

Case Report

Longitudinal brain functional and structural connectivity changes after hemispherotomy in two pediatric patients with drug-resistant epilepsy

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ABSTRACT

The main focus of the present study was to explore the longitudinal changes in the brain executive control system and default mode network after hemispherotomy. Resting-state functional magnetic resonance imaging and diffusion tensor imaging were collected in two children with drug-resistant epilepsy underwent hemispherotomy. Two patients with different curative effects showed different trajectories of brain connectivity after surgery. The failed hemispherotomy might be due to the fact that the synchrony of epileptic neurons in both hemispheres is preserved by residual neural pathways. Loss of interhemispheric correlations with increased intrahemispheric correlations can be considered as neural marker for evaluating the success of hemispherotomy.

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1. Introduction

Drug-resistant epilepsy is one of the most common neurological disorders in childhood, and it is viewed as a disease of hypersynchronous neuronal activity in its electrophysiological substrates [34]. The normal developmental trajectory of the pediatric brain can be affected by epilepsy [21]. Achieving permanent seizure freedom is the ultimate goal in clinical practice. Surgical intervention is the most common treatment of drug-resistant epilepsy. For patients with multilobar or hemispheric drug-resistant epilepsy hemispheric disconnection has been long used in clinical practice. This surgical tool can be classified into two types: anatomic hemispherectomy and functional hemispherectomy [17]. Anatomic hemispherectomy was the first procedure of choice [2]. This procedure has classically involved removal of the temporal, frontal, parietal, and occipital lobes, sparing the thalamus, basal ganglia and insular cortex. Although seizure outcome was excellent after anatomic hemispherectomy, the technique has been abandoned in many centers because of the high incidence of delayed potentially fatal complications. To reduce the risk of complications, a new technique called functional

hemispherectomy (hemispherotomy) was developed. Hemispherotomy is a procedure to maximally disconnect the white matter connecting the diseased hemisphere, while performing minimal cortical resections [5]. Previous studies have shown that hemispherotomy is an important treatment for seizure reduction in patients with unilateral drug-resistant epilepsy [12,15,19]. As is known, the two hemispheres of the brain are mainly connected with the corpus callosum and subcortical pathways. The pathophysiologic basis for the use of hemispherotomy is based on the hypothesis that the spread of seizure activity between the two hemispheres of the brain is mainly transmitted through the corpus callosum and subcortical pathways [1,12,18]. Therefore, severing these major cortico-cortical connections between the two hemispheres should dramatically reduce seizures. Over the years, numerous studies in humans have proved the potential advantageous effects of this procedure [13, 24,26,32,39].

However, postoperative observations have shown that long-term rates of postoperative seizure freedom are in the range of 43–90% after hemispheric disconnection surgery [20,24,43]. Diverse hemispherotomy based epilepsy surgical outcomes might indicate that the neural mechanism underlying brain reorganization after this surgery is not completely understood. The explanation for the clinical phenomenon after hemispherotomy in these previous studies was mainly based on the anatomic pattern plasticity by severing the interhemispheric fiber bundle, such as the corpus callosum and subcortical pathways [19,20]. To understand the neural mechanism underlying this type of epilepsy and the diverse surgery outcomes, multimodal imaging methods would be necessary to give a relatively complete view on this topic. A single

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modality method may only partially detect the potentially important variation underlying the brain. Multimodal imaging methods can provide unprecedented opportunities to further deepen our understanding of the cross-information of the existing data and reveal the neural mechanism of the brain [6]. Such approaches can provide a wealth of information, enabling researchers to more confidently draw conclusions. In present day research, multimodal neuroimaging has become a mainstay of neuroscience in humans [25,41]. Furthermore, predictors of hemispherotomy outcomes are still unclear. Therefore, it is valuable to investigate the brain functional and structural network changes before and after this surgery. Brain functional and structural imaging data integration can yield further insights into brain reorganization processes after hemispherotomy.

To explore these issues, we studied brain connectivity patterns by magnetic resonance imaging (MRI) in two children with drug-resistant epilepsy both before and after hemispherotomy. A longitudinal and multimodal neuroimaging method, combining diffusion tensor imaging (DTI) and resting-state functional MRI, were used in the present study to evaluate brain structural and functional changes. DTI is an advanced MRI technique used to map white matter pathways [3,46]. Functional connectivity (FC) of resting-state functional MRI is a method to calculate the correlation or synchronization between the time course of activation between two regions. FC analyses have been used to examine brain connectivity changes before and after treatment in a variety of disorders, such as stroke [23,42] and epilepsy [22,31,32,44]. Longitudinal changes in the FC of these studies have suggested that the FC method may be useful in examining the neural mechanism underlying brain recovery.

The novelty in this study is the combination of fMRI and DTI to examine the longitudinal brain connectivity responsible for hemispherotomy in children with drug-resistant epilepsy. Our main focus was centered on two epilepsy-related local networks: the executive control system (ECS) network and default mode network (DMN). The reason for selecting these two networks is they play critical roles in maintaining the brain's integrity and effective dealing with motor functions [31]. Previous neuroimaging studies have demonstrated that resting-state FC and regional brain integrity in DMN were affected in children with epilepsy [10,22,44]. Based on previous data, we hypothesized that changes in brain connectivity of two patients, one seizure-free and the other with seizure recurrence, may be apparent following hemispherotomy.

2. Materials and methods

2.1. Subjects

Two patients (one male, age 81 months, epilepsy onset time at 6 months; the other female, age 7 months, epilepsy onset time at 3 months) with infantile spasms (IS) were recruited from Shenzhen Children's Hospital, Guangdong, China. The male patient was diagnosed with encephalomalacia in the left hemisphere, which was caused by ischemia injury involving part of the middle and superior temporal, precentral, postcentral and inferior frontal gyrus. The female patient

had focal cortical dysplasia in the right frontal and parietal lobes. These two patients were diagnosed with IS based on; (1) clinical and electroencephalography (EEG) findings supporting a diagnosis of IS; (2) clinical history of at least one seizure that was consistent with IS; and (3) no neurological diseases other than epilepsy.

Both patients were treated with antiepileptic drugs to control seizures after the diagnosis (the boy: carbamazepine tablets, clonazepam tablets and magnesium valproate tablets; the girl: levetiracetam tablets and oxcarbazepine oral suspension). No significant response to drug treatment was found in both patients. Therefore, surgical treatment with peri-insular hemispherotomy was performed on both patients. A complete section of the corpus callosum was performed at the level of the dome of the ventricle and the amygdalo-hippocampal structures were disconnected within the temporal horn. There were no complications. Patients were followed up with continuation of antiepileptic drugs. Longitudinal clinical phenomena were recorded for at least 12 months for both patients to judge the surgery curative effect. The boy was seizure-free, and intelligence and motor function markedly improved after the surgical intervention (Engel I). However, for the girl, complete cessation of seizures persisted only 4 months after surgery, and seizure was relapsed later (Engel III). Because patients were in different age stages, we enrolled two control groups to match the patients: typical-developing children group (C1: 10 people, 2 females, mean age = 81.9 ± 9.9 months), typical-developing infants group (C2: 9 people, 3 females, mean age = 10.3 ± 1.3 months). Both control groups consisted of 19 typical-developing volunteers with no history of neurological or psychiatric disorders.

All participants were scanned using rs-fMRI at the time of recruitment. Postoperative MRI images were also collected at two time points for both patients: the boy, 21 days and 115 days after surgery; the girl, 22 days and 221 days after surgery. All participants under the age of four were sedated with 10% chloral hydrate during the MRI scanning. Others (over the age of four) were instructed to rest, to not think of anything, to keep their eyes open and to not fall asleep. Information on both groups can be found in Table 1. Written informed consent forms were obtained from all participants' parents in accordance with the standards of the Declaration of Helsinki. The Ethics Committee of the Shenzhen Children Hospital approved this study (No. 2016008).

2.2. Image acquisition

Imaging data were collected using an eight-channel head coil with a 3 T Siemens scanner (MAGNETOM Trio Tim, Siemens, Germany) at the Shenzhen Children's Hospital, Guangdong, China. Foam cushions were used in the scanning process to reduce head movement. High-resolution T1-weighted 3D MPRAGE images were acquired for all subjects: TR/TE = 2300/2.26 ms, FOV = $200 \times 256 \text{ mm}^2$, 160 slices, 1 mm slice thickness, voxel size = $1 \times 1 \times 1 \text{ mm}$, acquisition matrix = 200×256 , flip angle = 8° . Resting-state fMRI was obtained using an echo-planar imaging sequence with the following scan parameters: TR/TE = 2000/30 ms, FOV = $220 \times 220 \text{ mm}^2$, matrix = 94×94 , flip angle = 90° , slice thickness = 3 mm, 36 interleaved axial slices, and 130 volumes. The

Table 1
Characteristics of the children with drug-resistant epilepsy and typical-developing volunteers.

Characteristics	Typical-developing volunteers (M $\pm$ SD)		Epilepsy children with corpus callosotomy	
	C1	C2	Seizure free	Seizure recurrence
Gender (male/female)	8/2	6/3	1/0	0/1
Age (months)	81.9 ± 9.9	10.3 ± 1.3	81	7
Handedness (right/left)	10/0	–	1/0	No
Epilepsy duration (months)	–	–	75	3
Epilepsy onset time (months)	–	–	6	3
Epilepsy type	–	–	Infantile spasm	Infantile spasm
Pathogeny	–	–	cerebromalacia (L)	Focal cortical dysplasia (R)
Time points of MRI	1	1	1 pre/2 post	1 pre/2 post

L, left hemisphere; R, right hemisphere; C1, the typical-developing group 1; C2, the typical-developing group 2.

DTI acquisition sequence was a single-shot spin-echo planar imaging sequence (TR/TE = 5500/95 ms, flip angle = 90°, slice thickness = 2.5 mm, matrix = 128 × 128, voxel size = 1.72 × 1.72 × 2.5 mm). Thirty non-collinear directions with a b value of 1000 s/mm² and one volumes with a b value of 0 s/mm² were acquired. To enhance the signal-to-noise ratio, imaging was repeated three times.

2.3. Imaging processing and statistical analysis

2.3.1. Resting-state fMRI data analysis

The resting-state fMRI data were processed using the Statistical Parametric Mapping (SPM8, <http://www.fil.ion.ucl.ac.uk/spm>) and REST (<http://www.restfmri.net>) package. The preprocessing steps included slice timing and spatial realignment and were co-registered with each subject's high-resolution anatomical image, normalized into standard Montreal Neurological Institute (MNI) space using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) template, and smoothing (8 mm FWHM Gaussian blur). During the normalization step, we used the DARTEL method to create two customized templates: the anatomical images of all typical-developing subjects in C1 were used to create template 1. The anatomical images of all typical-developing subjects in C2 were used to create template 2. The co-registered functional images of the boy patients and all subjects in the C1 group were normalized into MNI using template 1. Similarly, the co-registered functional images of the girl patients and all subjects in the C2 group were normalized into MNI using template 2. A temporal filter (0.01–0.08 Hz) was then applied to reduce the effect of very low frequency and high frequency physiological noise. Nuisance regression was performed using white matter, cerebrospinal fluid, and the six head motion parameters as covariates to reduced spurious variance. No participant had head motion with more than 2.0 mm maximum displacement or 2.0° of any angular motion.

FC maps were obtained using the voxel wise approach by computing the FC between the region of interest (ROI) and each voxel within the brain. We defined sixteen 10-mm-diameter spherical ROIs according to Pizoli et al. [31] and Fox et al. [11]: ECS network and DMN (Table 2). The selected ECS network ROIs included the bilateral anterior insula and anterior thalamus. The selected DMN ROIs included the bilateral parahippocampus, precuneus, inferior temporal lobe (ITL), superior frontal gyrus (SFG), and the anterior and posterior angular gyrus. BOLD time series were extracted from each seed ROI. Correlation maps were produced by computing the correlation coefficient between the time course from the seed and the time course from all other brain voxels. The obtained correlation maps were converted to a normal distribution

by Fisher's z-transform. Network models of connectivity were analyzed within the control group using a single sample t-test threshold at FDR-corrected $p < 0.01$. Age and gender were used as covariates of interest in this statistical analysis process. Generated correlation maps both before and after transection surgery of the corpus callosum in both patients were listed and compared with the normal network models of the controls.

Also, to further confirm our ROI-based FC results, we used a technique called voxel-mirrored homotopic connectivity (VMHC) to calculate the functional connectivity between symmetric interhemispheric voxels [49]. For each subject, Pearson correlation coefficient was calculated between each voxel's residual time series and that of its mirrored interhemispheric voxel. The coefficients were Fisher z-transformed and the VMHC maps were generated.

2.3.2. Diffusion tensor imaging analysis

The DTI data were analyzed using the FMRIB Software Library (University of Oxford, FSL v5.0.8, www.fmrib.ox.ac.uk/fsl). Standard processing steps were used. First, eddy currents and head motion correction were performed using affine registration to the imaging without diffusion weighting. The data were subsequently skull-stripped by using the FMRIB Brain Extraction Tool (BET v2.1). Subsequently, the FMRIB Diffusion Toolbox (FDT v3.0) was used to fit the diffusion tensor.

To assess the pattern of structural connections of selected ROIs, fiber tracking was carried out using a probabilistic tractography algorithm implemented in FSL (Probtrackx) and based on the Bayesian estimation of diffusion parameters (Bedpostx) [4]. Briefly, bedpostx runs Markov Chain Monte Carlo sampling to build up distributions on principal diffusion directions at each brain voxel, which allows modeling of crossing fibers. Probtrackx then repetitively sampled from the distributions of the voxel-wise principal diffusion directions, each time computing a streamline through these local samples to generate a probabilistic streamline or a sample from the distribution at the location of the true streamline. By taking many such samples, the posterior distribution on the streamline location or the connectivity distribution was determined. All brain voxels had a value representing the connectivity value between that voxel and the seed voxel. Fiber tracking was initiated from all voxels within the seed mask in the diffusion space to generate 5000 streamline samples, with a step length of 0.5 mm, a curvature threshold of 0.2, and a maximum of 2000 steps. The selected sixteen 10-mm-diameter spherical ROIs were also used here for tractography. The ROIs were linearly transformed into the native space of each subject, where the probtrackx analysis was performed. Then, a connectivity distribution was generated for each ROI.

After all tracts were calculated for each subject, the tracking results were thresholded to include only those voxels receiving at least 500 streamlines passing in a voxel. The purpose of the threshold setting was to reject low-probability voxels and reduce outlier-induced noise. The selected pathways of each ROI were transformed to the MNI 152 brain standard space to generate individual probabilistic maps for this ROI. For both patients, the thresholded and transformed probabilistic maps of each ROI represented the pattern of structural connections. For both control groups, the transformed individual probabilistic maps of each ROI were binarized, and then overlaid to produce population probability maps for each pathway reflecting the proportion of the population. The produced population probability maps of both control groups were thresholded to include only the tract presenting more than 3 individuals of each control group. The thresholded control group's probability maps represented the normal pattern of structural connection of each ROI.

3. Results

3.1. Seed-based FC analyses

Functional networks correlating with each of the seed ROIs are shown in Figs. 1 and 2. In both control groups, correlation maps

Table 2
The location of seed regions using for seed-based FC.

Network	ROI	Areas	MNI coordinates		
			X	Y	Z
Executive control system	1	Right anterior insula	40	19	−3
	2	Left anterior insula	−37	17	0
	3	Right anterior thalamus	12	−14	6
	4	Left anterior thalamus	−12	−14	5
Default mode network	5	Right anterior angular	54	−60	39
	6	Left anterior angular	−48	−63	37
	7	Right posterior angular	44	−74	34
	8	Left posterior angular	−42	−77	28
	9	Right parahippocampus	30	−41	−16
	10	Left parahippocampus	−27	−46	−12
	11	Right precuneus	6	−51	35
	12	Left precuneus	−5	−56	31
	13	Right inferior temporal	57	−35	−19
	14	Left inferior temporal	−60	−28	−17
	15	Right superior frontal	24	35	46
	16	Left superior frontal	−17	32	54

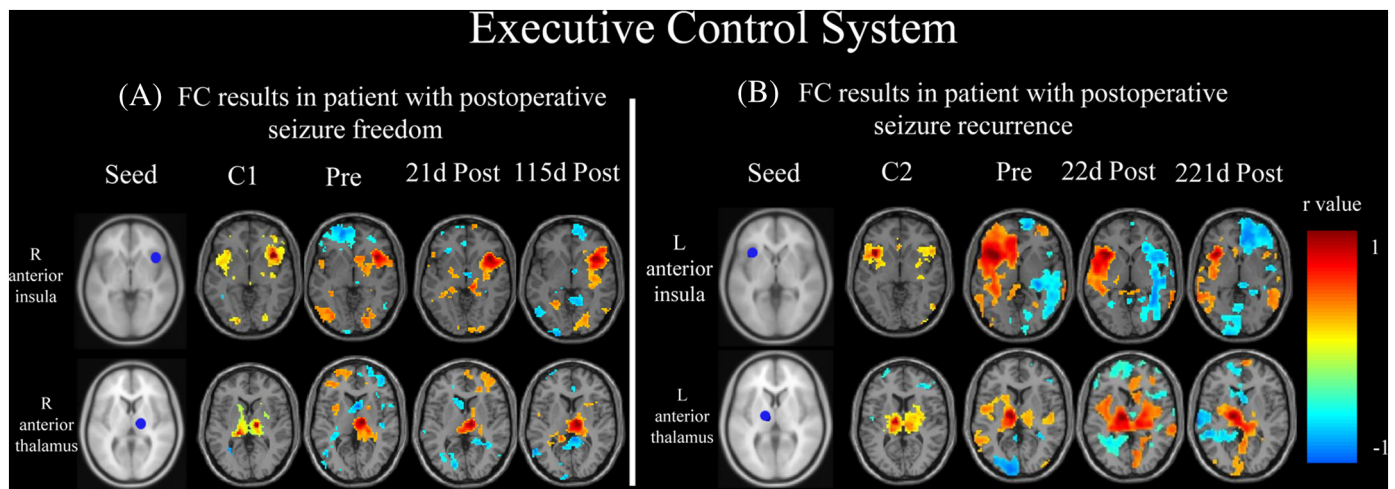


Fig. 1. Selected seed-based FC correlation maps of seeds within the executive control system. (A) FC results of right ROIs in the control group and the patient with postoperative seizure freedom. (B) FC results of left ROIs in the control group and the patient with postoperative seizure recurrence. Pre, preoperative (correlation coefficient thresholds at ± 0.3); post, postoperative (correlation coefficient thresholds at ± 0.3); C1 = control 1 group, C2 = control 2 group, t-statistical maps ($p < 0.01$, FDR corrected); Seed, Seed ROI location.

corresponding to all seed regions showed strong bilateral and recognizable resting state network architecture. In the two patients, the preoperative correlation maps corresponding to most seed regions were indeed present bilaterally. However, the connectivity patterns

of the two patients differed dramatically from the controls. Their resting-state network architectures were reorganized with a widely scattered distribution of network connections with the seed nodes.

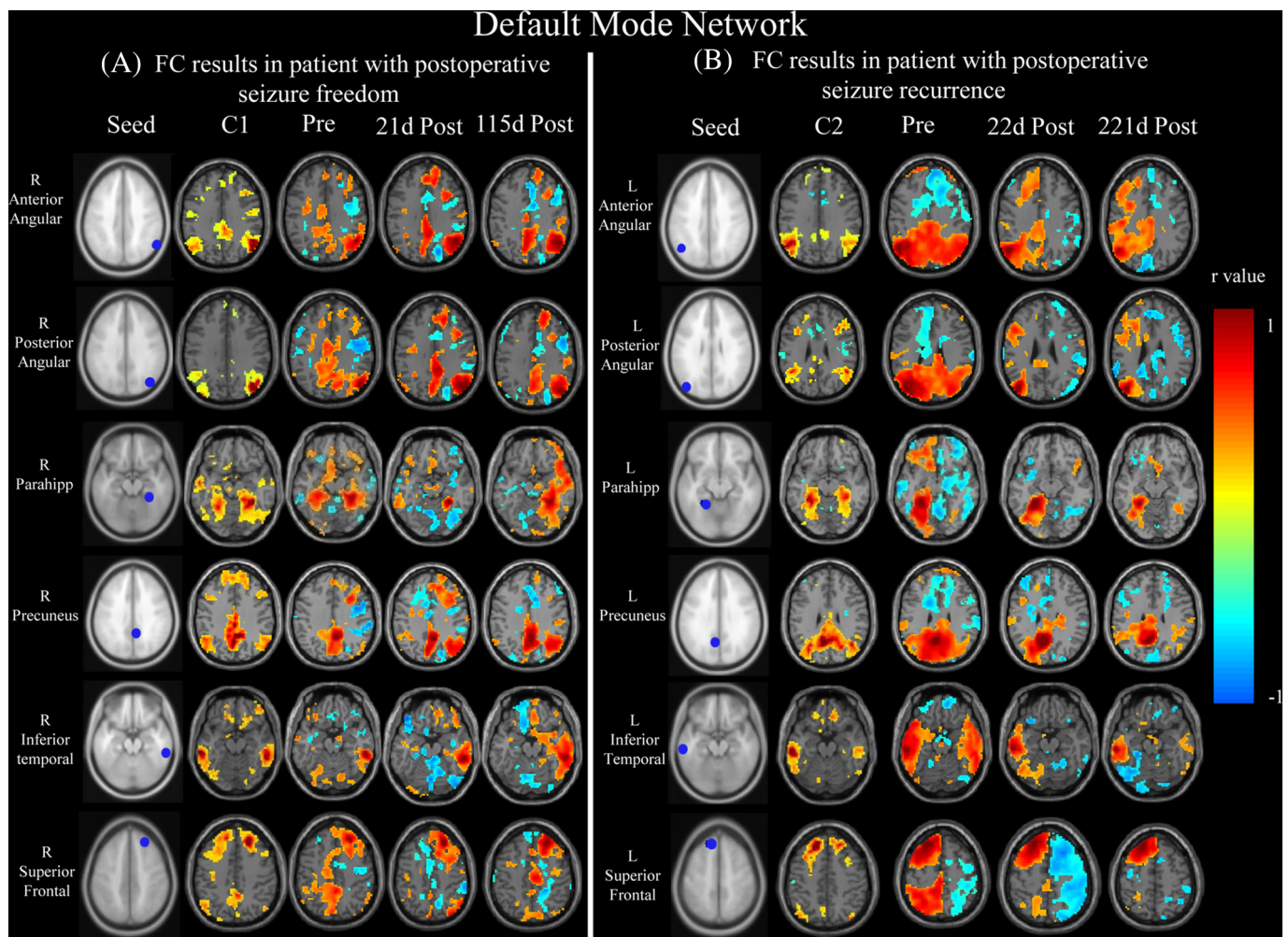


Fig. 2. Selected seed-based FC correlation maps of seeds within the default mode network. (A) FC results of right ROIs in the C1 and the patient with postoperative seizure freedom. (B) FC results of left ROIs in the C2 and the patient with postoperative seizure recurrence.

Postoperatively, the functional correlation results showed a different pattern between the two patients. For the boy patient with complete seizure remission, all correlation maps showed a loss of interhemispheric FC after surgery as an exception. Intrahemispheric anterior–posterior connectivity correlations in the healthy hemisphere increased over time. At the second time point after surgery, a restoration of some FC pathways of the seeds within the ECS and DMN was found in this patient with complete seizure remission. The FC architectures of this patient showed a trend similar to that of the control group.

For the girl with postoperative seizure recurrence, interhemispheric FC showed a significant decreased but not complete loss at the first time point after the surgery. Some regions in the right hemisphere still showed FC with the left seeds, such as the seed of left insula, thalamus, posterior angular, parahippocampus and precuneus. At the second time point after surgery, interhemisphere FC of some seeds were still present, such as the left parahippocampus, left precuneus, left ITL, left anterior insula and thalamus. Intrahemispheric anterior–posterior connectivity correlations in the healthy hemisphere of this girl patient showed a modulation after surgery.

3.2. VMHC analysis

VMHC results for each group and each patient were calculated and shown in Fig. 3. In the two control groups, most of symmetric interhemispheric voxels were shown high homotopic connectivity. For the two patients before surgery, although the pattern of their VMHC maps showed a changes comparing with the normal controls, some regions like bilateral hippocampus, fusiform, inferior parietal lobe, superior frontal gyrus and cerebellum showed high homotopic connectivity.

After surgery, the longitudinal changes of VMHC patterns were different between two patients. The homotopic connectivity between two hemispheres was broken in the boy patient with complete seizure

remission excepting the bilateral cerebellum. For the girl with postoperative seizure recurrence, VMHC between the two hemispheres of thalamus, postcentral gyrus were still high.

3.3. Seed-based probabilistic fiber tracking analyses

Fiber tracking results with each of the seed ROIs are shown in Figs. 4 and 5. In the control group, the fibers from most ROIs crossed the corpus callosum to connect with the contralateral hemisphere: bilateral anterior thalamus, bilateral anterior and posterior angular, bilateral precuneus, ITL and SFG. In both patients, the preoperative connectivity distribution of each seed ROI was changed compared with the control groups. The pathways of some fibers were broken, or the directions were changed.

Postoperatively, the fiber pathways also showed different patterns between the two patients. For the patient with complete seizure remission, all fiber tracking results showed a loss of the interhemispheric fiber connectivity after callosotomy. At the second time point after surgery, fiber tracking analysis showed that the complete loss of interhemispheric correlations was preserved. Intrahemispheric anterior–posterior or up-down fiber connectivity intensity in the healthy hemisphere was increased with the brain developing after surgery. The typical examples were that the fiber tracking pathways connecting the seeds of the right precuneus and right anterior thalamus showed partial restoration of structural pathways from pre- to post-surgery.

For the patient with postoperative seizure recurrence, some interhemispheric fiber pathways showed reconstruction but not complete loss at the first time point after the surgery: left anterior thalamus, left precuneus, left SFG, and left anterior and posterior angular gyrus. At the second time point after surgery, interhemisphere fiber connectivity intensity of some seeds even showed an increase but not a decrease in this patient.

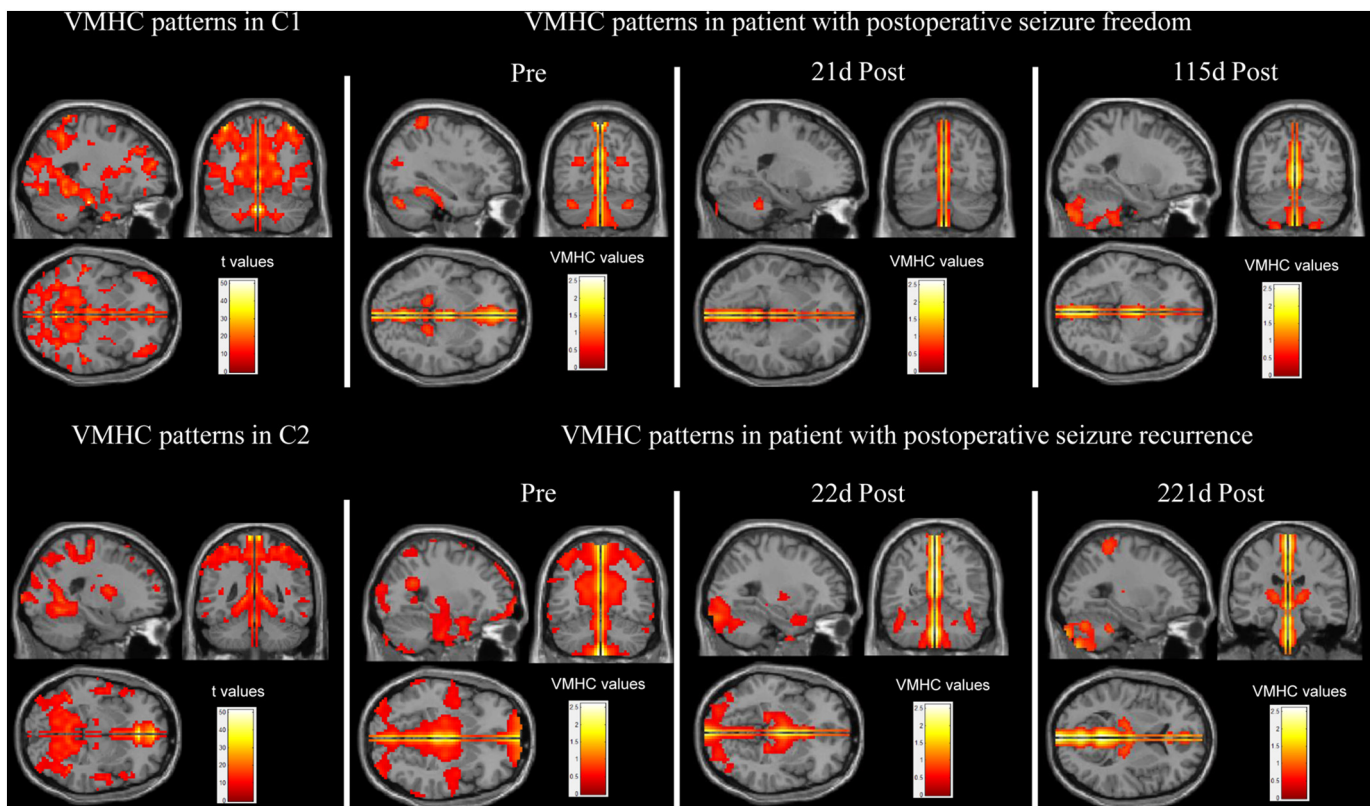


Fig. 3. VMHC maps of each patient and the two groups. The significant regions indicate that the functional connectivity between the voxel and its mirrored interhemispheric voxel is high. C1 = control 1 group, C2 = control 2 group.

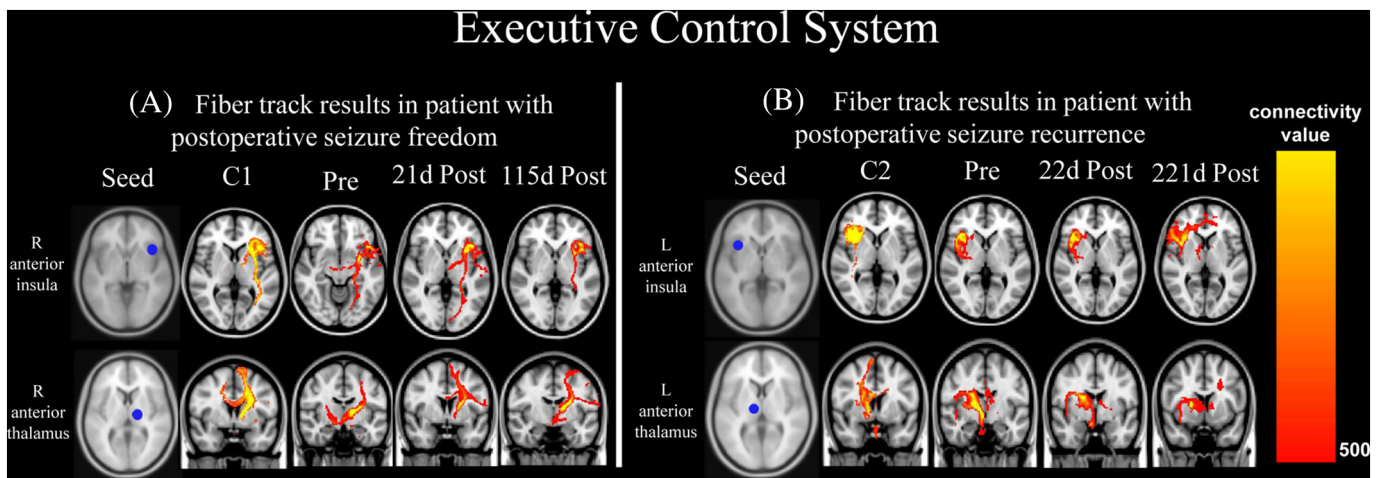


Fig. 4. Selected seed-based fiber tracking correlation maps of seeds within the executive control system. (A) Fiber tracking results of right ROIs in the C1 and the patient with postoperative seizure freedom. (B) Fiber tracking results of left ROIs in the C2 and the patient with postoperative seizure recurrence. Pre, preoperative (at least 500 streamlines passing in each voxel); Post, postoperative (at least 500 streamlines passing in each voxel); C1 and C2, population probability maps of the two normal groups (display paths at least 50% of all subjects); Seed ROI location.

4. Discussion

The present study used a longitudinal and multimodal neuroimaging method to explore the alterations of brain functional and structural

networks in children with drug-resistant epilepsy during the resting state. First, both patients' brain functional and structural network patterns were changed compared with the control group before surgery. Second, the trajectories of brain plasticity with hemispherotomy in

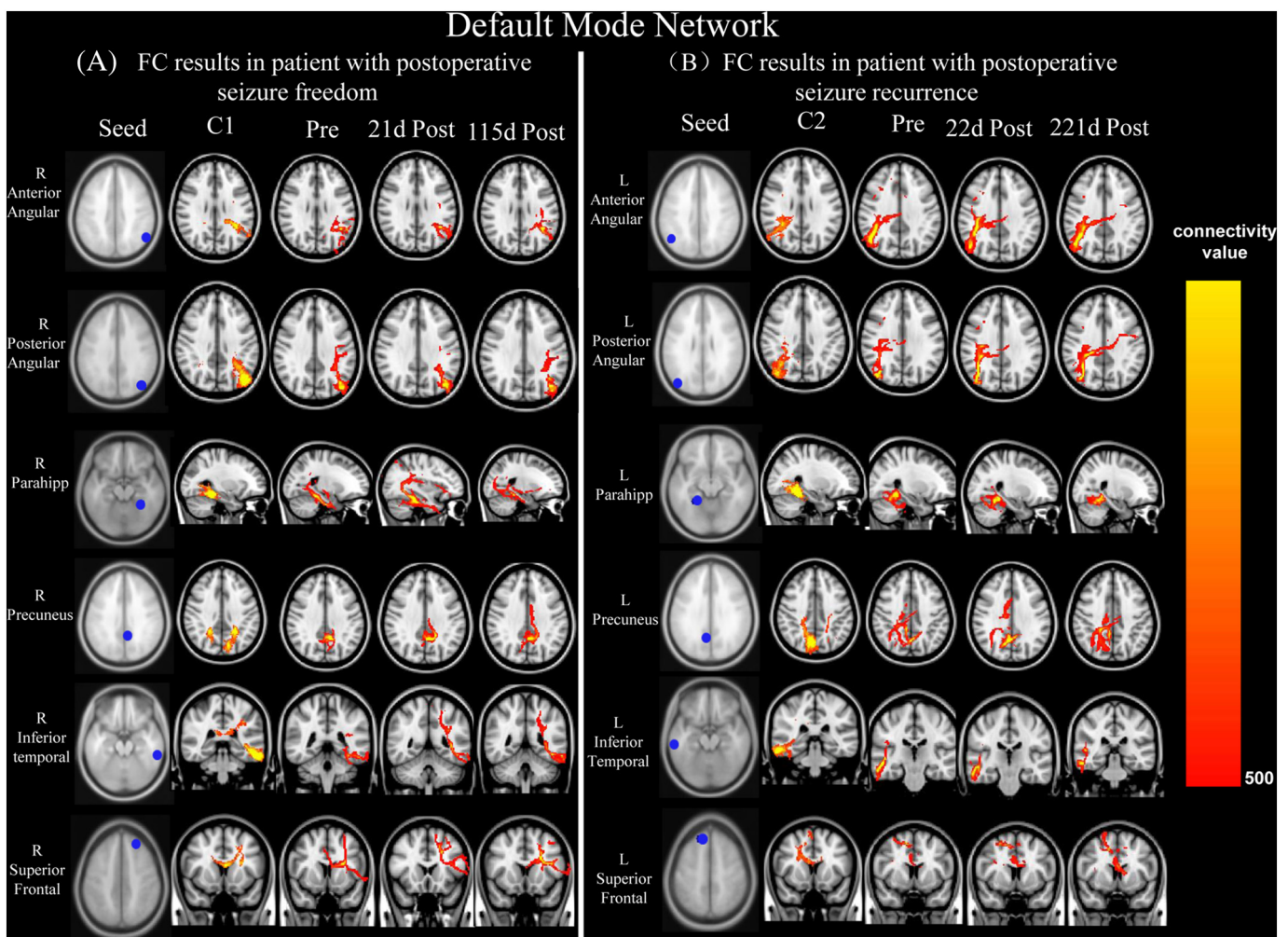


Fig. 5. Selected seed-based fiber tracking correlation maps of seeds within the default mode network. (A) Fiber tracking results of right ROIs in the C1 and the patient with postoperative seizure freedom. (B) Fiber tracking results of left ROIs in the C2 and the patient with postoperative seizure recurrence.

both patients were different. The patient with seizure freedom after surgery showed a loss of interhemispheric correlations and increased intrahemispheric correlations in the healthy hemisphere. The patient with seizure recurrence after surgery showed a preserved interhemispheric connectivity. VMHC results were consistent with our ROI-based FC results. All of these results were consistent with our hypotheses and provided relatively more information of hemispherotomy effects in brain plasticity of children.

4.1. Neuroimaging technology and connectivity

In the present study, our research subjects were children with drug-resistant IS with clusters and hypsarrhythmia [30,44]. Functional and structural connectivity analyses in the present study showed that both patients' ECS and DMN connectivity patterns were changed compared with the control groups. These results were consistent with our previous studies in that IS children showed significant changes in brain functional connectivity and regional homogeneity values in the DMN, hippocampus, caudate, thalamus and insula regions [38,44]. The locations of the regions showed significant differences between groups were similar in these studies, which might indicate that epileptic seizures have some negative effects on children's motor, executive and cognitive functional development [10,30,44]. In the present study, the longitudinal changes of brain connectivity pattern of DMN and ECS gave more information on the seizure effects on children's brain development. The present changed connectivity pattern results can also be supported by a previous EEG study of brain signal changes in IS. EEG signals in children with IS had marked abnormalities in coherence and spectral power compared with the normal group [7]. Combining these previous studies and our results, we found IS can induce changes in children's brain connectivity and integration in some local regions.

4.2. Effects of hemispherotomy on brain connectivity in the case of seizure freedom

Numerous studies have shown that disconnection procedures, such as corpus callosotomy and hemispherotomy, are cornerstones of surgical management of drug-resistant epilepsy in children [16,26,36,39]. For the hemispherotomy procedure used in our present study, outcomes were dependent on achieving a complete disconnection between the two hemispheres. As we expected, the patient with seizure freedom showed a loss of interhemispheric correlations and increased intrahemispheric correlations in the unaffected hemisphere. These changes were found in both functional and structural connectivity analyses. Severing of major cortico-cortical connections between the hemispheres may block the seizure activity spreading from the affected hemisphere to the normal hemisphere [16,18,31]. Similar functional and structural connectivity results of this patients may be based on a central assumption of systems neuroscience that the structure of the brain can predict and/or is related to FC [27,37]. Our FC analyses of all ROIs also showed a complete loss of interhemispheric connections in this patient. This may suggest that alterations in neuronal functioning are directly related to alterations in structure [35].

Increased intrahemispheric correlation in the unaffected hemisphere is another important finding that may reflect brain neuroplasticity. Evidence from neuroplasticity studies suggested that novel experience, environmental changes, brain-damage and surgery could cause functional and structural reorganization of the brain [14,15,27]. With hemispherotomy surgery intervention, a dramatic loss of interhemispheric neural pathways was found in the present study. Therefore, the brain must reallocate the remaining physiological resources to maintain a satisfactory level of function in cognitive and social activity. This highly adaptive process exemplifies that the human brain showed a plasticity as a consequence of surgery [14,33]. In clinical practice, the aim of the surgery for children with drug-resistant epilepsy is to prevent cognitive decline and improve behavioral function [26].

Our previous longitudinal neuroimaging study has shown that brain surgery can induce alterations in spontaneous brain activity and functional network reorganization in children with drug-resistant epilepsy [22]. A previous longitudinal study of human brain development has demonstrated that synchronicity is present between structural and functional changes during childhood and adolescence [8]. Therefore, the reorganization of the brain network pattern in the healthy hemisphere might be caused by the combination of surgery and brain development. In the present study, the FC pattern in this patient showed a tendency similar to the pattern of control group with time passing in some ROIs, such as the right precuneus, inferior temporal, anterior angular and thalamus. All of these regions have an important role in advanced cognition, such as attention and executive control processing. Previous studies on children with epilepsy have demonstrated that the function of these regions might be affected by seizures [38,47]. After surgery, recovery of FC in these regions might imply that patient's attention and executive control functions were improved after surgery. The neuroimaging features suggest the relevant functional pathways recover to some extent when surgery is successful.

Another explanation for complete seizure remission after disconnection surgery in this patient might be that the synchrony of epilepsy in both hemispheres was disrupted [15,16]. The FC analyses supports this viewpoint. In the normal group, all ROIs have strong FC with the contralateral hemisphere, which might indicate the synchrony between both hemispheres was significant. For the patient with seizure freedom, the interhemispheric synchrony was broken by hemispherotomy surgery. Whole brain VMHC analysis results also confirmed the view that interhemispheric connections of this patient were complete loss after hemispherotomy surgery. Meanwhile, the synchrony of the regions in the healthy hemisphere was increased. From our neuroimaging results, we suspect the interruption of interhemispheric synchrony and severing the transmission pathways associated with seizures combined together would produce complete seizure remission.

4.3. Effects of hemispherotomy on brain connectivity in the case of seizure recurrence

Although most patients who receive hemispherotomy achieve control of seizures, recurrence is still present in some patients [20,24]. For these patients, the mechanism of seizure recurrence and the new microstructural environment changes after hemispherotomy need to be elucidated. The child with seizure recurrence showed the presence of interhemispheric functional and structural connectivity for some ROIs. These multimodal metrics provided support that residual fiber connections were still present in the patient with seizure recurrence after surgery because seizure activity spreading from one hemisphere to the contralateral hemisphere was not blocked. Subcortical interhemisphere pathways may suffice to transfer seizure and cognitive information [40]. Our connectivity results are consistent with the claim that residual interhemispheric pathways operate in seizure recurrence after hemispherotomy.

For the patient with seizure recurrence, interhemisphere connections of some ROIs were still present after surgery. For example, the structural connectivities from the left anterior insula, left thalamus and left angular to the contralateral hemisphere were presented during the recovery process. FC of these ROIs also showed an appearance of interhemispheric FC correlations after surgery. The reason for the interhemispheric connectivity appearing in these ROIs but not the other might be that these regions play an important role in the seizure propagation. Previous studies have shown that epileptic seizures have some effects on the brain activity of insula, thalamus and angular gyrus function [38,44]. Numerous studies have indicated that the thalamus plays an important role in the generalization of epileptic seizures [28,29,48]. Abnormal cortical-subcortical electrical discharges spread through the thalamus to generate epileptic spasm-induced motor activity and

cognitive impairment. A prior study in patients with drug-resistant hemispherical epilepsy also found an enhanced thalamocortical connectivity following functional hemispherotomy [15]. So the regions, such as insula, thalamus, angular gyrus and the residual interhemispheric regions, appear to form a pathway for seizure propagation. As a result, this patient showed clinical recurrence of seizures after surgery. Whole brain WMHC analysis results found that interhemispheric connections of this patient were still present even after surgery. The VMHC value was high in the bilateral thalamus and postcentral gyrus. This may indicate that information exchange and synchronization were present between these regions. Previous clinical studies have shown that recurrence of seizures can develop following surgery in some patients [19,24]. The conclusion of the studies indicated that reorganization of some transected white matter tracts may relate to seizure recurrence. Our neuroimaging results were consistent with these previous studies and indicated that residual interhemisphere pathways play an important role in seizure propagation to the healthy hemisphere. This observation gave us a hypothesis involving clinical treatment as a means to achieve total control of seizures [20]. We used the combination of fMRI and DTI as a non-invasive technology to identify areas of persistent connectivity between the two hemispheres. This method might be beneficial regarding reoperations in children with recurrent seizures after unsuccessful hemispheric disconnection surgery. Moreover, this multimodal neuroimaging method may be of value in identifying patients with residual connectivity between the two hemispheres. The identified patients might have a high potential for seizure recurrence in the future. Repeat hemispherotomy by disconnection of these residual areas of connectivity would improve seizure outcomes and the future quality of life in patients.

The main reason for the two patients showing different trajectories of brain connectivity after surgery may be based on the difference in their clinical history. Current age and the age of seizure onset differences may have had an effect on brain plasticity as the main feature of the child's developing brain and environmental changes [27]. Compared with the child with seizure recurrence, the child with seizure freedom have had long-term normal development, which could continue to improve following complete section of the interhemispheric connections. This may be one reason leading to different surgical outcomes. And also, the child with seizure free was diagnosed with cerebromalacia in the left hemisphere. The child with seizure recurrence was diagnosed with focal cortical dysplasia in the right hemisphere. The different clinical pathogeny pathologies may be another reason to explain different surgical outcomes.

4.4. Limitations

The present study has several limitations. First, our data represent the longitudinal brain connectivity changes after surgery in two children. Future investigations with larger sample sizes are required to replicate our findings. Additionally, the ages and genders of the two patients were different which may alter our connectivity results. Third, the use of anti-seizure drugs after surgery may be another limitation confound in the present study. Fourth, although we have collected patients' EEG data to support their epilepsy syndrome and seizure outcomes after surgery, the EEG data were not collected during the MRI scanning. Therefore, the connectivity results could not be completely exclude the effect of epileptiform discharges on imaging. Finally, sedatives were used in some subjects during the scanning but not in others. It has been recognized that MRI scanning in infants using chloral hydrate sedation showed a relatively low risk of significant adverse effects [9]. Although sedatives are safe and frequently used in infants for fMRI, a previous study on infants has shown that sedation can induce reduction in brain activity [45]. We recognized drug effects could influence our final results. Future studies should consider and control for this factor to improve the reliability of the results.

5. Conclusions

This study used a multimodal neuroimaging method to study the longitudinal effect following hemispherotomy surgery in two individuals with epilepsy. The results demonstrated that the brain connection pattern in children with drug-resistant epilepsy is altered following hemispherotomy. Longitudinal multimodal connection analyses of ROIs in brain ECS and DMN found that the children with different surgical outcomes demonstrated different trajectories of their brain reorganization. The child with seizure freedom showed a loss of interhemispheric correlations and increased intrahemispheric correlations in the unaffected hemisphere. Our findings support the contention that residual interhemispheric pathways is a primary reason for seizure recurrence in children after unsuccessful hemispherotomy. Our present study provided a non-invasive means of demonstrating persistent connectivity between the two hemispheres. The longitudinal outcome analysis and multimodal technology can be used for predicting the need for repeat hemispherotomy. Using multimodal neuroimaging our method may have potential in identifying patients with a high risk of seizure recurrence after hemispherotomy.

Conflict of interest

None of the authors has any conflict of interest to disclose.

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Author contributions

Conceived and designed the experiments: YL, QC, WH. Performed the experiments: ZT, QC, YW. Analyzed the data: YL, YW. Contributed reagents/materials/analysis tools: YL, WH. Responsible for patient management and conceptualized the study: ZT, YW, QC, WH. Wrote and revised the paper: YL.

Ethical statement

The authors declare that they have no conflict of interest. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

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