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FULL-LENGTH ORIGINAL RESEARCH

Early recovery of interhemispheric functional connectivity after corpus callosotomy

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Abstract

Objective: To investigate whether interhemispheric functional connectivity (FC) recovers in the first year after total callosotomy.

Methods: Eight epilepsy patients undergoing total callosotomy were recruited. Resting-state functional magnetic resonance imaging was acquired before and after surgery. The precallosotomy and postcallosotomy interhemispheric and intrahemispheric FC was analyzed by using graph theory and voxel-mirrored homotopic connectivity (VMHC). The seizure outcome was scored using the Engel surgical outcome scale.

Results: After callosotomy (mean postoperative interval = 4 months), the network density, average node degree, characteristic path length, and global efficiency of the whole interhemispheric networks were significantly decreased, compared to those in the precallosotomy networks. However, postcallosotomy interhemispheric FC and homotopic VMHC were not significantly reduced in bilateral frontal and temporal lobes. The network density and average node degree of the intrahemispheric networks were significantly increased. The characteristic path length and global efficiency of intrahemispheric networks were unchanged.

Significance: The interhemispheric FC may be preserved or recover early within the first postoperative year after total callosotomy, particularly in the frontal and anterior temporal lobes.

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KEYWORDS
corpus callosotomy, graph theory, interhemispheric functional connectivity, voxel-mirrored homotopic connectivity

1 | INTRODUCTION

Corpus callosotomy is a palliative treatment for patients with generalized, multifocal refractory epilepsy, or disabling seizures, such as debilitating drop attacks, or atonic, tonic, or myoclonic seizures. The corpus callosum is the largest commissure connecting the two hemispheres of the brain. It is supposed that the corpus callosum accounts for the spread of epileptic activity between the two hemispheres of the brain. The pathophysiological basis of corpus callosotomy is that separation of the corpus callosum could stop the interhemispheric transmission of abnormal neuronal discharges and reduce the frequency of generalized seizures. A recent systemic review showed that total callosotomy could achieve a worthwhile reduction in seizures in 88.2% of patients using the Engel surgical outcome scale, and only 12.5% of patients developed transient disconnection syndrome.[1]

The temporal correlation of infraslow (<0.1 Hz) intrinsic brain activity in the absence of overt stimulation or task demands within functionally related brain areas is known as resting state networks.[2] This phenomenon of intrinsic correlation between brain activities is known as functional connectivity (FC). Resting state functional magnetic resonance imaging (rs-fMRI) has been increasingly used to understand the global organization of the normal brain[3,4] and to detect brain changes in disease. It is generally accepted that in the healthy brain, FC correlates with structural connectivity (white matter connections).[3,5] Because the corpus callosum is the major commissure between the two hemispheres, it is unsurprising that complete section of the corpus callosum has been reported to markedly reduce the interhemispheric FC within the first week after total callosotomy in epilepsy patients.[6,7] One case report showed recovery interhemispheric FCs in a patient 50 years after callosotomy.[8] Experimental observations of a callosotomized rhesus monkey also showed that interhemispheric FC recovered by 8 months after callosotomy with intact anterior commissure. Furthermore, in prior electroencephalographic observations, interhemispheric connection could already recover as early as 3 months after surgery.[9] This reestablishment of interhemispheric connectivity has been attributed to the presence of a polysynaptic connection via the anterior commissure or subcortical structures. However, the physiological brain alterations after callosotomy and when the interhemispheric FC starts to recover remain incompletely understood.

Key Points

- The interhemispheric FC recovers within the first year after total callosotomy with intact anterior commissure
- The intrahemispheric FC increases after total callosotomy
- The nodes of interhemispheric FC are clustered in the inferior and medial frontal, and medial temporal lobes, which may suggest the role of the anterior commissure

In this study, our primary purpose is to investigate whether the interhemispheric FC can recover in the early postoperative period after total callosotomy. We expect that the interhemispheric FC can recover in the early postoperative period after total callosotomy with intact anterior commissure. Another assumption is that the interhemispheric FC may recover earlier in the frontal and temporal lobes than the parietal and occipital lobes because of the anatomic distribution of the anterior commissure.

2 | MATERIALS AND METHODS

2.1 | Standard protocol approvals, registrations, and patient consents

This study was approved by the institutional review board of Taipei Veterans General Hospital, Taiwan. Subjects gave informed written consent.

2.2 | Patients

The inclusion criteria were: (1) pediatric patients (<18 years old at the time of surgery), (2) intractable epilepsy, (3) no large encephalomalacia or cortical malformation identified on neuroimaging, and (4) indicated for total callosotomy following the consensus of a comprehensive epilepsy team at Taipei Veterans General Hospital. Between 2014 and 2017, 20 patients underwent total callosotomy at Taipei Veterans General Hospital. Eight patients gave written consent. We acquired brain rs-fMRI data for these eight epilepsy patients before and within 1 year after receiving total callosotomy.

The surgical outcome was evaluated by an experienced epilepsy neurosurgeon (C.-C.L.) >1 year after surgery using Engel outcome scale.

2.3 | Presurgical evaluation

For the presurgical evaluation, we follow the International League Against Epilepsy guidelines. All patients had been admitted to the Pediatric Epilepsy Monitoring Unit of Taipei Veterans General Hospital and received 24-hour digital 32-channel telemetric video-electroencephalographic (EEG) monitoring with a Cadwell system. Each patient was required to have at least three habitual seizures recorded during the monitoring period. Each video-EEG was reviewed by a qualified pediatric epileptologist. Preresection MRI was performed for all patients, with details showed below. Positron emission tomography scans, using 18-fluorodeoxyglucose as the tracer to measure cerebral glucose metabolism, was also performed for all patients. Other presurgical evaluations that were routinely performed included determination of current serum antiepileptic drug levels, neuropsychological assessment, and magnetoencephalography.

2.4 | Corpus callosotomy

Under general anesthesia, all patients underwent left craniotomy, approached through the coronal suture dissecting through the interhemispheric fissure to reach the corpus callosum. The corpus callosum was divided from the rostrum backward to the splenium. The surgical technique was performed by an experienced pediatric neurosurgeon under direct visualization by means of an operative microscope. The lateral ventricles were not opened, and extreme care was taken to preserve the bridging veins. Total corpus callosotomy was performed from the rostrum to the splenium. The anterior commissure, hippocampal commissure, and fornices were spared in all subjects; this was confirmed by follow-up MRI after surgery. Routinely, an intraoperative precallosotomy electrocorticogram was performed for 30 minutes with an 18-channel Grass EEG machine. After callosotomy, an intraoperative postcallosotomy electrocorticogram was performed immediately for another 30 minutes. The extent of callosotomy was confirmed by postoperative MRI (Figure 1).

2.5 | Image acquisition

Magnetic resonance images were acquired on a 3-T scanner (Discovery MR750, GE Healthcare). In addition to a 3-dimensional T1 fast spoiled gradient echo sequence (repetition time [TR] = 9.384 milliseconds, echo time [TE] = 4.036 milliseconds, flip angle = 12°, voxel size = $1.0 \times 1.0 \times 1.0\ mm^3$), T2*-weighted images with blood oxygen level–dependent contrast imaging contrast were acquired using a gradient echo-planar imaging sequence (TR = 2500 milliseconds, TE = 30 milliseconds, flip angle = 90°, voxel size = $3.5 \times 3.5 \times 3.5\ mm^3$, 200 frames). For the patients who did not receive sedation during the scanning, the subjects were instructed to keep their eyes closed, and not to think about anything and stay awake during the entire session of the functional scans. After the scanning, the subjects were asked whether they remained awake during the entire procedure. The duration of the rs-fMRI scanning procedure was approximately 8.5 minutes for each subject.

2.6 | Preprocessing of rs-fMRI

rs-fMRI data preprocessing was then performed with the SPM8 software package (http://www.fil.ion.ucl.ac.uk/spm/),

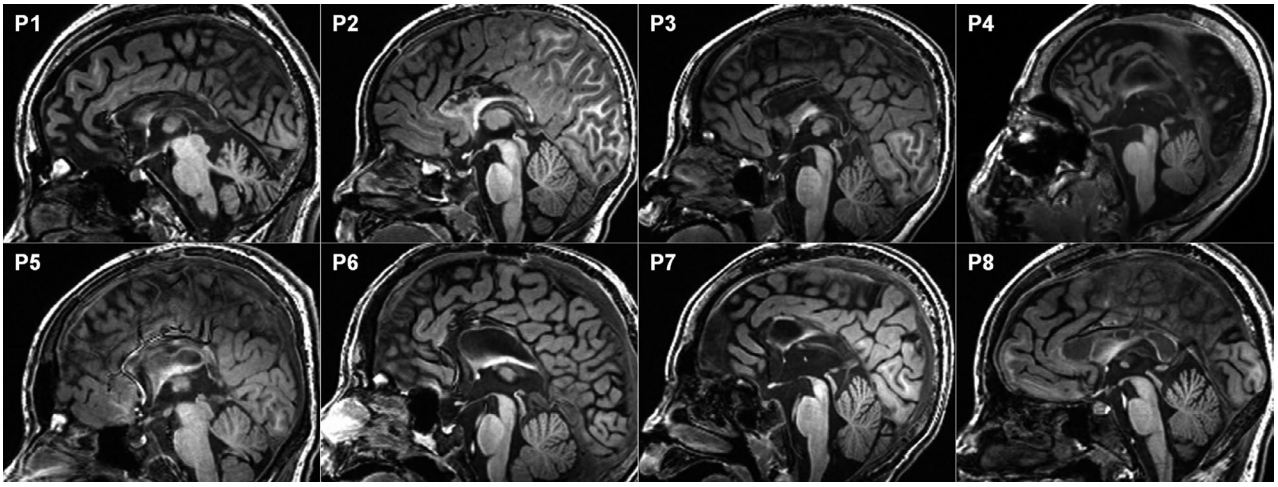

FIGURE 1 Composite picture of postoperative magnetic resonance imaging in the midsagittal plane of eight patients undergoing total callosotomy. The anterior commissure is preserved

REST (http://restfmri.net/forum/rest)[10] and Data Processing Assistant for Resting-State fMRI running on MATLAB R2018a (MathWorks). Briefly, the preprocessing procedure included the following steps: (1) removal of the first 10 scans of rs-fMRI data due to allowing for magnetization equilibrium and the subjects' adaptation to the environment; (2) slice-timing correction for differences in the image acquisition time between slices; (3) six-parameter rigid body correction to realign for head movements during data acquisition; (4) coregistration of the T1 image to the mean rs-fMRI scans; (5) gray and white matter segmentation using "New Segment" and spatial normalization of the T1 image to a Montreal Neurological Institute space using the DARTEL toolbox[11]; (6) spatial normalization of the rs-fMRI data using the normalization parameters estimated in step 5 and voxel size resampling to $3 \times 3 \times 3\,mm^3$; (7) spatial smoothing with a Gaussian kernel of 4 mm full width at half maximum; (8) linearly detrended removal and temporal band-pass filtering within 0.01-0.08 Hz; and (9) regressing several nuisance covariates, including the six head motion parameters, global mean signal, white matter signal, and cerebrospinal fluid signal, to remove spurious signals that were unlikely to reflect neural activity. According to the records of head movements within the rs-fMRI data, all subjects had <1 mm maximum translation in the x, y, or z plane and <1° of angular rotation about each axis.

2.7 | Network analyses

For the region-of-interest–based network analyses, we obtained the mean time series of each of the 90 cerebral regions of the Anatomical Automatic Labeling template by averaging the preprocessed rs-fMRI time series over all voxels in the region.[12,13] Pearson correlation coefficients were computed between each pair of all 90 cerebral regions. Then, a Fisher *r*-to-*z* transformation was applied to improve the normality of these correlation coefficients. The *z* values were entered into a random effect paired sample *t* test to determine the cerebral regions showing differences in correlations between the precallosotomy and postcallosotomy groups. The functional connections of each edge that were considered significantly different between the precallosotomy and postcallosotomy group must satisfy $P < 0.05$ corrected for multiple comparison by false discovery rate (FDR). For each pair of seed regions within one hemisphere, the homotopic regions in the opposite hemisphere identified the intrahemispheric and interhemispheric network. Furthermore, for identification of the nodes with persistent interhemispheric connectivity, intersection of the nodes in all eight subjects was evaluated to identify the key nodes for reestablishing postcallosotomy interhemispheric FC.

Proportional thresholding was also performed on the FC matrices by selecting the 15% strongest connections of the derived FC matrix and setting these connections to 1, with all other connections set to 0. After thresholding, topological properties of the reconstructed binary connectivity matrices were quantified using graph theoretical analysis. We focus on the commonly used basic metrics of global efficiency, network density, nodal degrees, and characteristic path length, defined as previously described[10] and computed as implemented in the Brain Connectivity Toolbox.[14] Global efficiency was calculated as the inverse of the harmonic mean of the shortest path length between all pairs of nodes in the network, with higher levels of global efficiency often interpreted as a network topology better suited for efficient network transfer. Network density was defined as the number of edges in the network divided by the total possible number of edges. Nodal degrees were the number of edges connected to a node, and provided information related to the centrality of a node by determining nodes with a large number of connections. Characteristic path length was the average shortest path length between all pairs of nodes in the network and was a measure of functional integration. A short characteristic path length indicated a more compact network and more efficient global information processing. Statistical estimation of differences between precallosotomy and postcallosotomy groups in graph theory was assessed using paired samples *t* tests. A significant difference was accepted if the *P* value was less than 0.01.

2.8 | Voxel-mirrored homotopic connectivity

REST was also used to analyze voxel-mirrored homotopic connectivity (VMHC), and the details of VMHC computation has been elaborated in a previous study.[15] Individual VMHC maps were generated for each subject and all rs-fMRI data by computing correlation (Fisher *r*-to-*z* transformed) between a given voxel and a corresponding voxel in the contralateral hemisphere. The resultant values were applied for the precallosotomy and postcallosotomy group comparisons and generation of the VMHC maps. To identify the regional differences in the VMHC map between the precallosotomy and postcallosotomy groups, we performed a paired sample *t* test comparison between the precallosotomy and postcallosotomy groups, and a double statistical threshold was used (combined height threshold $P < 0.01$ and minimum cluster size = 19 voxels, as determined by the AlphaSim correction using REST software).

3 | RESULTS

Table 1 shows the demographics of eight patients who received total callosotomy. The age at seizure onset ranges from 6 months to 10 years old (median = 1 year old), and the age at surgery ranges from 3 to 16 years old (median = 7 years old). The mean interval between callosotomy and follow-up rs-fMRI is 4 ± 3.1 months (range = 0.8-11 months). All patients had successful seizure reduction after total callosotomy. Two developed transient disconnection syndromes after surgery. Two received stereoelectroencephalographic

TABLE 1 Clinical information and outcomes of patients

Patient no.	Sex	Age at onset/ surgery, y	Seizure type	Epileptic syndrome	Preoperative seizure frequency	Postoperative seizure frequency at last follow-up	Disconnection syndrome	Further study after callosotomy	Further resection surgery	Preoperative ECoG	Postoperative ECoG
1	F	10/15	Drop attack, absence, GTCS	No	2-3/d	1-2/d, only absence	Yes	No	No	Bisynchronized	Independent
2	M	1.5/5	Epileptic spasms, GTCS, dialeptic seizure	LGS	3-4/d	1/d, only dialeptic seizure	No	SEEG	Yes (MCD)	Bisynchronized	Independent
3	M	0.5/3	Automotor, tonic	No	10/mo	3/mo	No	No	No	Independent	Independent
4	M	0.8/3	GTCS	No	2-3/d	0.5/mo	No	No	No	Bisynchronized	Independent
5	M	0.5/13	Partial seizure, atypical absence	LGS	3-4/d	Rare	No	No	No	Bisynchronized and independent	Independent
6	M	6/9	Drop attack, GTCS	No	1-3/d	1-3/d	No	No	No	Bisynchronized	Independent
7	M	2/6	Drop attack, GTCS	No	2-3/d	Rare	No	No	No	Bisynchronized	Independent
8	F	6/16	CPS with GTCS, drop attack	No	2-3/d	4-5/mo	Yes	SEEG	No	Bisynchronized and independent	Independent

Abbreviations: CPS, complex partial seizure; ECoG, electrocorticogram; F, female; GTCS, generalized tonic-clonic seizures; LGS, Lennox-Gastaut syndrome; M, male; MCD, malformation of cortical development; SEEG, stereoelectroencephalography.

studies following callosotomy, which identified seizure foci in the frontal lobes. Five patients were successfully lateralized, but only one patient received further resection surgery.

3.1 | FC maps

Figure 2 shows the degree of nodes and edges that were significantly decreased (1A) or increased (1B) after total callosotomy ($P < 0.05$ corrected for multiple comparison by FDR). Compared with the precallosotomy FC, the postcallosotomy FC shows a reduction in FC between the hemispheres. The intrahemispheric FC between anterior temporal lobe and several parasagittal nodes is identified. The interhemispheric FC is also preserved between a small number of nodes (Figure 3). Figure 3 summarizes the intersection of the nodes, showing persistent postcallosotomy interhemispheric connectivity in all eight subjects. These nodes are mainly located in the medial frontal, orbitofrontal, and medial temporal lobes. These are consistent with the anatomic territory of the anterior commissure. The bilateral paracentral lobules, Heschl's gyri, left anterior cingulate gyrus, and left thalamus are key nodes with interhemispheric FC as well.

In Table 2, the topological properties of brain networks show a significant decrease in the network density, average node degree, characteristic path length, and global efficiency of interhemispheric networks. The network density and average node degrees of intrahemispheric networks are significantly increased. The global efficiencies of intrahemispheric networks are not significantly changed.

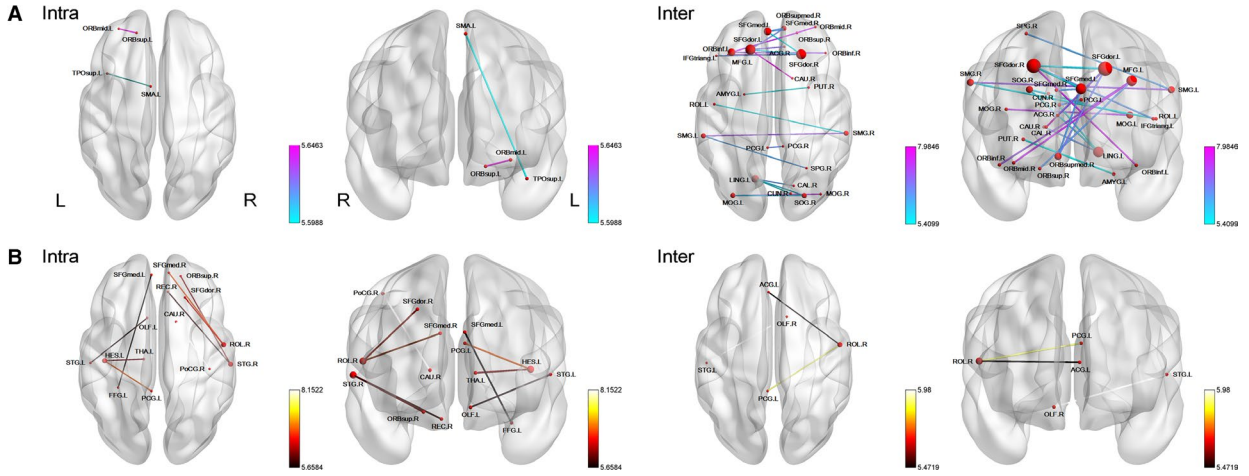

FIGURE 2 Network changes after total callosotomy. Edges and nodal degrees that are significantly decreased (A) and increased (B) after total callosotomy are presented ($P < 0.05$ corrected for multiple comparison by false discovery rate). ACG, anterior cingulate gyrus; AMYG, amygdala; CAL, calcarine sulcus; CAU, caudate nucleus; CUN, cuneus; FFG, fusiform gyrus; HES, transverse temporal gyrus; IFGtriang, inferior frontal gyrus, pars triangularis; L, left; LING, lingual gyrus; MFG, middle frontal gyrus; MOG, middle occipital gyrus; OLF, olfactory cortex; ORBinf, inferior frontal gyrus; pars orbitalisORBmid, Frontal_Mid_Orb; ORBsup, medial orbitofrontal cortex; ORBsupmed, medial orbitofrontal cortex; PCG, posterior cingulate gyrus; PoCG, postcentral gyrus; PUT, putamen; R, right; REC, precentral gyrus; ROL, rolandic operculum; SFGdor, superior frontal gyrus; SFGmed, medial frontal gyrus; SMA, supplementary motor area; SMG, supramarginal gyrus; SOG, superior occipital;SPG: superior parietal lobule; STG, superior temporal gyrus; THA, thalamus; TPOsup, superior temporal pole

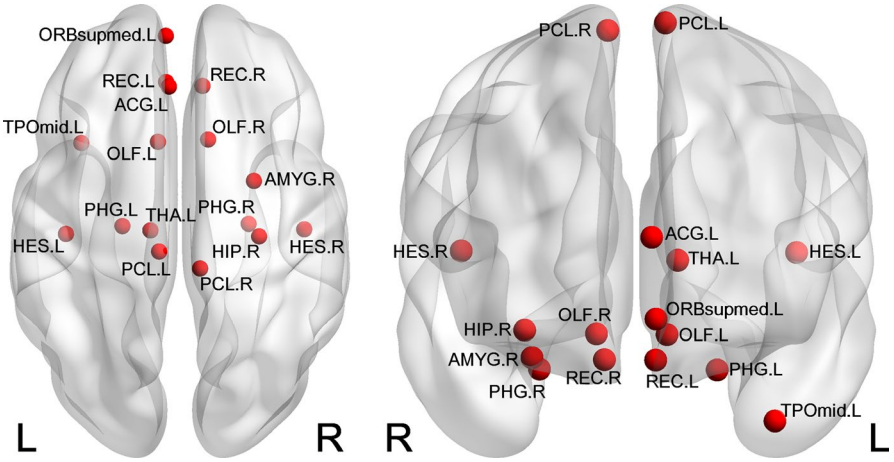

FIGURE 3 Summary of the nodes showing persistent interhemispheric connectivity after callosotomy. This intersection of the nodes shows significant connection with the other hemisphere in all eight subjects. ACG, anterior cingulate gyrus; AMYG, amygdala; HES, transverse temporal gyrus; HIP, hippocampus; L, left; OLF, olfactory cortex; ORBsupmed, medial orbitofrontal cortex; PCL, paracentral lobule; PHG, parahippocampal gyrus; R, right; REC, precuneus; THA, thalamus; TPOmid, middle temporal pole

TABLE 2 Summary of topological properties of networks by selecting the strongest 10% of connections

Topological properties		Precallosotomy	Postcallosotomy	*P*
Network density	Intra	0.172 ± 0.015	0.214 ± 0.030	0.021*
	Inter	0.129 ± 0.015	0.088 ± 0.029	0.021*
Average node degree	Intra	7.558 ± 0.657	9.408 ± 1.319	0.021*
	Inter	5.797 ± 0.657	3.947 ± 1.319	0.021*
Characteristic path length	Intra	5.448 ± 0.557	5.235 ± 0.406	0.574
	Inter	5.608 ± 0.482	6.273 ± 0.375	0.010*
Global efficiency	Intra	0.110 ± 0.014	0.116 ± 0.008	0.328
	Inter	0.156 ± 0.020	0.087 ± 0.034	0.003**

Note: Abbreviations: Intra, intrahemispheric network; inter, interhemispheric network.
*$P < 0.05$, **$P < 0.01$, significant difference with respect to precallosotomy.

3.2 | Voxel-mirrored homotopic connectivity

The present data show that the postcallosotomy VMHC is significantly reduced in bilateral parietal lobes, including paracentral lobules and occipital lobes. The regions with the most pronounced decrease are summarized in Table 3. The VMHC is preserved in most of bilateral frontal and temporal lobes (Figure 4 and Table 3).

4 | DISCUSSION

Our study yields several important findings. First, complete resection of the total corpus callosum significantly reduces the interhemispheric FC and increases the intrahemispheric FC, which are consistent as previously reported in one study.[7] Second, this study addresses the question of interhemispheric FC recovery after a prolonged postoperative interval. In contrast to a previous report in which the data were acquired in the immediate postoperative period, our data show interhemispheric FC recovers in the first year after total callosotomy. The most consistent nodes involved in the postcallosotomy interhemispheric FC are clustered in the medial frontal, orbitofrontal, and medial temporal lobes. This may suggest that the anterior commissure plays a role in reorganizing interhemispheric FC in the early postoperative period. Third, the extent of VMHC recovery is larger than the anatomic territory of both the anterior commissure and the nodes as shown in Figure 3. This again supports the idea that polysynaptic connections also contribute to maintenance of interhemispheric FC via the anterior commissure or subcortical structures.

TABLE 3 Regions showing significant differences in voxel-mirrored homotopic connectivity map between postcallosotomy and precallosotomy groups

Regions	MNI coordinate	Peak *t* score	Number of voxels
Parietal and occipital lobe	±30, −66, 21	−15.67	3055
Superior frontal gyrus, orbital part	±9, 21, −27	−7.99	33
Superior frontal gyrus, orbital part	±15, 66, −3	−6.08	60
Inferior frontal gyrus, pars orbitalis	±48, 48, −12	−7.64	33
Middle frontal gyrus	±39, 39, 6	−7.40	43
Superior frontal gyrus	±12, 51, 27	−13.69	128
Medial frontal gyrus	±6, 36, 54	−9.06	94
Midcingulate area	±6, 27, 36	−6.48	31
Inferior temporal gyrus	±51, −42, −24	−8.06	35
Superior temporal gyrus	±54, −21, −6	−7.74	38
Superior temporal pole	±60, 6, 0	−10.49	199
Putamen	±27, 3, 3	−6.99	201

Note: The values given are the stereotactic MNI coordinates and the *t* score of each anatomical region. SPM maps were thresholded at $P < 0.01$ (AlphaSim correction, voxel-level, minimum cluster size threshold = 19 voxels).
Abbreviation: MNI, Montreal Neurological Institute.

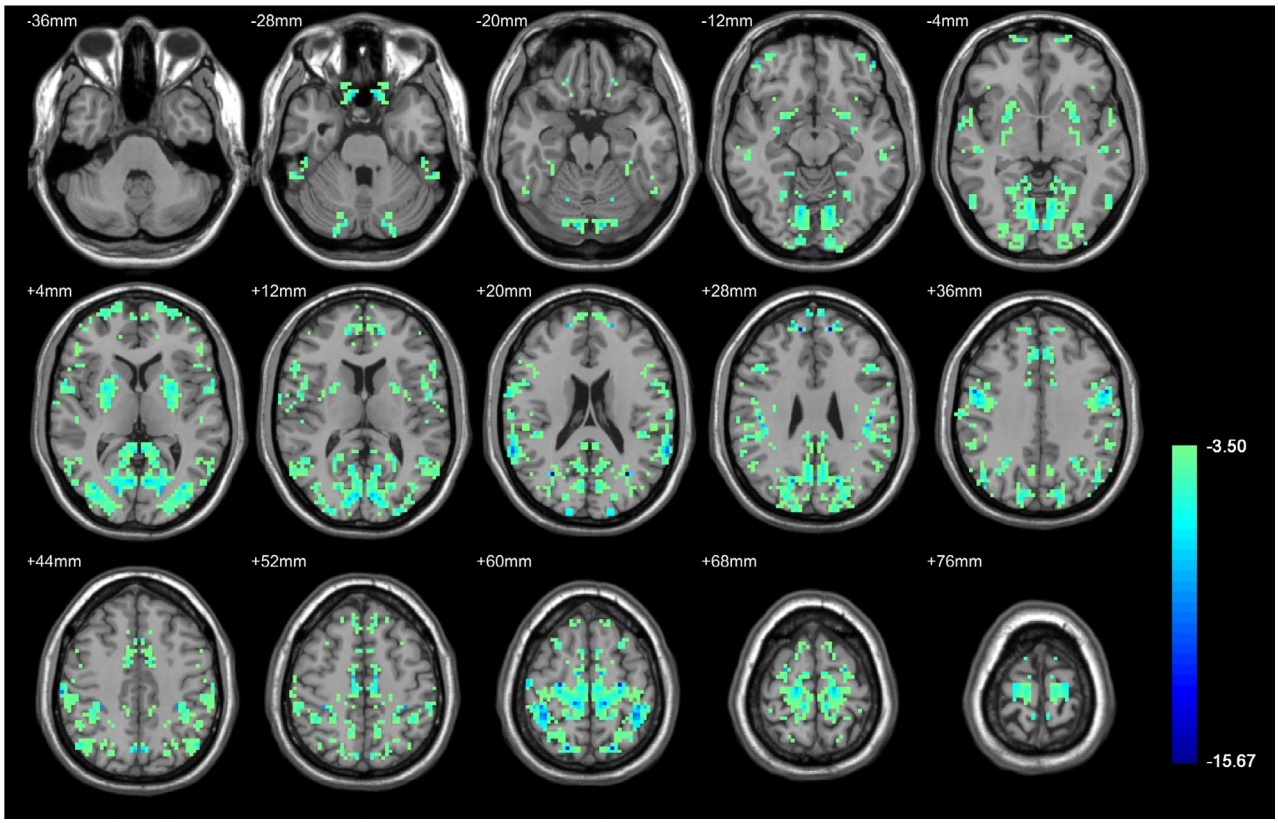

FIGURE 4 Distribution of voxel-mirrored homotopic connectivity (VMHC) changes after callosotomy. The VHMC map was computed as the Fisher *z*-transformed Pearson correlation between homotopic voxels. By definition, these displays are bilaterally symmetric. The underlay is the Montreal Neurological Institute T1-weighted template. A paired sample *t* test was performed to compare the precallosotomy and postcallosotomy VMHC maps ($P < 0.01$, minimum cluster size = 19 voxels, as determined by the AlphaSim correction with REST software). The postcallosotomy VMHC is significantly reduced in bilateral parietal lobes, including paracentral lobules and occipital lobes. The VMHC is preserved in most of the bilateral frontal and temporal lobes

The territory of the anterior commissure is best known around the posterior limb of the anterior commissure connecting bilateral amygdalae, temporal lobes, and some parieto-occipital lobes.[16] In our results, besides the nodes in the temporal lobes, we also observed some nodes in bilateral medial frontal and orbitofrontal regions. The course of axons conveyed from the orbitofrontal cortex has been shown through the anterior limb of the anterior commissure[17,18] or genu and rostrum of corpus callosum[16,19] in humans. It might be reasonable to expect that the anterior limb of the anterior commissure plays an important role in the reestablished bifrontal interhemispheric connectivity in our cases after total callosotomy.

Our results show that the interhemispheric FC can recover after callosotomy as early as the first postoperative year. In a cohort of 22 epilepsy patients, Roland et al[7] demonstrated that total callosotomy could almost completely interrupt the interhemispheric FC and VMHC in the immediate postoperative period (day 1). They focused on the perioperative changes of seven important functional networks in all patients, and two of the patients were also followed up at 2 years and 7 years after surgery. They did not identify any existent bilateral functional networks.[7] Therefore, they proposed that the compensatory re-establishment of the interhemispheric FC could not occur postnatally after age 2 years. In this study, we evaluated the regionwise and voxelwise interhemispheric FC after callosotomy. Based on the results, we suggest that interhemispheric FC can recover in the early postoperative period even in children up to 16 years old. This may also provide an explanation about why disconnection syndrome is always transient and resolves spontaneously within 6 weeks after total callosotomy.[1] A recent study of a large pediatric case series also emphasizes the prognostic benefit of the first year after surgery.[20] In the patients without a good outcome at final follow-up, 90% of them had drop attack recurrence within 12 months of surgery, and the patients who were seizure-free in the first year had a higher chance of good outcome (81%).[20]

The role of the anterior commissure in maintaining interhemispheric FC is supported by the location of the nodes and the extent of reserved interhemispheric FC in our results. Although the anterior commissure is a small compact bundle of fibers connecting bilateral anterior temporal lobes and

orbitofrontal cortices, it receives fibers from the entire temporal lobe, orbitofrontal cortices, and amygdalae.[21] O'Reilly et al demonstrated the role of the anterior commissure in interhemispheric FC by analyzing the homotopic FC in three Rhesus monkeys (two received forebrain commissurotomy, which included resection of the anterior commissure, and one received callosotomy, which spared the anterior commissure). The interhemispheric FC in the monkeys receiving forebrain commissurotomy was severely interrupted, but the whole brain interhemispheric FC was preserved in the monkey with intact anterior commissure.[22] In contrast to their results, our data show reserved interhemispheric FC only in the frontal and temporal lobes. There are two possible explanations for the difference. First, the size of the anterior commissure is smaller in humans (1% of area of the corpus callosum) than that in rhesus monkeys (5% of area of corpus callosum).[23] The smaller size of the anterior commissure in humans may contribute to smaller or slower compensation of interhemispheric FC. Second, the interval of follow-up is shorter in our study than in theirs (4 months vs 8 months). It is unknown whether the interhemispheric FC between parietal and occipital lobes will recover after a prolonged interval of follow-up in our patients. Therefore, future longitudinal follow-up of these cases is necessary.

In the study of Roland et al,[7] the homotopic FCs in primary sensorimotor and visual cortices was less affected than that in the frontal lobes after callosotomy. In our results, we observe that the sensorimotor, parietal lobe and visual regions have lower VMHC than frontal lobes. We propose that, although according to Roland's results, the interhemispheric FC is more prone to decrease after callosotomy in frontal lobes, the interhemispheric FC in frontal lobes also recovers faster than in other brain regions because of the anterior commissure. There is also some evidence showing that interhemispheric FC of parietal lobes and visual cortices eventually, at least in part, recovered after a prolonged interval after callosotomy.[8]

Our results demonstrate that the anterior commissure plays a vital role in postcallosotomy interhemispheric FC, and it is reasonable to expect that combined callosotomy and anterior commissurotomy may be better than callosotomy alone to interrupt interhemispheric connectivity, as shown in the prior rhesus monkey study.[22] However, we would be hesitant at this stage to propose routine commissurotomy in all patients receiving total callosotomy. Although this approach has been successful in reducing seizures in the past, it was abandoned in clinical practice because of morbidities associated with acute disconnection.[24] Not until recently, with the improvement of endoscopic surgical techniques, did a study again demonstrate that concomitant commissurotomy can completely stop drop attacks in patients with severe Lennox-Gastaut syndrome with moderate to severe mental retardation. In the patients who presented symptoms with acute disconnection, the symptoms improved within 3-6 months without any motor deficits or permanent deficits.[25] Therefore, with appropriate patient selection, combined total callosotomy and commissurotomy may still remain a surgical option. Nevertheless, long-term follow-up of large cohorts and randomized studies are necessary to better understand the clinical benefits of concomitant commissurotomy.

The extent of corpus callosotomy remains controversial. Traditionally, callosotomy targets the anterior corpus callosum; complete callosotomy is already known to be more associated with complete seizure freedom and drop attack freedom than partial callosotomy.[1,26] However, the relationship between the location of interhemispheric FC reduction and seizure outcome is rarely studied. A recent interesting study by Paglioli et al raised the possibility that posterior callosotomy may achieve outcomes in epileptic fall reduction comparable to those of total callosotomy because the crossing fibers from the premotor and primary motor cortex are posteriorly located in the mid to posterior half of corpus callosum.[27–29] Our study shows the interhemispheric FC is also more affected in the posterior hemispheres than in the anterior hemispheres. These similarities suggest a new direction for further investigation into whether interruption of posterior interhemispheric FC is more important in controlling drop attacks and more associated with surgical outcome than anterior interhemispheric FC.

This study provides evidence to support the role of the anterior commissure in the postoperative recovery of interhemispheric FC, which has been derived from a case study of rhesus monkeys[22] and a limited number of human case studies.[6,8] A potential limitation of our study is the lack of follow-up of interhemispheric FC at postoperative baseline and after a prolonged interval after 1 year. Without the postoperative baseline, it is unknown whether the high interhemispheric FC is due to the failure of callosotomy to interrupt the interhemispheric FC or to the overcompensation of the anterior commissure. However, a prior study shows the interhemispheric FC is completely interrupted between bilateral frontal lobes on postoperative day 1.[7] Therefore, we believe the interhemispheric FC we observed can be attributed to the gradual recovery of reestablished interhemispheric connections. Second, the trajectories of interhemispheric FC can help better understand the effect of callosotomy and the relationship between the recovery of interhemispheric FC and outcomes, such as seizure reduction and the development of disconnection syndrome. A longitudinal follow-up years after surgery can shed light on whether interhemispheric FC can recover to normal level as observed in the rhesus monkey as well as how long the full recovery of interhemispheric FC will take. Additionally, it may also help determine the relationship between the degree of recovered interhemispheric FC and the neurodevelopmental outcome after callosotomy.

5 | CONCLUSION

We expand the current knowledge regarding the postcallosotomy recovery of interhemispheric FC that was lacking as a result of the prior limited number of cases studies of corpus callosotomy. We found evidence showing that interhemispheric FC recovery can occur in the first year after surgery, particularly in bilateral frontal and anterior temporal lobes.

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DISCLOSURE

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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