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

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Introduction:

Functional MRI studies of the neural functional network during the resting state (resting state functional MRI, RS-fMRI) have demonstrated highly correlated slow fluctuations in the blood oxygenation level dependent (BOLD) signal across discrete brain regions. Test-retest studies in healthy individuals showed high reproducibility of these spatially coherent signal changes that are more than just noise but representing spontaneous and consistent fluctuations [1-2]. Mild traumatic brain injury (MTBI) accounts for at least 75 percent of all traumatic brain injuries and is a significant public health care problem. The thalamus is a complex deep grey matter mass that consists of many groups of nuclei and white matter bundles; it is vulnerable to damage during sudden acceleration or deceleration movements during the head trauma. Imaging markers for thalamic injury are still missing and little imaging evidence exists for the physiologic or structural origin of post concussive disorders. Therfore the purpose of this study is to investigate whether resting state network (RSN) associated with thalamic function is disrupted in patients with mild traumatic brain injury (MTBI) with RS-fMRI.

Method:

24 patients with MTBI and 17 age/sex-matched healthy volunteers were recruited. The patients had a varied degree of symptoms with mean disease duration of 22 days (3~55 days) after injury. Neuropsychological testing was conducted within 12 hours of fMRI in MTBI patients by a psychologist blind to the fMRI results. Neuropsychological measures assessed areas of cognitive functioning found to be impaired in patients with MTBI. Tests results were reported in standardized *z* scores (*M*=0, *SD*=±1). Functional MRI (fMRI) was performed on a 3T whole body scanner (Siemens MAGNETOM Trio, Siemens Medical Solutions, Erlangen, Germany) while subject is at wakeful rest with eyes closed using a gradient echo EPI sequence with parameters of TR/TE = 2sec / 30msec, flip angle = 75^o, FOV = 220 x 220 mm^2 and acquisition matrix size = 128x128. 20 slices were collected parallel to a line passing through the anterior-posterior commissure (AC-PC line) with 5 mm slice thickness and 1mm gap and positioned to cover nearly the entire cerebrum, then 2D T1-weighted anatomic images were collected in the same planes, and sagittal MPRAGE scan were also performed. Data were preprocessed using SPM2 and custom analysis running under MATLAB.

We analyzed the RS-fMRI data using standard seed-based whole brain correlation methods and the cortical functional connectivity with thalamic and motor seed ROIs was probed. To quantify the thalamic functional connectivity, the number of voxels meets the statistical significance criterion ($P < 0.001$), and we use the percentage of the overlap of the two RSNs to study the conjugate symmetry property between the left and right thalamic RSNs, so the higher overlapping percentage ($\%_{overlap}$) represents the higher symmetry between left and right thalamic RSNs. After Z transformation to normalize all quantification, the student *T* test was used to assess differences between groups. Finally, the results of thalamic RSNs from were correlated with neurocognitive tests to evaluate the sensitivity of thalamocortical connectivity to neurocognitive performance.

Results:

A consistent and symmetric normal pattern of thalamic RSNs is demonstrated in healthy subjects showing relatively low and restrictive functional connectivity at rest while increased task-related neural connectivity associated with a finger tapping test, suggesting an inhibitory property of the thalamic neurons during the resting state (figure not showed). In patients with MTBI, such normal pattern of thalamic RSNs is disrupted with apparent functional redistributive discrepancy and increased thalamic resting state neural connectivity as compared to normal controls ($P < 0.01$) (Figure 1). Comparison of the voxel numbers between subjects from two groups showed the significant different (Table 1, Figure 2a). These diferences remained significant even after the correlation threshold was raised from R = 0.25 ($P<0.001$) to R = 0.6 ($P << 0.001$). However, we found no statistical difference in motor RSNs between patients and controls, which is in accordance with clinical findings that motor function is only minimally disrupted.

And Comparison of the symmetric property between MTBI patients and normal controls showing significantly lower symmetry in patients ($P = 0.03$) (Figure 2b). Symmetric property is defined as the degree of overlap between left thalamic RSN and right thalamic RSN and is expressed in percentage ($N_{overlap}/N_{total}$ *100%).

In addition, we found that the increment of thalamocortical functional RSNs correlated with neurocognitive performance in patients with MTBI. All cognitive data except clinical measures (i.e. depression, anxiety, fatigue, post-concussive symptoms) are in Z score format with higher scores indicating better performance. In patients with MTBI, correlating cognitive scores with the total involved voxel numbers of both left and right thalamic RSNs, we found that there was generally more voxels increment involved in thalamic RSNs in patients who performed poorer in the cognitive exams ($P<0.05$), especially memory related exams, e.g. The Symbol Digit Modality Test (SDMT), the California Verbal Learning Test (CVLT) and Rey Complex Figure Test (RCFT). Meanwhile, patients with more clinical symptoms (depressive and Postconcussive Symptoms) or older patients showed lower degree of symmetric property of thalamic RSNs ($P<0.05$). These results suggested a relationship between the degrees of compensation for restoration (i.e. increased thalamic RSNs) associated with thalamic injury and neurocognitive performance.

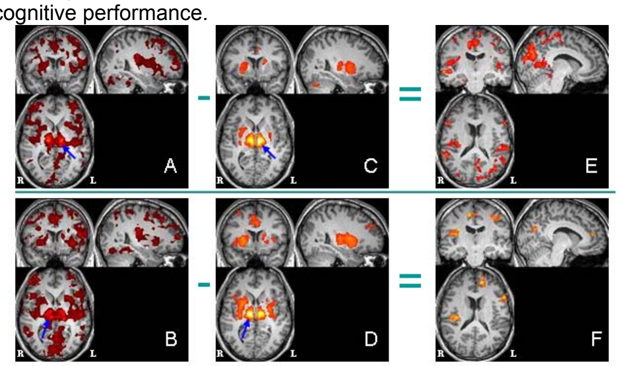

Figure 1. Group thalamic RSNs in MTBI patients (A, B) and controls (C, D). The difference maps (E, F) (patient > normal) were compared using two sample T-test ($P<0.01$, $k>100$). The blue arrows show where the seed are placed

Thalamic RSNs	Control	MTBI	P-value
Left	71234 / 27399	102480 / 33489	0.001
Right	78126 / 29063	103060 / 28865	0.005
Total	89180 / 32505	130776 / 34905	0.0002

Table 1. Comparison of voxel number (mean/SD) of thalamic RSNs between groups of MTBI patients (n = 24) and normal controls (n = 17) with two sample t-test.

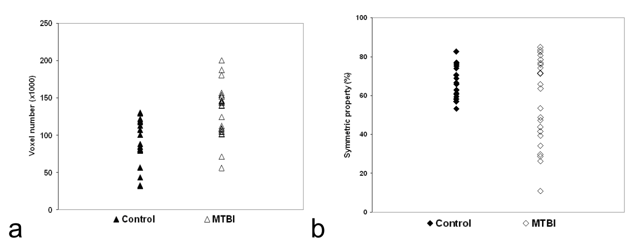

Figure 2. **a.** Comparison of the number of voxels (N_{total}) shows significant difference ($P = 0.0002$) of the thalamic RSNs. **b.** Comparison of the symmetric property shows significantly lower symmetry in patients with MTBI ($P = 0.03$).

Discussion:

Thalamic RSNs are disrupted in patients with MTBI, indicating there is compensatory upregulation of neural connectivity associated with subtle thalamic injury that appears to be related to the performance in neurocognitive testing. RS-fMRI can be used as an additional imaging modality for detection of thalamic functional abnormalities and for better understanding the complex persistent postconcussive syndrome.

Reference:

[1] Damoiseaux, J.S. et. al, PNAS, 2006. **[2]** Meindl, T., et. al, HBM, 2010.