Seemingly Inconsistency between Damaged White Matter Structure and Increased Functional Connectivity in Cingulum: Initial Response of Brain Plasticity to Trauma

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Introduction: Traumatic brain injury (TBI) is a significant public health burden in the United States and worldwide. Most TBI is mild in severity, with over 1 million mild patients visiting emergency departments (EDs) annually in the U.S. The challenge for the physician is to differentiate between patients with mild trauma and patients with prolonged or permanent brain injury-related symptoms. Detection of the neuropathological or physiological substrates may hold the best opportunity to improve the diagnosis and proactive treatment of mTBI patients. We hypothesize that mTBI is associated with functional and structural connectivity of the brain network. The PCC is renowned as the brain's central hub, which integrates and relays the information; therefore, it involves many brain functional networks and regulates their activation based on information that it gathers from the entire central nervous system (CNS). Thus it is a good target for neuroscience study. In this study, we investigate the connections of the posterior cingulate with other brain area using region of interest (ROI) functional connectivity analysis and probabilistic tractography.

Subjects and Image acquisition: Data from7 healthy subjects (age: 27.71 +/-10.43 years), 7 Patients (age: 33.57+/- 8.44 years) with mTBI were acquired within 24 hours after injury. MRI data were collected on a 3-Tesla Siemens Verio scanner with a 32-channel radiofrequency head-only coil. Resting state functional imaging was performed using a gradient echo EPI sequence with the following imaging parameters: TR/TE = 2000/30 ms, slice thickness = 3.5 mm, slice gap = 0.595 mm, pixel size = 3.125 mm in-plane, matrix size = 64 x 64, flip angle = 90°, 240 volumes for whole-brain coverage, acquisition time of 8 minutes. During resting state scans, subjects were instructed to keep their eyes closed. Diffusion imaging was acquired twice using a gradient echo EPI sequence with b= 0 and b = 1000 in 30 diffusion gradients directions with following parameters: TR/TE = 13300/124 ms, slice thickness = 2 mm, pixel size = 1.333 mm in-plane, matrix size = 192 x 192, flip angle = 90°. In addition, structural high-resolution T1-weighted imaging was also performed by using the MPRAGE sequence with TR = 1950 ms, TE =2.26 ms, slice thickness = 1 mm, flip angle=9 degrees, field of view= 256x256 mm, matrix size=256x256, and voxel size 1 mm isotropic.

Resting-state fMRI and diffusion MRI analyses: Preprocessing steps for both diffusion and resting-state fMRI data were performed by FSL software (http://www.fmrib.ox.ac.uk/fsl/) . Deleting the first 5 volumes, high pass filtering, motion correction, slice timing, brain extraction, spatial smoothing, and resizing were performed for resting state fMRI data; motion correction and resizing were applied for diffusion data. Data was nonlinearly transformed to MNI 2x2x2 mm3 standard space, in order to be able to perform structural and functional analysis in the standard space. For resting-state fMRI, region of interest (ROI) functional connectivity analysis was performed by choosing the posterior cingulate cortex (PCC) as the ROI. Regressing out for white matter, CSF, global mean signal were performed using MATLAB software (http://www.mathworks.com/). The PCC mask was chosen using the Harvard-Oxford cortical probabilistic atlas included in FSL. We used two different thresholds of 50% and 75% to increase the accuracy and confidence. For each case, the reference signal was obtained by averaging the signal time series of all voxels in the ROI to decrease the effect of local fluctuation and reduce dependency on ROI selection. The cross-correlation value was measured and transformed using Fisher z-transformation. A two sample t-test with spatial correction was applied. Diffusion analysis was performed using FMRIB's Diffusion Toolbox. Diffusion parameters were estimated using BEDPOSTX (two fibers modeled per voxel) and probabilistic tractography was performed using PROBTRACKX. Our seed space is a single mask created using voxels with both a 10% probability of belonging to the cingulum bundle according to the JHU white-matter tractography probabilistic atlas and a 10% probability of belonging to the PCC according to the Harvard-Oxford cortical probabilistic atlases. The Waypoint mask was created using the voxels at the border between the anterior cingulate cortex (Brodmann area 24) and the PCC (Brodmann area 23). Because connectivity values calculated by probabilistic tractography are highest near the seed point and fall off as a function of distance, we normalized voxels using the local values to reduce the false connections and enhance the true connections at greater distances. As with the functional connectivity analysis, a two sample t-test with spatial correction was applied.

Results and Discussion:

Functional analysis showed a decreased strength of connectivities within the DMN but an increased connectivity between PCC and other brain regions (especially Supplementary Motor Cortex) in mTBI patients, which is consistent with our previous work [1] and other studies [2]. The tractography analysis also showed structural alterations in the cingulate bundle, which gives rise to the cortical area of cingulate with functional alterations. Statistical analysis on the functional connectivity map demonstrated significantly decreased connectivity in the angular gyrus (p-value = 0.0005) with cluster size = 64, PCC (p-value = 0.005), and orbitofrontal gyrus (p-value = 0.005) (see Fig 1). In other brain areas, such as in a big cluster in the supplementary motor cortex (Brodmann area 6), connectivity was significantly increased (p-value = 0.0005) with cluster size = 116, which may be related to motor disabilities after injury (see Fig 2). The PCC also showed higher connectivity with the middle cingulate gyrus (MCC) in the patient group than in the control group. This region of high functional connectivity closely opposes a region of lower structural connectivity (diffusion probabilistic analysis) in the middle part of cingulum bundle in patients (p=0.05) (see Fig 3). Our data represent the first report regarding the relationship between structural damage and functional response in mTBI at the hyperacute stage. It suggests that, along with structural damage in white matter tract after TBI, the brain is trying to recruit more neuronal resources to compensate.

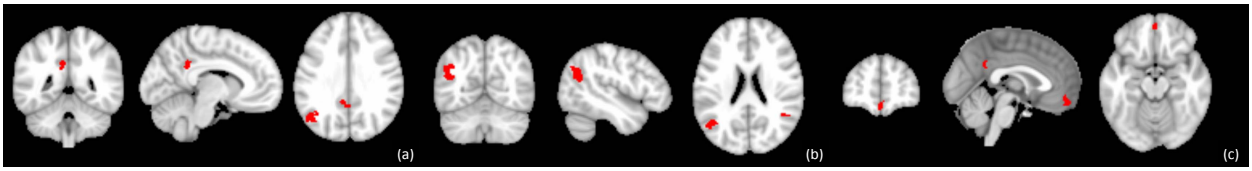

Fig 1. Two-sample t-test (p = 0.005) for resting-state functional connectivity: The warm color shows the areas which have higher connectivity with the posterior cingulate cortex in healthy subjects' group. Cross bar located in different positions in images (a) the PCC, (b) the angular gyrus, and (c) the orbitofrontal gyrus.

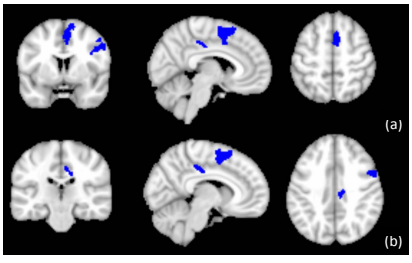

Fig 2. Two-sample t-test (p = 0.005) for resting-state functional connectivity: The cold color shows the areas in which the patients group has more correlation with the posterior cingulate cortex. Cross bar located in different positions in images (a) the supplementary motor cortex and (b) the middle cingulate cortex.

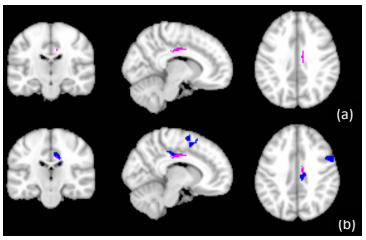

Fig 3. (a) Two-sample t-test (p = 0.05) for structural connectivity: The pink color shows the areas in which the patients group has lower connectivity value. (b) Overlay functional and structural connectivity.

Table 1. Number of voxels in healthy group (H) and patient group (P) for p-value = 0.005

Region	H>P	Region	H<P
Orbitofrontal gyrus	76	Supplementary motor cortex	432
PCC	100	MCC	106
Angular gyrus	317		

References:

[1] Iraji A., et all. Proc. Intl. Soc. Mag. Reson. Med. 21 (2013)

[2] Mayer A. R, et all. Human Brain Mapping 32:1825–1835 (2011)