Resting State fMRI Reveals Altered Functional Connectivity in Cortical and Subcortical Networks One Month after Mild Traumatic Brain Injury

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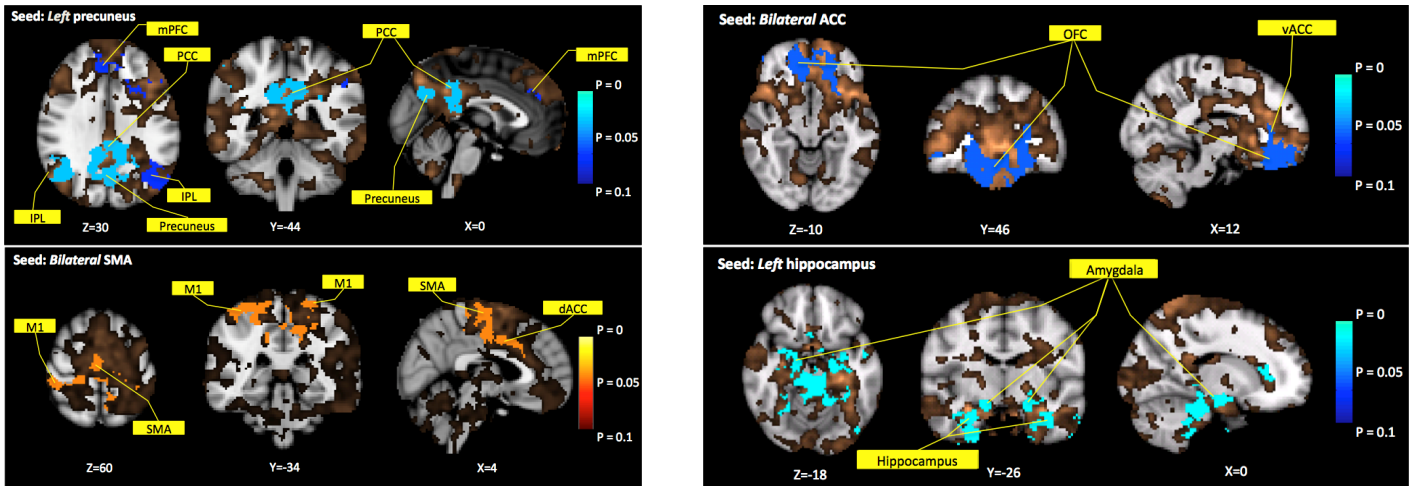
Objectives Several studies using resting state fMRI (rs-fMRI) have reported that traumatic brain injury (TBI) affects functional connectivity [1-10]. These prior studies have been limited by factors such as small sample size, a wide spectrum of injury severity, and/or evaluation of patients at variable time points, usually late after injury. In this study, we analyzed rs-fMRI in a cohort of 51 mild TBI (mTBI) patients at a well-defined time point earlier (1 month) post-injury and compared them with 45 healthy controls matched by age, gender, handedness and years of education. Furthermore, prior TBI studies have often examined only one or a few resting state networks, such as the default mode network, but here we investigate changes in functional connectivity of a broad array of resting state networks in mTBI patients versus controls.

Methods Fifty-one mild TBI patients (mean age 30 ± 8 years, 34 male, 49 right-handed) and 45 healthy controls (29 ± 9 years, 28 male, 43 right-handed) underwent a 7 minute resting state fMRI gradient-echo EPI sequence with 2s TR and 28ms TE, on a GE 3T scanner. Preprocessing included motion correction, brain extraction, band-pass filtering, regression of irrelevant signals, registration onto the MNI152 template, and spatial smoothing using FSL tools [11]. Functional connectivity maps were calculated from fourteen seed regions summarized from currently published rs-fMRI studies of TBI [1-10]. Two-sample permutation testing was performed on all connectivity maps using the "randomise" function in FSL with cluster-based thresholding to determine statistically significant differences between patient and control groups after correction for multiple voxel-wise comparisons.

Results Four resting state connectivity maps showed significant group differences: those seeded from the precuneus, anterior cingulate cortex (ACC), supplementary motor area (SMA), and hippocampus. The copper regions in each map show the underlying resting state connectivity associated with each seed. Decreased functional connectivity of mTBI patients versus controls (blue-light blue scale) was found bilaterally in the default mode network (DMN), executive control network, and the hippocampal network, including the following regions: ventral anterior cingulate cortex (vACC), dorsal anterior cingulate cortex (dACC), orbitofrontal cortex (OFC), posterior cingulate cortex (PCC), precuneus, medial prefrontal cortex (mPFC), inferior parietal lobule (IPL), hippocampus, and amygdala. *Increased* functional connectivity of mTBI versus controls (red-yellow scale) was found in bilateral SMA, primary motor cortex (M1), and dACC.



Discussion Resting state fMRI of a relatively large cohort of mTBI patients revealed reduced functional connectivity versus matched controls across multiple networks, most prominently the default mode network and hippocampus; however, connectivity was increased in mTBI for a motor-SMA network that includes the dACC. Contrary to the increased connectivity at DMN found by Sharp et al. [5], we observed decreased connectivity in DMN. This could be attributable to the earlier post-injury stage in the current study, as compared to the chronic phase of recovery in [5]. Concordant with our results, decreased DMN connectivity was also reported for a group of semi-acute mTBI patients by Mayer et al. [3]. We are presently investigating how these findings correlate with neurocognitive performance. These initial results demonstrate that resting state fMRI may have promise as an imaging biomarker for clinical outcome after mTBI.

References [1]Hillary FG, et al., Int J Psychophysiol.2011, [2]Johnson B, et al. Neuroimage.2011, [3]Mayer AR, et al. Hum Brain Mapp.2011, [4]Nakamura T, et al.. PLoS One 4:e8220.2009. [5]Sharp DJ, et al. Brain 134:2233-2247.2011. [6]Slobounov SM, et al., Neuroimage 55:1716-1727.2011, [7]Marquez de la Plata CD, et al., Arch Neurol 68:74-84.2011, [8] Kasahara et al., Neurology 75:168-176.2010, [9]Lotze et al., Neurorehabil Neural Repair 2006, [10]Tang et al., Radiology.2011,,[11] http://www.fmrib.ox.ac.uk/fsl/