Inter-hemispheric functional and anatomical connectivity abnormalities in traffic accident-induced PTSD: a study combining fMRI and DTI

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Aims and objectives

Post-traumatic stress disorder (PTSD) is a blend of intrusive memories of the traumatic event, avoidance of reminders, emotional numbing and hyperarousal, which may develop after exposure to traumatic events such as natural disasters, terrorism and war [1].

In recent studies, aberrant brain functional and structural changes have been considered as one of the important mechanisms underlying PTSD. However, the exact pathophysiological mechanisms underlying PTSD remain unclear, especially the causal relationship between the traumatic event and the subsequent onset of PTSD. It is possible that because PTSD by definition is caused by a psychologically traumatic event, brain abnormalities found in PTSD could be induced by trauma. It is also tempting to assume that there is an abnormality pre-dates the traumatic event and it increased the risk of development of the disorder upon traumatic exposure [2].

The corpus callosum (CC) is an important target for PTSD researches. Results from previous investigations suggest that maltreated children with PTSD would show decreased volumes of CC that may be vulnerable to stress during developmental processes [3-5]. In this way, PTSD in maltreated children may be regarded as an environmentally induced complex developmental disorder. It is possible that CC abnormalities observed in PTSD represent a pre-existing vulnerability factor, which is due to developmental/genetic factors and predispose individuals to develop PTSD after exposure to trauma [6]. In this context, characterizing inter-hemispheric functional synchronization and associated anatomical connectivity is crucial to understand disease-related mechanisms of PTSD.

The current study is aimed to identify the inter-hemispheric functional and anatomical connectivity changes in patients who consequently develop PTSD. We would like to investigate the potential factors relating to the development of PTSD using the voxel-mirrored homotopic connectivity (VMHC) analysis based on the resting-state fMRI data [7], and diffusion tractography techniques. A secondary aim was to examine the ability of the factors to predict the future severity of PTSD.
Methods and materials

Participants

The participants were recruited from patients admitted to the Emergency Department after a traffic accident. All of them completed the baseline evaluation within 2 days. The psychiatric clinical interview included the Mini-International Neuropsychiatric Interview (M.I.N.I) [8], and the acute stress disorder inventory (ASDI) [9] was made by two experienced psychiatrists. Resting-state fMRI and DTI were acquired on victims who had experienced traffic accidents within 2 days after the trauma. The diagnosis was made using the CAPS at 1 and 6 months after the accident, which was the psychometric measure for PTSD diagnosis and symptom severity [10]. Fifteen trauma-exposed victims met the criteria for diagnosis of PTSD and 14 trauma-exposed victims who did not develop PTSD at 6 months after trauma were selected as the control.

The exclusion criteria were:

1. ages < 18 or > 60 years old, education < 9 years;
2. ASDI < 3 (improving the positive predictive power for developing PTSD);
3. significant head injuries (i.e., abnormalities on conventional MRI, neurological abnormality during emergency department evaluation, or loss of consciousness longer than several seconds during the accident);
4. a history of neurological disorders;
5. current and past psychiatric Axis I disorders, as assessed using the M.I.N.I;
6. substance abuse (drug or alcohol abuse/dependence within 6 months);
7. medications (using psychotropics within 4 weeks);
8. MRI safety contraindications.

Acquisition of Imaging Data

A gradient-echo echo-planar sequence was used to acquire functional images (TR = 2000 ms, TE = 30 ms, FOV = 230 mm × 230 mm, matrix = 64 × 64, thickness = 4 mm, and slice gap = 0).

A high-resolution 3D T1-weighted anatomical images were acquired in sagittal orientation using a three-dimensional fast spoiled gradient-recalled sequence (TR = 9.4 ms, TE = 4.6 ms, flip angle = 15°, slice thickness = 1 mm, gap = 0 mm, FOV = 256 mm × 256 mm, matrix = 256 × 256, and slices = 155).
DTI data was acquired using a spin-echo single shot echo-planar pulse sequence (TR = 15000 ms, TE = 68 ms, matrix = 110 × 110, FOV = 220 mm × 220 mm, NEX = 1, slice thickness = 2 mm, gap = 0). The diffusion-sensitizing gradients were applied along 20 non-collinear directions with a b value of 1000 s/mm², together with a b0 image (b = 0).

Data Processing

Rs-fMRI data preprocessing

Rs-fMRI preprocessing was performed using the DPARSFA toolkit (http://www.restfmri.net). The first 10 images were discarded. The remaining 210 images were subsequently corrected for slice timing and realigned to the first image for rigid-body head movement correction. No participant had motion of more than 1 mm with maximum translation in x, y, or z, or 1° of any angular motion throughout the course of scan. We then co-registered the individual T1 images to functional images. The T1 images were segmented and normalized into standard stereotaxic anatomical Montreal Neurological Institute (MNI) space using a 12-parameter nonlinear transformation. These transformation parameters were applied to the functional images. The normalized volumes were resampled to 3 × 3 × 3 mm³. The images were spatially smoothed with a 6 mm FWHM Gaussian Kernel, temporally bandpass filtered (0.01-0.08 Hz) and linearly detrended. Finally, linear regression was applied to remove nine nuisance signals (global mean, white matter, cerebrospinal fluid signals and six head motion parameters).

Calculation of VMHC

We transformed the preprocessed functional images to a symmetric space. The data preprocessing included these steps: (1) all subjects' normalized T1 images were averaged to create a mean normalized structural image; (2) averaging with its left-right mirrored version to generate a group-specific symmetrical template; (3) registering normalized individual T1 images to the symmetric T1 template; (4) applying the nonlinear transformation to each subject's normalized functional images; (5) computing the Pearson correlations between every pair of symmetrical inter-hemispheric voxel's time series; (6) the resulting correlations for each paired voxel constituted a VMHC brain map (Fisher Z-transformed); (7) calculating global VMHC by averaging VMHC values across all brain voxels within a unilateral hemispheric grey matter mask (there is only one correlation for each pair of homotopic voxels). The mask was segmented from the grey matter segmentation of symmetric T1 template.

DTI data analysis

DTI tractography was preprocessed and analyzed using the PANDA toolkit (http://www.nitrc.org/projects/panda). The DTI data were geometrically corrected using a non-diffusion-weighted B0 image (b = 0 s/mm²) and a field map, to account for eddy current distortions. The data were co-registered to the B0 image using affine transformations.
Diffusion tensor models were estimated by linear least-squares fitting at each voxel. Whole brain fiber tracking was performed in the DTI native space for each subject using the Fiber Assignment by Continuous Tracking algorithm implemented [11]. Path tracking proceeded until either the FA was <0.15 or the angle between the current and the previous path segment was >35°, as in previous studies [12]. After whole fiber tracking, short fibers <10mm, and obvious false paths were discarded. Then, the regions showing abnormal inter-hemispheric functional connectivity were adopted as regions of interest (ROI) for an analysis of DTI tractography. As the ROIs were derived from the normalized MNI space, the inverse transformation of the spatial normalization was applied to acquire the ROIs in the native diffusion space [13]. Firstly, we transformed the ROIs from the normalized symmetric space to each individual's native functional space. Then, the mean functional images (native functional space) were co-registered to the B0 image (native diffusion space) and applied the transformation to all ROIs. More specifically, the ROIs were dilated 1 voxel into the white matter to ensure that they were in contact with the fibers. Fiber bundles connecting symmetrical ROIs in the two hemispheres were then extracted from the total collection of brain fibers. By TrackVis software (http://www.trackvis.org/), we selected the first ROI and the tracts reached the ROI were chosen from all fibers. The second ROI in the other hemisphere was then retrieved. Only those tracts that reached the second ROI were picked from the resulting tracts. Two basic indices of fiber connectivity obtained from TrackVis were involved in analysis, including path length and FA of each fiber pathways.

**Statistical Analysis**

Individual-level VHMC maps were entered into a group-level voxel-wise t-test analysis. The statistical threshold was set at corrected $p < 0.05$ for AlphaSim (combination of $p < 0.05$ and a minimum cluster size of 51 voxels).

To examine the differences in VMHC between victims with and without PTSD, the individual VMHC maps were entered into a voxel-wise two-tailed t-test. The results were set at corrected $p < 0.05$ for AlphaSim (combination of $p < 0.01$ and a minimum cluster size of 35 voxels).

The identified clusters from the group comparison were defined as ROIs for DTI tractography. Fiber length and FA of the commissural tracts connecting the bilateral ROIs were compared between groups using a two-sample t test.

Symptom severity was represented by the total score received on the CAPS (the composite of frequency and intensity score) of victims with PTSD at diagnosis. A Pearson correlation was carried out to test the correlation between the CAPS scores and the mean VMHC values extracted in the ROIs, as well as the fiber length/FA values of the commissural tracts connecting the bilateral ROIs.
Results

VMHC Differences between Groups

Fig. 1 shows the VMHC patterns in victims with and without PTSD. Both groups had robust homotopic functional connectivity with regional differences in strength and did not differ on global VMHC (victims with PTSD = 0.63±0.17; victims without PTSD = 0.60±0.12; p = 0.70 t = 0.40). The victims with PTSD showed significant decrease in VMHC in the superior/middle frontal gyrus before diagnosis (p < 0.05 corrected for AlphaSim) (Table 2, Fig. 2). There was no correlation between the CAPS scores and VMHC values of the superior/middle frontal gyrus (r = -0.210, p = 0.435).

DTI

The commissural tracts (corpus callosum genu) that connect the bilateral superior/middle frontal gyrus were detected in all subjects. We performed a between-group analysis for the fiber length and FA of commissural tracts connecting bilateral superior/middle frontal gyrus. Decreased FA values was found in the victims with PTSD (victims with PTSD = 0.58±0.04; victims without PTSD = 0.61±0.03; p = 0.042 t = 2.137). However, no significant differences were detected for fiber length (victims with PTSD = 60.15±4.66; victims without PTSD = 61.83±4.63; p = 0.339 t = 0.974) (Fig. 3).

We correlated the FA of the commissural fibers with CAPS scores in the victims with PTSD using Pearson’s correlation. The FA values tended to correlate negatively with the CAPS scores (r = -0.534, p = 0.040) (Fig. 4).
Fig. 1: Within-group patterns of VMHC (p < 0.05, AlphaSim corrected). A. VMHC pattern in victims with PTSD; B. VMHC pattern in victims without PTSD. VHMC = voxel-mirrored homotopic connectivity; PTSD = posttraumatic stress disorder.

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**Fig. 2:** The brain regions with between-group difference in VMHC. Brain regions showing significant decreased (cool color) VMHC victims with PTSD. These clusters were shown in the bilateral superior/middle frontal gyrus (p < 0.05, AlphaSim corrected).

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Fig. 3: The left column is an example of diffusion tractography from a single control subject. The right two columns are scatter plots illustrating the between-group comparison for the fiber length and FA of commissure tracts. FA = fractional anisotropy; PTSD = posttraumatic stress disorder.
**Fig. 4:** Scatter plot illustrating the relationship between the FA values in the commissural tracts that connected the bilateral superior/middle frontal gyrus in victims with PTSD and CAPS scores at diagnosis. FA = fractional anisotropy; PTSD = posttraumatic stress disorder; CAPS = Clinician-Administered PTSD Scale

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Conclusion

The current study focused on the possible alteration in inter-hemispheric interactions in trauma-exposed victims who went on to develop PTSD before diagnosis using resting-state fMRI and diffusion tractography techniques. We found abnormal functional synchronization and anatomical connectivity efficiency between the bilateral superior frontal gyrus and middle frontal gyrus, suggesting that the bilateral prefrontal regions may play an important role in the pathophysiology of PTSD. In addition, it was identified within 2 days after trauma in the individuals who developed PTSD at a later date and the FA values between bilateral prefrontal regions correlated negatively with the CAPS scores, suggesting that these imaging results may provide important implications for the PTSD-related mechanisms, which might be detectable through the use of neuroimaging on people at risk of developing PTSD.
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References


