Resting-state Functional Connectivity Alterations after Corpus Callosotomy in Rats

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INTRODUCTION

Resting-state functional connectivity MRI (fcMRI) has been increasingly used in the diagnosis of a variety of brain diseases including Alzheimer's, schizophrenia and autism [1]. However, the underlying mechanism of the spontaneous fluctuations in fcMRI signals remains largely unexplored. It may reflect the anatomical connectivity via the midline commissural structures, such as the corpus callosum (CC), who serves an important role in coordinating the activity of contralateral cortical areas [2]. Previous human studies with callosal agenesis or corpus callosotomy (single-case) found reduced or even loss of interhemispheric correlation in fcMRI [3, 4]. In this study, we employed a well-controlled animal model of corpus callosotomy to evaluate the role of CC in the interhemispheric functional connectivity.

MATERIALS AND METHODS

Animal Preparation: Adult Sprague-Dawley rats (220~250g, 3 months, N=6) were subjected to a complete transection of the corpus callosum while the animals in the sham group (N=4) had a skull opening only. After 7 days of recovery, animals were MRI scanned under mechanical ventilation with isoflurane anesthesia (1%). ***MRI Protocols:*** All MRI experiments were conducted using a 7 T Bruker scanner with a surface coil. Five resting-state fcMRI acquisitions were performed using a single-shot GE-EPI sequence with TR/TE=1000/18ms, flip angle=30^o, FOV=$32\times32mm^2$, 64×64 matrix, nine 1-mm-thick contiguous slices and a total of 280 data points. Diffusion-weighted (DW) images were acquired with the same slice geometry and TR/TE=3000/28.6ms, δ/Δ=5/17ms, 96×96 matrix, b-value=$1000s/mm^2$ to assess the white matter integrity of CC in all animals. RARE T2W images were acquired using TR/TE=4200/36ms as an anatomic reference for EPI data. ***Data Analysis:*** All fcMRI data was slice-timing corrected, co-registered, detrended and temporally low-pass filtered. Cross-correlation analysis based on the 2×2-pixel seed voxels selected from atlas was performed using the STIMULATE software with a correlation threshold of 0.35 considered as strong cross correlated and a cluster of 2 pixels. Statistical evaluation of the differences between the cross correlation coefficients in the two groups was performed using Mann-Whitney test with $p<0.05$ considered to be significant.

RESULTS

In FA and color FA maps of DWI (Fig. 1), fiber disruption in the CC region was observed in all animals, validating the corpus callosotomy surgery. In Fig. 2, the resting-state fcMRI cross-correlation maps shows that with the CC severed, interhemispheric correlations presented in the sham animals prominently disappeared, though the intrahemispheric connections were preserved. Fig. 2 shows the typical time-courses (100s duration) of the fcMRI signal from the left and right primary somatosensory cortex (S1L and S1R) in each group. Synchronized time courses were seen in the sham animal but not the CC-severed one. Cross-correlation coefficients between the cortical regions of primary and secondary somatosensory cortex (S1 and S2) were listed in Tab. 1. There was significant reduction of the cross-correlation coefficients in the interhemispheric connection in the CC severed animals comparing to the sham controls.

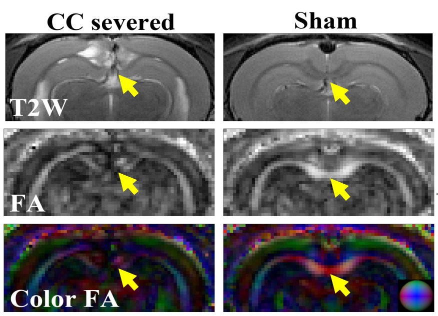

Fig.1 Representative T2WI, FA and color-encoded FA maps between the CC severed animal and sham control. Lower FA in the severed CC indicates fiber disruption compared to sham.

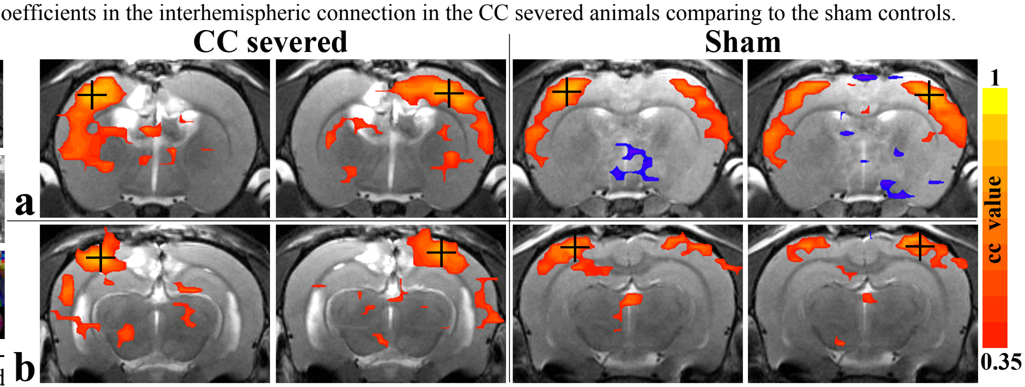

Fig.2 Typical resting-state fcMRI cross-correlation maps with the seed voxels in primary somatosensory cortex (a) and primary visual cortex (b) from CC severed animal and sham control are overlaid on T2W images. Black crosses indicate the center of the seed voxels.

DISCUSSION AND CONCLUSION

The loss of interhemispheric correlations in the resting-state fcMRI signal with the CC severed indicates the crucial role of CC in coordinating the spontaneous neural activity of the contralateral hemispheres. Since most of the cortex is connected by the callosum [2], this result also suggests the spontaneous fluctuations in fcMRI signal largely reflex the anatomical connections. Note that in Fig. 2, the area that was strongly correlated with the seed voxel appeared to be expanded intrahemispherically in the CC severed animals, which was observed in several CC-severed animals, possibly due to neural plasticity [5] at a early stage after CC section. Quantitative evaluation of this expansion will be carried out at a later time-point with histology to assess the surgical effect. In conclusion, the results of this study provide direct evidence of the role of CC in spontaneous neural activity detected by resting-state fcMRI.

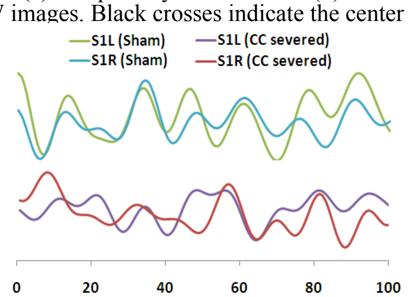

Fig.3 Typical time-courses of the fcMRI signal from the left and right primary somatosensory cortex (S1L and S1R) in each group.

		CC severed	Sham
Seed: S1L	S2L	0.56	0.59
	S1R	0.25*	0.79
	S2R	0.20*	0.67
Seed: S1R	S2R	0.57	0.64
	S1L	0.23*	0.81
	S2L	0.22*	0.69

Tab. 1 Average inter- and intra hemisphere resting fcMRI correlation coefficients between cortical regions (*$p<0.01$).

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