

# Discrete Wavelet Analysis of Longitudinal Resting State fMRI in Mild TBI Patients

Chandler Sours<sup>1,2</sup>, Haoxing Chen<sup>3</sup>, Steven Roys<sup>1</sup>, and Rao P. Gullapalli<sup>1,2</sup>

<sup>1</sup>Diagnostic Radiology and Nuclear Medicine, University of Maryland School of Medicine, Baltimore, Maryland, United States, <sup>2</sup>Magnetic Resonance Research Center (MRRC), Baltimore, MD, United States, <sup>3</sup>University of Maryland School of Medicine, Baltimore, Maryland, United States

**Purpose:** To investigate the mechanisms of recovery following mild traumatic brain injury (mTBI) using discrete wavelet analysis of resting state fMRI (rs-fMRI) and its relationship with post concussive syndrome (PCS). Wavelet transform analysis has shown to be effective in the analysis of rs-fMRI for example in the case of schizophrenia.<sup>1</sup> Wavelet analysis is able to analyze coherence between time series as a function of frequency while maintaining temporal information as opposed to conventional Fourier analysis.<sup>2,3</sup> In this study our aim was to investigate if wavelet analysis provides insights into dynamic processes involved in resting state processes to gain further insights on specific frequency ranges that may be affected by mTBI through analysis of the Default Mode Network (DMN). Our secondary goal was to examine longitudinal alterations in rs-FC properties in mTBI patient with and without PCS.

**Methods:** Participants included 32 mTBI patients (41±17yrs, 21M:11F) who received rs-fMRI at acute (within 10 days of injury) and chronic (6 months post injury) time points and 31 controls (HC) (37±17yrs, 17M:14F). mTBI patients were divided into those with PCS (PCS+, N=15) and without PCS (PCS-, N=17) based on self reported symptoms on the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) at the chronic stage.<sup>4</sup> All 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 (TE = 3.44 ms, TR = 2250ms, TI = 900ms, flip angle = 9°, resolution = 256 × 256 × 96, FOV = 22 cm, sl. Thick. = 1.5 mm) 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.

Rs-fMRI data was preprocessed using AFNI (slice time correction, realignment, coregistration to structural image, spatial smoothing (6mm Gaussian Kernel) and regression of whole brain signal and 6 motion parameters). For each participant, time series were extracted from 8 representative DMN ROIs transformed to patient space (Fig. 1). Each time series was processed using discrete wavelet transform analysis using the Wavelet Toolkit for MATLAB (modwt.m function). This analysis divides the time series into multiple frequency ranges based on 4 scaling factors (SF1: 0.125-0.250 Hz, SF2: 0.060-0.125 Hz, SF3: 0.030-0.060 Hz, SF4: 0.015-0.030 Hz). For each SF a series of wavelet coefficients are extracted which measures how similar the scaled wavelet is to the time series at that temporal point of analysis.

Within each SF, average 8X8 wavelet coherence matrices were created for each group (HC, PCS+, PCS-) by computing the Pearson's correlation between wavelet coefficients from each time series. For each SF, we calculated two bivariate measures of rs-FC; strength of node  $i$  (mean of  $i^{th}$  column of the connectivity matrix) and diversity of node  $i$  (variance of the  $i^{th}$  column).<sup>5</sup> Average network strength and diversity for each SF were compared using ANOVAs for each time point. Longitudinal changes in mTBI groups were computed using repeated measures ANOVAs.

**Results and Discussion:** In the acute stage, significant differences were found between the three groups in strength within SF1 ( $p=0.005$ ), SF2 ( $p=0.044$ ), and SF3 ( $p=0.046$ ) (Fig. 2A), with reduced strength in the PCS+ group compared to the PCS- group within SF1 ( $p=0.005$ ), SF2 ( $p=0.035$ ), and SF3 ( $p=0.040$ ). At the sub-acute stage, only the strength in SF1 was increased significantly in the PCS- group ( $p=0.036$ ). However, a significant difference in strength between the PCS+ & PCS- groups was observed SF1 ( $p=0.023$ ), with PCS- group demonstrating increased strength compared to the HC group ( $p=0.017$ ) (Fig. 2B). No significant differences in diversity were noted.

Longitudinal analysis of PCS+ and PCS- mTBI groups revealed significant differences in SF1 ( $p=0.021$ ) and SF2 ( $p=0.025$ ), but a non-significant trend in increased strength between the acute and chronic visits in SF1 ( $p=0.061$ ) (Fig.2). The differences in strength for SF1 can be visualized in the wavelet coherences matrices shown in Fig. 3 for each of the ROI.

**Conclusion:** Our results demonstrate reduced strength of coherence in PCS+ patients compared to PCS- patients at multiple frequency ranges during both the acute and chronic stages of injury, as well as recovery across the two time points. Furthermore, the PCS- group shows greater network strength compared to controls at both time points suggesting a potential compensatory or protective mechanism in these patients. These findings stress the importance of investigating resting state coherence within multiple frequency ranges: however, many of our findings are within SF1, which may overlap with frequencies associated with cardiac and respiratory activity. Further research that incorporates cardiac and respiratory information, as well as a sliding window analysis to fully characterize the dynamic properties of resting state coherence in mTBI.

**References:** <sup>1</sup>Bassett et al. 2012. *NeuroImage*. <sup>2</sup>Bullmore et al. 2004. *NeuroImage*. <sup>3</sup>Chang and Glover 2010. *NeuroImage* <sup>4</sup>King et al., 1995. *J Neurol*. <sup>5</sup>Lynall et al., 2011. *J Neurosci*.

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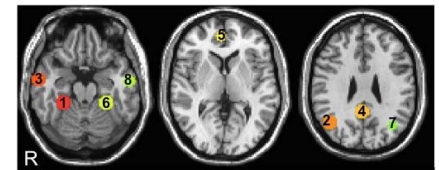


Figure 1: Location of DMN ROIs

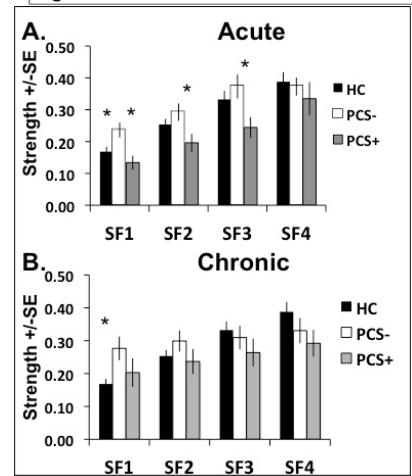


Figure 2: Average Network Strength A. Acute B. Chronic. \*  $p < 0.05$

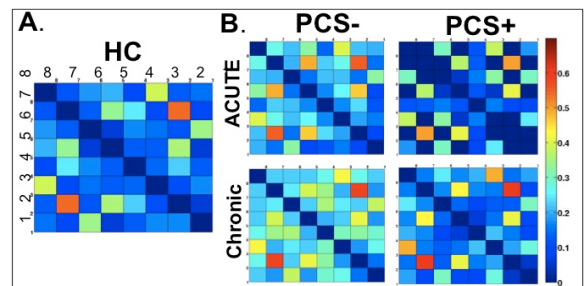


Figure 3: Average Wavelet Coherence Matrices for SF 1. A. HC B. mTBI patients. Numbers correspond to labels in Fig.1