Longitudinal Analysis of Structural and Functional Connectivity of the Thalamus and Anterior Cingulate Cortex in Mild Traumatic Brain Injury

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Introduction: Traumatic brain injury (TBI) affects over 1.5 million Americans each year, and more than 75% of TBI cases are classified as mild (mTBI). Most mTBI patients have normal findings in clinical neuroimaging and most have the highest GCS score; however, there are several cognitive and emotional symptoms that can significantly impact patients' quality of life. Therefore, we expected to see changes in brain regions associated with higher order functions. The thalamus and anterior cingulate cortex (ACC) are the two main centers of information processing, cognitive and affective functions, and regulation in the brain, and are structurally and functionally connected to each other. Therefore, we investigated the connections between these two regions of the brain to investigate the effect of mTBI.

Subjects and Image Acquisition: In total, 17 mTBI patients (age: 28.00±7.55 years) and 24 healthy controls (age: 34.52±13.85 years) participated in this study. All patients were recruited at the emergency department of Detroit Receiving Hospital, a Level-I trauma center. All participants were followed-up with structural, diffusion and functional MRI images three months after the first scan. For the patients, the first scan was acquired during the acute stage (24 hours after injury, when possible).

Materials and Methods: All processing steps for both diffusion and resting-state functional MRI (dMRI and rsfMRI) data were performed by FSL software (http://www.fmrib.ox.ac.uk/fsl/). For diffusion data, preprocessing included brain extraction, motion correction, and eddy current correction. For rsfMRI data, it included eliminating the first five volumes, brain extraction, motion correction, slicing timing, temporal high-pass filtering, grand mean removal, and spatial smoothing. Nonlinear registration was applied using FNIRT toolbox. For diffusion data, the transformation matrix was obtained by registration of the FA map of each subject to the default FA atlas image (FMRIB58_FA). For the rsfMRI data, the data was registered to standard space (warp resolution = 10mm) and resampled to 3mm isotropic voxel size. FDT Toolbox was used for analyzing diffusion data and tractography.

ROIs extraction: *Seed and Target masks* were obtained by thresholding the prefrontal cortex map of the Oxford Thalamic Connectivity Probability Atlas (PFMT) and the anterior cingulate cortex probability map of the Harvard-Oxford Cortical Structural Atlas with threshold value = 50. *Termination and Exclusion masks* have also defined to decrease false positive error and avoid trajectories that go to other fiber bundles, which are close to the desired fiber bundle. The average of normalized tract density maps of the healthy controls was then used as the mask to extract FA value along the structural connection for voxel-wise statistical analysis (see Fig 1). Moreover, Functional connectivity (FC) analysis was performed by measuring the Pearson correlation value.

Statistical analysis: **A** mixed design analysis of variance have been used for this longitudinal study: One independent variable is a "between-groups" variable (group: patients vs. healthy controls), and the other independent variable is a "repeated-measures" or "within-groups" variable (time: acute vs. sub-acute).

Results and Discussion: A voxel-wise longitudinal statistical analysis on FA values revealed that there is no significant interaction or time effects. However, an area with volume equal to 103 mm^3 revealed a significant difference at the main group effect in the part of pathway that is between the ACC and cortex (see Fig 2A). Measuring the FA value shows the patient group has a smaller FA value in the affected region (see Fig 2B). In addition, FC between the ACC and thalamus was investigated, because FC can be altered due to the mTBI, despite normal structural connectivity between the ACC and thalamus. FC analysis revealed areas in the dorsal and ventral parts of the ACC showing significant the interaction and group main effects, respectively (see Fig 3). Further investigation for the area that showed significant interaction effects using two-sample unpaired t-tests at each time point separately revealed a significant difference between the two groups at the acute stage but not at the sub-acute stage. Measuring the correlation values in the affected regions showed that FC is higher in the patient group in the affected areas. Moreover, in the regions which show significant interaction effect, FC goes back to normal at subacute stage (see Fig 4). It is worth mentioning that the results are similar whether left or right PFMT was choose as seed mask ROI.

Conclusion: Our data represent the longitudinal relationship between structural damage and functional response at the acute and subacute stages. It suggests that, along with structural damage in white matter tract after TBI, the higher order regions of the brain try to recruit more neuronal resources to compensate.

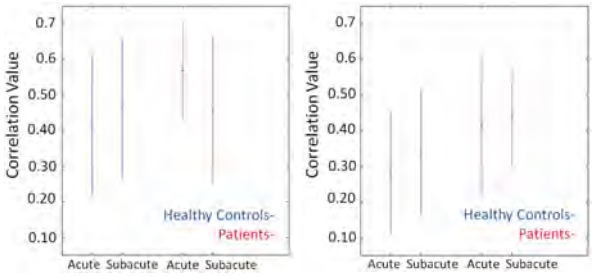

Fig 4. Correlation value in the areas which show (A) a significant interaction effect, and (B) a significant group main effect at both time-points between healthy control subjects and mTBI patients.

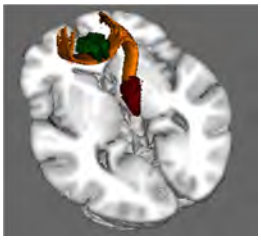

Fig 1. The average of normalized tract density for the healthy group at first time point when the right PFMT is the seed.

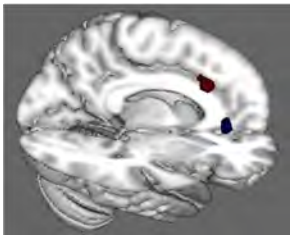

Fig 3. The areas in blue and red area show significant group and interaction differences, respectively.

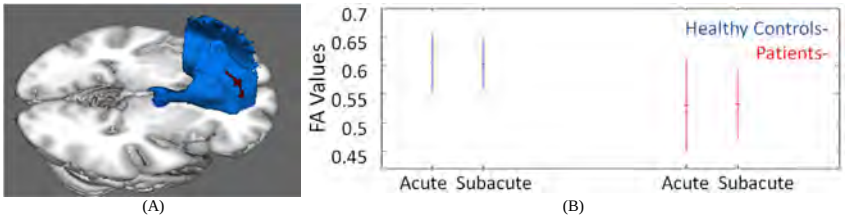

Fig 2. Voxel-wise statistical analysis of FA value. (A) shows the overlay of the red area, which shows significant group difference of the voxel-wise longitudinal analysis, on the white matter pathway. (B) Mean and standard deviation of FA value in the area, which is statistically significant for a group main effect but not a time effect. For both time points, the FA value in patients is smaller than in healthy controls.

References

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