controls. Of these patients, 20 had functional connectivity data at the acute visit. Because several patients were still hospitalized during the acute stage, an insufficient amount of ANAM data from this stage was available for analysis. Age did not differ significantly among groups. Patients with PCS completed fewer years of education than controls (13.6 vs. 15.1, respectively), which was marginally significant (p=0.052).

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 CONN-fMRI Functional Connectivity toolbox v13.h[11] was used to process the resting state data, and included slice time correction, realignment, co-registration 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. Mean BOLD time series from 5mm spherical ROI's in the bilateral DLPFC and thalamus were extracted. IH-FC for each individual was determined by correlations between the right and left ROIs for each region.

**Results and Discussion:** mTBI patients demonstrated significantly reduced IH-FC at the sub-acute stage in both the thalamus (p=0.012) and the DLPFC (p=0.038; Fig. 1), but not at the acute stage. When further separating the patients to those with PCS vs. No PCS, the PCS group had significantly reduced thalamic IH-FC at the sub-acute stage compared to controls, while the No PCS group did not (Fig. 2). Within the PCS group, there was a significant reduction in thalamic IH-FC from the acute stage to the sub-acute stage. There were no significant differences in DLPFC IH-FC between controls and either PCS group at the either time point.

Overall, mTBI patients had significantly lower ANAM weighted throughput scores at the sub-acute stage than controls, indicating a worse overall performance (p=0.034). Only the PCS group had significantly lower weighted throughput scores at the acute stage than controls (p=0.014; Fig. 3). On individual subtests, the PCS group also had significantly lower throughput scores than the No PCS group on the Code Substitution (CS; p=0.009), Delayed Code Substitution (CSD; p= 0.002), and Procedural Reaction Time (PRT; p=0.040), indicating deficits in visual tracking and attention, delayed visual recognition, and processing efficiency, respectively.[8] The decreased throughput score on the CS and PRT tests primarily resulted from increased response times, while on the CSD test it represented both increased response time and reduced accuracy. Interestingly, the No PCS group performed significantly better on CSD than controls (p=0.008).

**Conclusion:** Our results suggest that mTBI patients have reduced IH-FC in both the thalamus and the DLPFC at the sub-acute stage, but not the acute stage. Furthermore, patients with PCS have greater neuropsychological deficits as measured by the ANAM, as well as a greater reduction in thalamic IH-FC, compared to those without PCS. We propose that the persistence of post-concussive symptoms in the sub-acute stage may be related to this reduction in thalamic IH-FC. Reduced IH-FC is likely one of the contributing factors to the persistent impairments noted following mTBI.

Fig. 1: IH-FC By Injury Stage

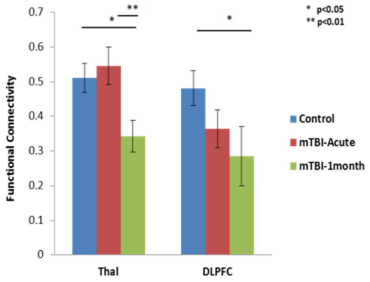



Fig. 2: IH-FC: PCS vs. No PCS

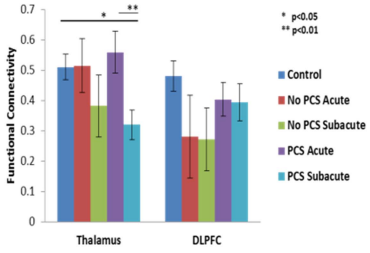
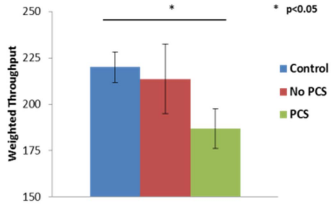



Fig. 3: ANAM Weighted Throughput at Sub-acute




**References:** [1]Johnson et al, 2012. [2]Grossman et al, 2012. [3]Slobounov et al, 2011. [4]Tang et al, 2011. [5]Lipton et al, 2009. [6]Gosselin et al, 2011. [7]Benton, 1989, [8]Kane et al, 2007, [9]King et al, 1995, [10]American Psychiatric Association, DSM-IV TR, 2000. [11] http://www.nitrc.org/projects/conn