Functional connectivity in posterior cingulate cortex alters in brain concussion patients at the acute stage

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Introduction: Mild traumatic brain injury (mTBI) leads to over 1 million emergency visits in the United States each year. The patients that present to the emergency room often have negative findings in standard clinical imaging. However, attention and memory deficits are wide-spread symptoms in mTBI patients. We hypothesize that mTBI is associated with alterations in the activities in the posterior cingulate cortex (PCC) and functional connectivity at rest. Based on the resting-state brain activity theory, the interactions among different parts of the brain also exist at rest, as well as spontaneous neural activities that can be determined by measuring temporal fluctuation of low frequency (0.01 Hz ~ 0.1 Hz) signals. In this study, we investigate the effect of mTBI on the resting-state brain activity in the PCC area of patients in the acute stage in relation with patients' cognitive assessment.

Materials and Methods:

Subjects and Image acquisition: Data from15 healthy subjects, 9 males and 6 females (mean age, 32.87; range, 21-65 years) and 9 patients with mTBI, 5 males and 4 females (mean age, 37.89; range, 19-56 years)- were acquired within 24 hours after injury. Resting state functional imaging was obtained using a 3-Tesla Siemens MRI system with gradient echo EPI sequence: TR/TE = 2000/30 ms, slice gap = 4.1 mm, voxel size = 3.125 *3.125 *3.5 mm^3, flip angle = 90°, resolution = 64*64, scan time = 8 min, and 240 volumes. Subjects were instructed to keep their eyes closed during the study. Preprocessing steps were performed by FMRIB Software Library FSL. T1-equilibration effects, motion, slice timing, and brain extraction were applied. fMRI volumes were affine registered to the individual's T1-weighted images and then wrapped to the MNI standard space with 10 mm warp resolution and resliced to 3*3*3 voxels. In seed point analysis, detrending, filtering and regressing out for white matter, CSF, global mean signal were performed using the Data Processing Assistant for Resting-State fMRI (DPARSF). In ICA, a temporal high-pass filter in order to remove low frequency drifts, grand mean scaling, and variance normalization were performed. Before MRI, all patients were tested by using standard assessment of concussion (SAC) instrument to assess their neural cognitive status including orientation, attention, and memory.

Resting-state-fMRI analysis: ICA analysis was performed in both group and individuals by using Group ICA of fMRI Toolbox (GIFT). In the group ICA step, cross-validation was performed to allow statistical analysis. In addition to two common methods, dual regression and back-projection, we applied spatially constrained ICA [1] using RSNs extracted from 603 subjects [2] as spatial template in the individual step. As a result, the RSNs extracted are more reliable since we used the atlas as a common space and not the components extracted from a group of data. The results among different studies with different data sets are only dependent on individual subjects' data and the atlas. This atlas is common between different studies and subjects and does not depend on the whole data set. So the difference between different subjects is the intrinsic variability between each pair of them. The results indicate the preference of the proposed method to the other two common methods. In seed point analysis, the reference signal is obtained by registering the images on AAL atlas and averaging the signal time series of all voxels in the region of interest (ROI) to decrease the effect of local fluctuation and sensitivity to ROI selection. The cross-correlation value (r) was converted by using the Fisher z-transformation to maintain the statistical analysis eligibility. Statistical one-sample and two-sample t-tests were performed and spatial correction was also performed to decrease type I error.

Results and Discussion: Neurocognitive testing reveals that mTBI patients had significantly lower SAC scores than controls (P-value=0.05), particularly in delayed recall (memory) than controls (P-value=0.02). Group-ICA shows a decrease in the number of voxels in Default Mode Network (DMN) in patients in several regions including PCC (H=226.67±3.93, P=210±6.13), Precuneus (H=1221.67±47.77, P=927.33±68.33), Brodmann area (BA) 10 (H=180±70.49, P=55.50±39.43), and BA11 (H=200.67±104.30, P= 46.83±33.64), while finding differences in voxel intensity only in PCC (H=9.99±0.86, P=8.29±0.53) and Precuneus (H=8.708±0.58, P=7.33±0.30). Among the four regions, the one sample t-test shows the number of statistically significant voxels in patients decrease, while the two sample t-test reveals the difference in DMN group-ICA (see Table 1). Individual-ICA, dual regression and back-projection were unable to discriminate the two groups. However, two sample t-tests on the individual-ICA extracted by the proposed method shows statistically significant differences, especially in PCC and the immediate surrounding areas like Precuneus. The statistical map for P-value=0.05 was corrected by spatial threshold using MonteCarlo simulation shows a cluster with 137 voxels, 55 of which are active in the PCC (see Fig 1). In the PCC correlation map, the number of active voxels in the PCC and Precuneus in the healthy subjects group is more than the patients group. This shows that DMN activation in patients decreases, confirming ICA analysis results and previous studies. The patients group, however, had a higher distribution and number of active voxels in frontal lobe and ACC. For P-value=0.01, BA32 (H=0, P=77), BA10 (H=59, P=262), and BA9 (H=0, P= 108) PCC (H=172, P=152) (see Fig 2). Two-sample t-test results show the difference between the two groups. For P-value=0.01, the two-sample t-test map includes two clusters with 117 and 223 voxels which have 77 and 87 voxels in (BA 9) respectively, and the larger cluster has 44 voxels in (BA32) (see Fig 3).

Our data demonstrate that a) mTBI patients have alterations in their resting-state functional connectivity in PCC and related areas at the acute stage, and b) this functional connectivity change may reflect their memory alteration symptoms. This work could have potential applications in clinical diagnosis of mTBI in patients that present to the emergency department, which currently has no effective means of detecting mTBI acutely.

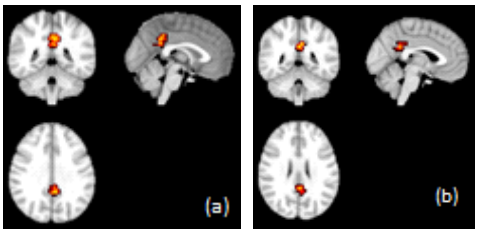

Fig 1. Two-sample t test results showing the difference between two groups in Individual ICA: (a) largest cluster statistically significant (P=0.05) and (b) the result in PCC.

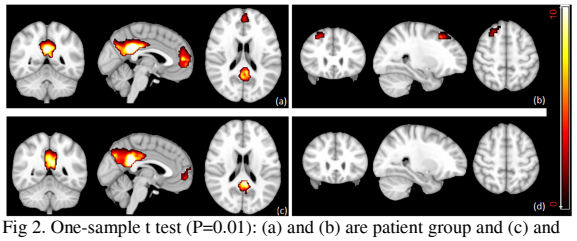

Fig 2. One-sample t test (P=0.01): (a) and (b) are patient group and (c) and (d) healthy group. More activity in BA 10 in patients group (a) compared to healthy group (c). Unlike healthy group, patient group shows significant activation in BA 32 (a) and BA 9 (b).

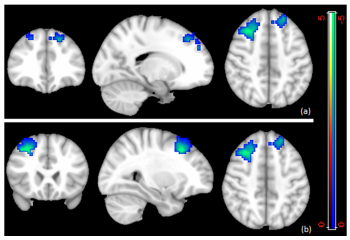

Fig 3. Two-sample t-test (p = 0.01): The minus belongs to the region where the patients group has more correlation with PCC.

Table 1. Group-ICA, one-sample and two-sample t-tests: Number of voxels in healthy groups and patients' one and group difference.

Region	No. Voxels in region	1 sample t-test			2 sample t-test	
		Healthy	Patients	P-value	Difference	P-value
PCC	246	219	190	0.001	50	0.001
Precuneus	2026	1024	734	0.001	442	0.001
BA 10	1397	58	0	0.05	33	0.01
BA 11	2447	81	0	0.05	48	0.01

References:

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