Changes of inter-hemispheric functional connectivity between motor cortices after brachial plexuses injury: a resting-state fMRI study

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Purpose

Peripheral nerve injury causes cortical representation areas reorganization and alters motor network functional connectivity. Cortical representation areas reorganization for hand movement after brachial plexus injury and nerve transfer were reported by many researchers using task related functional MRI or TMS\cite{1, 2}. Some researchers have observed the loss of inter-hemispheric cortical inhibition after brachial plexus injury\cite{3}. Peripheral nerve diseases also can cause the decrease of motor network functional connectivity, including intra-hemispheric connectivity \cite{4, 5}. One recent animal study reported that limb deafferentation lead to substantial disruption of inter-hemispheric sensorimotor cortical connectivity while intra-hemispheric connectivity are largely unaffected\cite{6}. It still remains unclear in the human brain whether peripheral nerve injury would cause the change of inter-hemispheric functional connectivity between motor areas.

Resting-state functional connectivity magnetic resonance image (fcMRI) is a useful technique to study the brain’s functional organization after brachial plexus nerve injury. Resting state fcMRI analysis has some advantages over task-driven analysis for the brachial plexus injury patients. Correlation in low-frequency blood oxygen-level depended blood oxygenation level depend (BOLD) fluctuations reflects cortico-cortical connections and it detects a more complete and more accurate map of human connectivity than does the task-driven analysis \cite{7}. For the patients with brachial plexus avulsion injury who had complete paralysis of the affected hand, task-driven analysis was impossible to achieve.

The purpose of this study was to detect the change of functional connectivity between the two hemisphere in patients with unilateral brachial plexus avulsion injury. We used resting-state fcMRI to explore the differences of inter-hemispheric functional connectivity between the patients and healthy subjects.
Methods and Materials

Subjects:

Eleven healthy male volunteers and nine male patients (age=30.33±10.19 years) who suffered from unilateral brachial plexus avulsion injury were recruited in this study. All patients had complete avulsion injury of the five roots of unilateral brachial plexus diagnosed by clinical evaluation and electromyography studies before MRI scan. Functional MRI examination was performed before surgical procedure for every patient. Pre-operative and intra-operative electromyography was performed to certify the diagnosis. Patients did not suffer from any neurogenic or organic disease of the brain. Due to gross head motion (translation > 3mm), two healthy volunteers were excluded. As a result, 9 healthy volunteers (age=26.11±1.83 years) finally retained in this study. There was no significant difference between healthy volunteers and brachial plexus injury patients in age (p=0.25, two-sample Satterthwaite’s approximate t test with unequal variances). The intervals between injury and fMRI scanning ranged from one month to six months. Clinical evaluation for residual motor functions of the affected side showed that the muscle grades were 0 for all relative muscles of all five fingers and of wrist joint.

Experimental design

First, all subjects were scanned under resting-state, healthy volunteers were scanned under additional motor task condition after resting-state scanning. Structural images were scanned at last. For the Resting-state scanning, the subjects were instructed to keep their eyes closed, and not to think of anything in particular as well as not to fall asleep during resting-state scanning. The scanning time lasted for 6 minutes and 52 seconds.

For the motor task scanning, block design was used. The motor task consisted of 3 blocks of unilateral hand grasping movement at a frequency of about 2 Hz for 30 seconds. Between active blocks there were 30 seconds rest.

fMRI and structural scanning

A GE Signa VH/I3.0T scanner was used. Foam pillows were used to restrict head movements. Functional resting-state data were scanned in an EPI session of 206 volumes for 412 seconds. The images taken in the first 12s were discarded to ensure the signal had achieved a steady state, so 200 volumes conserved. The resting-state gradient echo-planar imaging sequence parameters were as follows: repetition time (TR) = 2,000ms, echo time (TE) = 35ms, flip angle (FLA) = 90°#field of view (FOV) =240mm×240mm, acquisition matrix = 64×64, slice thickness =5mm and inter-slice space =0mm.
The following gradient echo-planar imaging sequence parameters were used for the acquisition of the functional images under motor task condition: TR = 3,000ms, TE = 35ms, FLA = 90°, and FOV = 240mm × 240mm. The acquisition matrix was 64 × 64 resulted in voxel resolution of 3mm × 3mm × 5mm. The images taken in the first 12s were discarded to ensure the signal had achieved a steady state.

For the structural images, fast spoiled gradient recalled echo inversion recovery (FSPGRIR) sequence was used to acquire 1mm thick axial section and the parameters were as follows: TR = 1,000ms, TE = 5ms, inversion time (IR) = 400ms, FLA = 20°, inter-slice space = 0mm, FOV = 240mm × 240mm, acquisition matrix = 256 × 256.

Data analysis

**Within group analysis**

Preprocessing for motor task and resting-state data. The motor paradigm images were analyzed for each healthy volunteer using SPM8 (Welcome Department of Cognitive Neurology) implemented in Matlab 7.1. The resting-state data were analyzed using DPARSF (Data Processing Assistant for Resting-state fMRI) which is based on SPM8 and Resting-state fMRI Data Analysis Toolkit (REST, by SONG Xiao-Wei et al. http://www.restfmri.net). First, differences in image acquisition time between slices in one volume were corrected by performing slice timing in SPM8 or in DPARSF. Then, the scans of each single session were realigned to the first scan for each sequence using a 6-parameter rigid-body transformation. The scans from all sessions were realigned to a mean image to correct for motion artifacts. The realigned images were then normalized into a Montreal Neurological Institute (MNI) standard space (EPI MNI-152 space). The voxel sizes of the written normalized images were 3mm × 3mm × 3mm.

For the motor task data, the voxels were spatially smoothed with 8-mm full-width at half-maximum Gaussian kernel after normalization. We made boxcar analysis for all sessions with T-contrast. The group analysis for each session across subjects were made using one sample t-test. Finally, a T-map of group analysis for each motor task was obtained. A p-value of 0.005 of voxel extent and p-value of 0.05 with cluster size of 27 voxels for cluster extent were used as the thresholds for activation (The correction thresholds determined by Monte Carlo simulations with the program AlphaSim in AFNI (Analysis of Functional NeuroImages), AlphaSim correction). We identify relevant areas as the regions of interest (ROI) for the analysis of resting-state data in this activation map.

For the resting-state data, the voxels were spatially smoothed with 6-mm full-width at half-maximum Gaussian kernel. Then, all images were temporarily low-pass filtered (0.01Hz < frequency < 0.08Hz) to reduce the effect of high-frequency noise. The linear trend was removed after temporary low-pass filter. Before functional connectivity was computed,
several sources of variance for the resting-state data were removed as covariance by linear regression as follows: (a) 6 head motion parameters (b) global mean signal (c) white matter signal (d) cerebrospinal fluid signal. To compute functional connectivity maps (FC maps) based on ROI, we first defined the ROIs on the task related T-map of group analysis. Clusters of the maximum activation strength in the contralateral (to the moving hand) motor areas were extracted as the regions of interest (ROI). Four areas were defined as ROIs: the two primary motor areas (M1 areas) and two supplementary motor areas (SMA) represented for the hand grasping movement in the two hemispheres. The MNI coordinates of the local maximum of the ROIs were: (-45, -22, 40) and (42, -16, 46) for the left and right M1 areas; (-9, -7, 49) and (9, 7, 55) for the left and right SMA. The voxels for the ROIs were: 104 and 98 voxels for the left and right M1 areas; 102 and 103 voxels for the left and right SMA. The time course of each ROI was then extracted before functional connectivity analysis. After the ROIs were defined, we computed the Pearson correlation coefficients between the time course of the ROIs and that of every voxel in the whole brain (voxel-wise analysis). A fisher z-transform was used to normalize the correlation coefficients ($z=0.5\log(1+r)/(1-r)$, $r$ is the correlation coefficient). The Z scores of every subject were applied to SPM8 to perform one-sample t-test in order to obtain the group analysis t-score maps. As a result, brain areas with significant connectivity to the ROIs within each group were obtained with a p-value < 0.005 (uncorrected) for the voxel extent and p-value < 0.05 with extent threshold of 27 voxels for the clusters.

For the patient group, we calculated the functional connectivity maps using all 9 patients as a group although there are 3 patients with left brachial plexus injury. Because our interest was the status of functional connectivity after brachial plexus injury and we focused on the inter-hemispheric functional connectivity, whether the left or right brachial plexus was injured would not affect the correlation coefficient of one ROI in one hemisphere to another ROI in the other hemisphere.

**Between group comparisons**

The Pearson correlation coefficients between every two ROIs were calculated (ROI-wise analysis) and the same z-transforms were applied. At last, the z-transformed correlation coefficients of the patients were compared with that of normal control group using the two sample t-test.
Results

For the motor task, unilateral hand grasping movement of the healthy volunteers mainly activates contralateral (to the moving hand) primary motor area and supplementary motor areas in both hemispheres (Fig. 1). Ipsilateral primary motor area activation is also activated (see Fig. 1.).

For the healthy volunteers, within group voxel-wise functional connectivity analysis shows that voxels with functional connectivity to the seed region, either M1 area or SMA area, mainly located along the precentral sulcus and supplementary motor areas of both hemispheres (Fig. 2).

For the patient group, when M1 area is chosen as the seed region, dispersed small clusters in the contralateral hemisphere shows positive functional connectivity to the M1 areas (see Fig. 2). When SMA is chosen as the seed region, symmetrical voxels functionally connected locate in the motor areas of the two hemispheres (see Fig. 2).

Weakened inter-hemispheric functional connectivity between the two M1 areas in the patients is observed after performing two sample t-test. The correlation coefficients between the two primary motor areas (ROI-wise functional connectivity) were calculated. The two-sample t-test result shows that the correlation coefficient of the patients between the two areas is significantly decreased (p<0.005) than that of the healthy group (see Fig. 3).

The two-sample t-test results demonstrate no significant different correlation coefficient of the two SMA areas (p = 0.54) between the healthy controls and patients, no significant difference of correlation coefficient of left M1 area and right SMA (p = 0.45), and no significant different correlation coefficient of right M1 area and left SMA (p = 0.42).
**Fig. 1:** Activation areas of unilateral hand grasping movement. A, areas represent for right hand grasping movement. B, areas represent for left hand grasping movement. The coordinates represent the values in x, y, and z orientations in MNI standard space. The images are in radiological format.

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Fig. 2: Functional connectivity maps of the healthy volunteers and brachial plexus injury patients for the four seed regions. L represents left. LM1 is left primary motor area and LSMA is left supplementary motor area. R represents Right. RM1 is right primary motor area primary motor area and RSMA is right supplementary motor area. All slices were the same axial slices in MNI stand space and z= 48.

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Fig. 3: Significant differences of functional connectivity of the two primary motor areas between healthy controls and patients. The left primary motor area is used as the seed region. The coordinates represent the values in x, y, and z orientations in MNI standard space. The images are in radiological format.

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**Fig. 4:** Correlation coefficients between other ROIs. L represents left and R represents right. Time course of left M1 area, right M1 area and left SMA area are defined as seed regions. No significant differences of correlation coefficients between the controls and patients are found.

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Conclusion

Alterations of inter-hemispheric functional connectivity after brachial plexus avulsion injury was measured to investigate cortical reorganization due to peripheral nerve injury. Our results showed that inter-hemispheric functional connectivity between the two primary motor areas was weakened because of peripheral nerve injury. Our results are consistent with the previous studies which have reported that after other peripheral nerve disease such as facial nerve palsy, motor network functional connectivity decreased, including decreased intra-hemispheric connectivity\cite{4, 5}. Furthermore, after central nervous systems diseases such as stroke, inter-hemispheric functional connectivity of the brain areas was weakened or disrupted\cite{8, 9}. More important, the phenomenon that limb deafferentation induced the decrease of inter-hemispheric functional connectivity between motor cortices was observed by Pawela et al. (2010)\cite{6} in animal models. Our study verified that this phenomenon also can happen in patients with brachial plexus avulsion injury.

It has been suggested that the spontaneous neuronal activity is on the basis of resting-state functional connectivity\cite{10} and the strength of functional connectivity is in accordance with the degree of spontaneous neuronal activity synchronization. What’s more, functional connectivity reflects the efficiency of information transfer and collaboration between brain areas\cite{4, 11}. Therefore, we believe that the temporal correlations between the motor areas are not immutable nor frozen but can be modified or changed as conditions change, and the decreased inter-hemispheric functional connectivity implies the desynchronization of brain areas and the declined efficiency of information transfer and collaboration between the two hemispheres after brachial plexus avulsion injury.

In this study, no significant different coefficients of SMA and other ROIs were found between the brachial plexus injury patients and healthy controls. SMA is a rough somatotopic map and the representations of different body parts area were found to overlap extensively in SMA area\cite{12, 13}. The SMA areas as seed regions in this study may not only represents for the movement of hand but also may represents for the movement of other body parts which were not affected by BPAI. So we hypothesis this may be the reason why there were no differences between the two groups when SMA areas were chosen as seed regions.

In conclusion, this is the first study to demonstrate that correlation in low-frequency BOLD fluctuations between the two primary motor areas reduced in patients with brachial plexus injury. This result implies that peripheral nerve injury can cause the changes in the
spontaneous functional architecture of the resting-state brain. This result provides new insight into functional reorganization of the brain after brachial plexus injury.
References:


