Brain Function Disruption of Thalamus Related Resting State Networks in Patients with Mild Traumatic Brain Injury

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Introduction:

Research interests on the study of functional MRI during resting state (RS-fMRI) have demonstrated a consistent pattern of slow fluctuations in the blood oxygenation level dependent (BOLD) signal referred to as the "default mode" of brain function [1]. Such spontaneous neuronal activity plays a role in maintaining baseline human cognition and metabolic equilibrium in the resting brain. Mild traumatic brain injury (MTBI) is often associated with long-lasting post concussive syndrome (PCS). The pathophysiologic mechanism of MTBI and PCS is still poorly understood and it is not currently possible to detect patients at risk of developing PCS on the basis of clinical presentation [2]. The thalamus, as the centrally located relay station for transmitting information throughout the brain, participates in communication with many associative brain regions and involves global multi-functional pathways. The purpose of this study was to investigate whether this low frequency resting state network (RSN) associated with thalamic function is disrupted in patients with MTBI using RS-fMRI.

Method:

Eleven right handed patients (age from 22 to 54, with a median age at 38 years, including 7 males and 4 females) with clinically definite MTBI and corresponding Glasgow Coma Score (GCS) scales of 13~15 were studied. All the patients with median disease duration of 4.8 years have various neurocognitive symptoms, including headache, dizziness, insomnia, fatigue, light sensitivity, attention, concentration, memory, executive functional deficits, or irritability. All subjects were recruited after meeting the following inclusion criteria: no history of alcohol or drug abuse; no history of neuropsychological diseases before injury; and no history of other neurologic diseases including stroke, epilepsy, and somatic disorders. Twelve right handed healthy subjects (age from 22 to 49, with a median age at 35.5 years, including 7 males and 5 females) were also recruited for comparison.

MR images were acquired on a 3T whole body scanner (Siemens Medical System, Erlangen, Germany). In addition to conventional T2-weighted imaging, twenty T1-weighted anatomic images were collected parallel to AC-PC line with 5mm slice thickness and 1mm gap and positioned to cover the whole cerebrum. The functional images were collected in the same planes, using a gradient echo EPI sequence (TR/TE=2s/30ms, flip angle=70^o, FOV=$22x22cm^2$ and acquisition matrix size=128x128), then a conventional T2-weighted sequence and a whole brain 3D T1-weighted MPRAGE sequence were also acquired. During the two RS-fMRI sessions, all subjects were instructed to close eyes but keep awake. Each scan lasted 5 minutes and 6 seconds. The repeated RS-fMRI was also performed in 2 volunteers from different days. And the patients had the neurocognitive exams to follow.

All MRI data were analyzed using SPM2 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk) and MRIcro (http://www.mricro.com) and additional in house programs running under MATLAB (Mathworks, Natick, MA). fMRI data were preprocessed for the analysis by first motion corrected, realigned, co-registered, then registered to standard Talaraich coordinates and spatial smoothed in SPM2. We used the signal from the seed regions – bilateral thalamus to define the reference time course, then calculated the correlation coefficient to all voxel's time series within the whole brain to generate a functional connectivity map. Fisher's z' transformation was used to compute Fisher's z' maps for each subject, and then one sample T-test was performed to get group contrast maps which show all areas that are significantly correlated to the thalamus (R>0.5 so z'>0.55) for both group. Two sample T-test was also performed to get the comparison maps between the thalamic RSN of MTBI patients vs. normal controls.

Results:

In healthy volunteers, a consistent pattern of thalamic RSN was found in different sessions including data acquired in the same day or different days. The thalamic functional network shown on RS-fMRI only includes both sides of the thalamus (Figure 1, 2nd column). This pattern was consistent when the seed regions were placed in either the right or left side of thalamus.

In MTBI patient group, though no lesions were found in the thalamic regions on conventional T2-weighted images, a wider distributed functional connectivity was shown for thalamic RSN which includes not only both sides of the thalamus but also cingulated gyrus and superior temporal gyrus (Figure 1, 1st column, P<0.005). Difference maps between two groups indicated that parts of cingulated gyrus, temporal gyrus and frontal gyrus in patients shown more functional connectivity with the thalamus comparing to that of normal control group (Figure 1, 3rd column). After quantitatively analyzing the total number of voxels involved in resting-state thalamic functional correlation maps, the values are found to be significantly higher in patients in both left side (33,597) and right side (32,089) when compared to healthy volunteers (1,419 for left side and 1,478 for right side; respectively). These increased resting-state thalamic activities in patients with MTBI are mainly from positive correlations, indicating these regions tend to be correlated in their spontaneous BOLD activity with similar functionality.

All cognitive data except clinical measures (19th~22nd: depression, anxiety, fatigue, post-concussive symptoms) is in z score format with higher scores indicating better performance. Correlated the cognitive scores with total involved voxel number obtained from functional RSN associated with left or right thalamus for every patient (Figure 2), we found that there are generally more voxels involved in the thalamic RSN for those patients who performed better in the cognitive exams and shown less clinical symptoms. Those exceptions usually are non-significant.

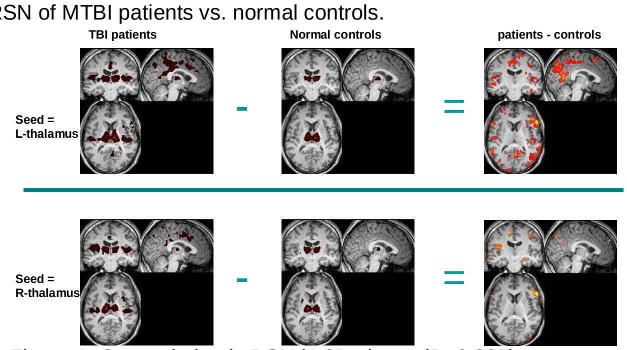

Figure 1. Group thalamic RSN in 3D views, (P<0.005).

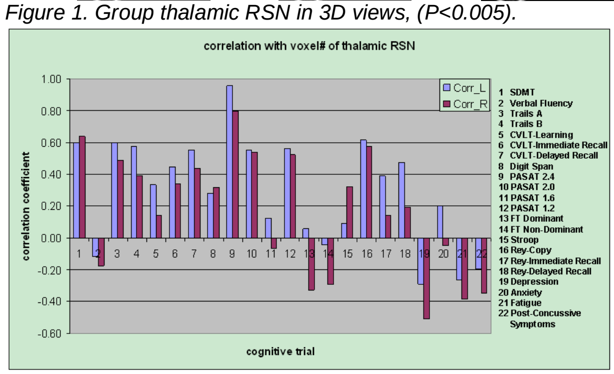

Figure 2. Correlation between cognitive scores and total voxel number involved in the thalamic RSN.

Conclusion & Discussion:

This study demonstrates for the first time, disruption of thalamic functional network during resting state in patients with MTBI. The well-defined homogeneous thalamic functional connectivity maps were shown in healthy volunteers, meanwhile such functional activities have been shown to be significantly increased in patients with MTBI as compared to controls. This suggests that the subtle tissue damage to the thalamus may upregulate the default function in the associative regions of brain in order to compensate for its reduced functionality.

Our method using RS-fMRI in investigations in the MTBI may contribute to better understanding the complex persistent post-concussive syndrome in these patients and to monitor the disease recovery progress and guide the effective therapy.

Reference: [1] Fox MD, Raichle ME. Nat Rev Neurosci 2007; 8(9): 700-11. [2] Kushner D. Arch Intern Med 1998; 158(15): 1617-24.

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