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Validation of corpus callosotomy after laser interstitial thermal therapy: a multimodal approach

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OBJECTIVE Disconnection of the cerebral hemispheres by corpus callosotomy (CC) is an established means to palliate refractory generalized epilepsy. Laser interstitial thermal therapy (LITT) is gaining acceptance as a minimally invasive approach to treating epilepsy, but this method has not been evaluated in clinical series using established methodologies to assess connectivity. The goal in this study was to demonstrate the safety and feasibility of MRI-guided LITT for CC and to assess disconnection by using electrophysiology- and imaging-based methods.

METHODS Retrospective chart and imaging review was performed in 5 patients undergoing LITT callosotomy at a single center. Diffusion tensor imaging and resting functional MRI were performed in all patients to assess anatomical and functional connectivity. In 3 patients undergoing simultaneous intracranial electroencephalography monitoring, corticocortical evoked potentials and resting electrocorticography were used to assess electrophysiological correlates.

RESULTS All patients had generalized or multifocal seizure onsets. Three patients with preoperative evidence for possible lateralization underwent stereoelectroencephalography depth electrode implantation during the perioperative period. LITT ablation of the anterior corpus callosum was completed in a single procedure in 4 patients. One complication involving misplaced devices required a second procedure. Adequacy of the anterior callosotomy was confirmed using contrast-enhanced MRI and diffusion tensor imaging. Resting functional MRI, corticocortical evoked potentials, and resting electrocorticography demonstrated functional disconnection of the hemispheres. Postcallosotomy monitoring revealed lateralization of the seizures in all 3 patients with preoperatively suspected occult lateralization. Four of 5 patients experienced > 80% reduction in generalized seizure frequency. Two patients undergoing subsequent focal resection are free of clinical seizures at 2 years. One patient developed a 9-mm intraparenchymal hematoma at the site of entry and continued to have seizures after the procedure.

CONCLUSIONS MRI-guided LITT provides an effective minimally invasive alternative method for CC in the treatment of seizures associated with drop attacks, bilaterally synchronous onset, and rapid secondary generalization. The disconnection is confirmed using anatomical and functional neuroimaging and electrophysiological measures.

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KEYWORDS drug-resistant epilepsy; corpus callosum; lasers; magnetic resonance imaging; surgical technique

Corpus callosotomy (CC) is a commonly performed procedure to disconnect the cerebral hemispheres to treat refractory epilepsy. The most consistent improvements after callosotomy have been observed in patients with frequent atonic seizures, also known as "drop attacks."[6,16,28,42] In addition to drop attacks, atypical absence, generalized tonic-clonic (GTC) seizures, and tonic seizures have been reported to respond favorably to CC.[3] In particular, seizures with generalized interictal and ictal electroencephalography (EEG) abnormalities with multifocal spike–slow wave activity respond well to CC, as do patients displaying generalized seizures with rapid secondary bisynchronous EEG activity.[34,42] Although in certain individuals lateralization of seizure foci after callosotomy has been seen, it is unclear whether a subsequent resective procedure results in seizure freedom.[9,30,40]

ABBREVIATIONS AED = antiepileptic drug; BOLD = blood oxygen level–dependent; CC = corpus callosotomy; CCEPs = corticocortical evoked potentials; CPS = complex partial seizures; DTI = diffusion tensor imaging; ECoG = electrocorticography; EEG = electroencephalography; GTC = generalized tonic-clonic; HGP = high gamma power; LITT = laser interstitial thermal therapy; rfMRI = resting functional MRI; SEEG = stereoelectroencephalography; SMA = supplementary motor area; SRS = stereotactic radiosurgery; VNS = vagal nerve stimulator.

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MRI-guided laser interstitial thermal therapy (LITT) is a minimally invasive procedure that has been used to treat tumors, vascular malformations, radiation necrosis, and epileptic foci.[10,31] The procedure involves stereotactic placement of an irrigant-cooled catheter-fiberoptic assembly that transmits laser light energy to produce thermal injury that is monitored with MRI thermometry. Due to limited experience, the effectiveness of LITT compared to craniotomy for callosotomy may take time to establish. However, novel methods of resolving brain connectivity including diffusion tensor imaging (DTI) and resting functional MRI (rfMRI) may help better establish the effectiveness of disconnection techniques.[36] To additionally validate disconnection, emerging electrophysiological measures of connectivity involving corticocortical evoked potentials (CCEPs) and correlations in the resting electrocorticography (ECoG) can be used in patients undergoing invasive intracranial monitoring.[25,26]

Here, we demonstrate the feasibility of MRI-guided LITT for anterior callosotomy and assess the effectiveness of this procedure by using multiple measures including clinical outcome, electrophysiology, and neuroimaging. In a series of 5 patients, laser ablation of the anterior corpus callosum was achieved as assessed by neuroimaging, DTI, and electrophysiological connectivity measures. Four of 5 patients experienced > 80% seizure reduction. Three patients had concomitant stereoelectroencephalography (SEEG) monitoring, all of whom demonstrated anatomical, functional neuroimaging, and functional electrophysiological disconnection; seizures lateralized and reduced in frequency postcallosotomy. Two of these patients underwent subsequent resection of lateralized frontal epileptic foci following CC and achieved seizure freedom.

Methods

Patients and Clinical Course

A retrospective review including outpatient visits, operative reports, EEG reports, and MRI was conducted in all patients who underwent CC using LITT at our institution between January 2015 and October 2017. Telephone contact was made with patients to supplement follow-up results. All procedures and chart review were performed in accordance with local IRB approval.

Diffusion Tensor Imaging

Images were acquired in a 1.5-T GE whole-body MR scanner with an 8-channel head coil in parallel imaging mode with an acceleration factor of 2. A single-shot spin-echo echo planar imaging sequence was used, with 5 images obtained without diffusion weighting and 33 isotropically distributed diffusion gradient directions. The b value in the diffusion-weighted images was 1000 sec/mm^2. The TE was 90.3 msec, and the TR was 14,000 msec, but may have varied up to 14,800 msec in some patients. Images were zero filled to a matrix size of 128 × 128, yielding an image resolution of 0.9 × 0.9 × 3 mm^3.

From the diffusion-weighted images, maps of fractional anisotropy, mean diffusivity, and V1 images (the main vector of the diffusion tensor) were calculated using FSL (http://www.fmrib.ox.ac.uk/fsl) software.

Resting Functional MRI Studies

The rfMRI scans were acquired, comprising a total of 150 echo planar imaging volumes with the following parameters: TR 2000 msec, TE 30 msec, matrix 64*64, field of view 240 mm, slice thickness 3 mm, and 40 continuous axial oblique slices (1 voxel = 3.75 × 3.75 × 3 mm). During the acquisition all subjects were instructed to close their eyes and not think of anything in particular.

FSL and AFNI-based script libraries (http://afni.nimh.nih.gov/afni) from the 1000 Functional Connectomes Project (http://www.nitrc.org/projects/fcon_1000) were used for preprocessing, and a lab-developed script in the R statistical language was used for additional analysis.[5] All resting-state scans were preprocessed (including motion estimation and correction, slice-timing correction, and functional outlier detection) by using the CONN functional connectivity toolbox. Standard registration and normalization to MNI152 space was done using SPM software (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) directly applied to each individual's functional dataset, and spatial smoothing (6-mm full width at half maximum gaussian kernel) was performed. The time series were then high-pass and low-pass filtered (cutoff frequencies 0.008 Hz and 0.9 Hz, respectively). The 4D time series data were regressed on predictors for white matter, CSF, and 12 motion parameters (6 motion parameters and their first-order derivatives). Consistent with our prior work and that of others, we did not regress out global signal because it would have interfered with the connectivity strength calculation.[2,44]

Regional mean time series were computed for all individuals' rfMRI data by using a set of predefined homotopic seed regions. Correlations between these time series and the whole brain were calculated and these statistical images were called correlation maps. Precallosotomy and postcallosotomy correlation maps were then compared visually.

Intracranial Electrode Localization

Patients were selected for depth electrode placement based on either a generalized seizure onset or a rapidly generalizing seizure semiology and unclear lateralization of seizure onset on EEG. In these patients, it was hypothesized that callosotomy would reveal a unilateral seizure onset amenable to resection as described in Clarke et al.[9] For the 3 patients implanted with invasive electrodes, electrode locations were identified by aligning the postimplantation CT to the preimplantation MRI with the aid of FSL software's program FLIRT.[23] To minimize potential effects of brain shift as a result of electrode implantation, the CT was first aligned to the postimplantation MRI study. Intracranial EEG electrode localization and visualization were performed using the free iELVis toolbox.[17] Electrode contacts were manually identified in BioImageSuite, and contact locations were mapped to a pial surface reconstructed using Freesurfer.

CCEP Recording

In patients with SEEG electrodes, CCEP mapping was performed as previously described before and after cal-

TABLE 1. Clinical characteristics of patients undergoing MRI-guided LITT for CC

Case No.	Sex	Age (yrs)	Preop Generalized Sz Frequency	% Reduction of Generalized Szs	Predominant Sz Semiology	Drop Attacks	Preop MRI Findings	Neurocognitive Impairment	Postcallosotomy Procedures	Concurrent SEEG Depth Electrodes Placed
1	F	29	1/day	100	CPS w/ secondary generalization	No	Prior craniotomy	Mild	Rt frontal lobectomy	22
2	M	44	1/mo	83	CPS w/ secondary generalization	No	Prior lt frontal hemorrhage	None	None	20
3	F	23	1/day	100	CPS w/ secondary generalization	No	Rt frontal venous infarction, craniopharyngioma, partial callosotomy	None	Rt frontal lobectomy	18
4	F	24	15/day	100	GTC, CPS, tonic, & atonic	3/day	Partial agenesis of corpus callosum	Severe	None	No
5	M	21	2–3 times/wk, w/ ≥10/day	0	CPS, tonic, & atonic w/ secondary generalization	No	Decreased lt hippocampal size	Severe	None	No

Sz = seizure.

losotomy.[32] Neighboring contacts of electrodes in the medial frontal lobe were stimulated with a train of 20 biphasic square-wave pulses (4 mA, 1–1.5 Hz, 0.1-msec pulse width) using a Grass S12 cortical stimulator (Grass Technologies, Inc.). Evoked responses to stimulation (CCEPs) were recorded simultaneously from an anatomically homologous contralateral location with the clinical EEG recording system (Natus Neurolink IP; Natus Medical, Inc.) sampling at 512 Hz. Precallosotomy CCEP was conducted 3–6 days after implantation of intracranial electrodes. Postcallosotomy CCEP mapping was conducted 8–15 days after implant and 4 days after completed callosotomy. No clinical seizure had occurred within 4 hours of the CCEP recordings. CCEP data were analyzed in MATLAB using the Fieldtrip toolbox for EEG data[35] and custom scripts. Data were re-referenced to the common average and notch filtered (60, 120, and 180 Hz) to remove line noise. For case 3, data were further re-referenced using a bipolar montage to remove remaining line noise. One-second trials were defined for each stimulation pulse, starting at 200 msec before stimulation. Each trial was baseline corrected using the mean voltage from the trial start to 25 msec before stimulation, and the time-locked average responses in a nonstimulated electrode in the contralateral hemisphere were computed using 20 stimulation trials.

Resting ECoG

Resting state ECoG data were acquired pre- and postcallosotomy. The patient was asked to rest with eyes closed for 7–8 minutes. Precallosotomy and postcallosotomy resting state data were collected on the same days as CCEPs (see above). All ECoG data were collected at least 24 hours from clinical seizure. To calculate connectivity, we used methods described elsewhere.[12] The Hilbert transform was used to compute the signal envelope in 10-Hz bands from 50 to 150 Hz, and these band-limited signals were full-wave rectified and averaged over frequency bands to obtain band-limited high gamma power (HGP). The HGP was then filtered between 0.1 and 1 Hz to extract slow fluctuations.[22,25,33] Pearson's r (correlation coefficient) was computed for slow fluctuations in HGP over a 4.5- to 8-minute period for pre- and postcallosotomy resting states.

Results

Patient Demographic, Clinical, and Seizure Characteristics

Five patients underwent anterior CC with LITT for intractable seizures (Table 1).

The patient in case 1 was a 29-year-old woman with mild cognitive dysfunction and seizures beginning within 1 year of birth. Noninvasive video EEG studies showed bifrontal polyspikes and bilateral independent interictal discharges. Seizure onset was diffuse. Seizures were typically generalized with left greater than right tonic posturing and a versive head turn to the left. MRI was normal, and PET showed right temporal hypometabolism. Magnetoencephalography showed interictal source localization in the bilateral frontal and parietal regions. At the time of surgery 5 antiepileptic drugs (AEDs) had failed, and she had received a vagal nerve stimulator (VNS) implant, with little relief from seizures. Prior to the LITT procedure, she experienced GTC seizures 2–4 times per week.

The patient in case 2 was a 44-year-old man with seizures beginning at the age of 29 years. At the time of surgery 9 AEDs had failed, and he had received a VNS implant 6 years prior, with little seizure relief. He experienced complex partial seizures (CPS) and GTC episodes 1–2 times per month, resulting in repeated soft-tissue injury. MRI showed a left frontal encephalomalacia and hemosiderin deposition from a presumed prior intracerebral hemorrhage and an 8-mm right anterior temporal cavernoma. This patient expressed a strong desire to avoid any open cranial procedures if possible.

The patient in case 3 was a 23-year-old woman with

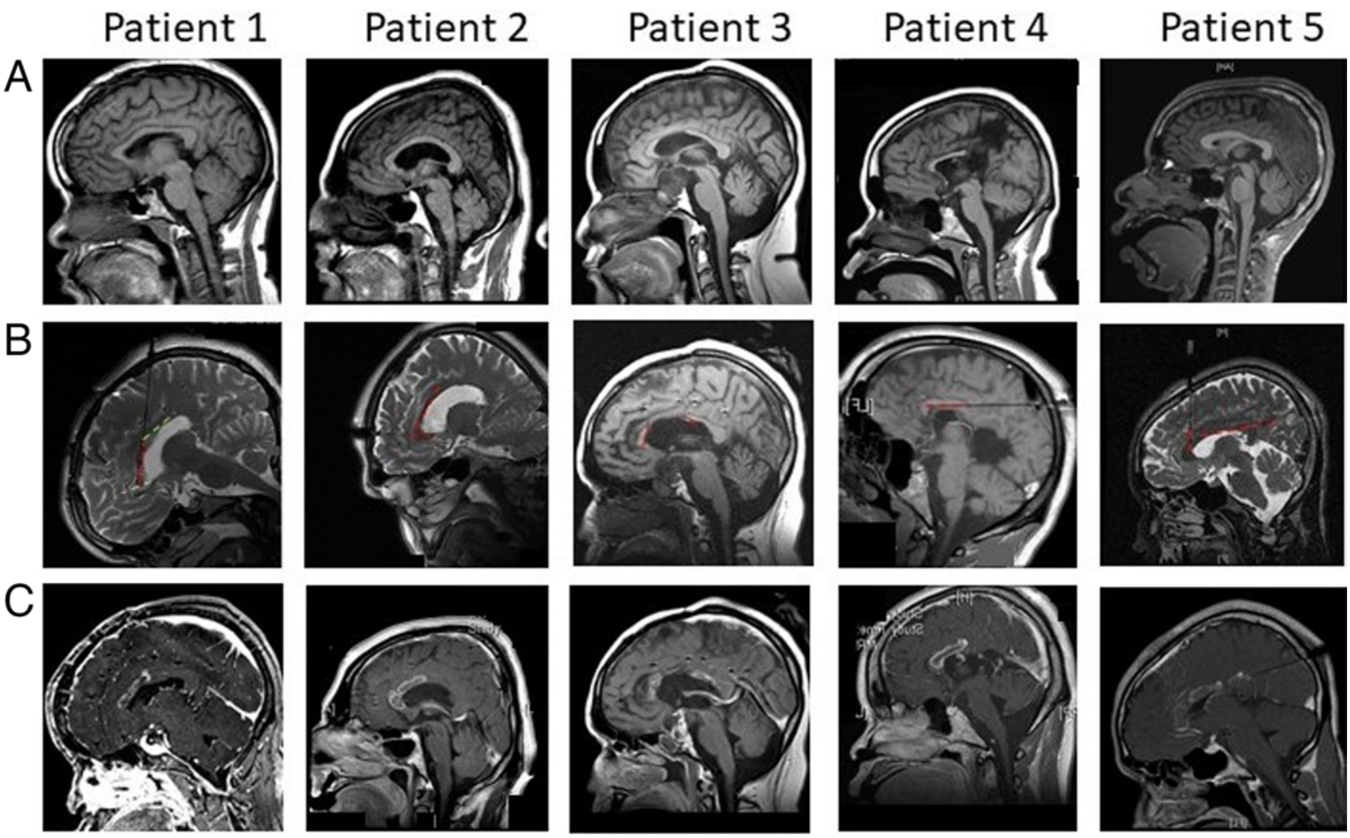

FIG. 1. Sagittal MRI sequences obtained in the patients in cases 1–5. **A:** Precallosotomy T1-weighted MRI. **B:** Intraoperative MRI with placement of probes within the corpus callosum demonstrated by *red dotted lines*. The *green dotted line* represents the deflected fiber of case 1, further illustrated in Fig. 3. **C:** Postcallosotomy contrast-enhanced T1-weighted MRI. The postcallosotomy image in case 1 was obtained 5 days after the initial operation with a single fiber in place, and contrast enhancement of the initial LITT lesions has faded. Figure is available in color online only.

seizures beginning after a transcallosal craniopharyngioma resection at the age of 12 years complicated by a right frontal venous infarction evident on preoperative MRI. At the time of surgery, 5 AEDs had failed, and she was having CPS and GTC seizures 1–2 times per day, resulting in facial fractures and 3 emergency admissions due to refractory status epilepticus. Noninvasive EEG showed seizures with both right and left frontal evolution and bilateral independent interictal discharges.

The patient in case 4 was a 24-year-old woman with Lennox-Gastaut syndrome diagnosed at the age of 2 years. Noninvasive EEG showed spike and wave discharges. MRI revealed partial agenesis of the corpus callosum, left parietal and posterior fossa arachnoid cyst, and right mesial temporal dysplasia. At the time of surgery, 12 AEDs had failed, she was severely cognitively impaired, and had mixed seizures with atonic, tonic, CPS, and GTC seizures (approximately 15 per day), with an average of 3 drop attacks per day.

The patient in case 5 was a 21-year-old autistic, nonverbal man with seizure onset at age 6 months with CPS, tonic, atonic, and GTC seizures occurring 2–3 times per week in clusters of 10 or more seizures per day with varying semiology, frequently including a brief aura, tonic limb stiffening, and vocalizations then generalization. He had undergone a VNS placement, 5 AEDs had failed, and he experienced multiple, daily, prolonged events. The MRI sequences were unremarkable. Video EEG studies obtained prior to surgery showed multifocal spikes and bifrontal polyspikes.

Seizures recorded via SEEG in the 3 patients with intracranial monitoring prior to surgery (cases 1–3) all demonstrated bilateral synchronous onsets and bilateral synchronous and independent interictal discharges. Noninvasive EEG in the fourth patient showed paracentral seizure onset with unclear lateralization and rapid bisynchronous generalization. Seizures were multifocal with varying semiology in the fifth patient.

Surgical Procedure

For the 3 patients who underwent invasive electrophysiological monitoring, bilateral SEEG procedures were performed 5–10 days prior to the LITT procedures. Monitoring of the intracranial EEG was performed with medication reduction to capture seizure onset.

All patients underwent anterior corpus callosotomy in which the Visualase LITT system (Medtronic, Inc.) was used under MRI guidance. Contrast-enhanced MR images obtained preoperatively, at placement of laser devices, and post-LITT are shown in Fig. 1A. Briefly, the catheter/

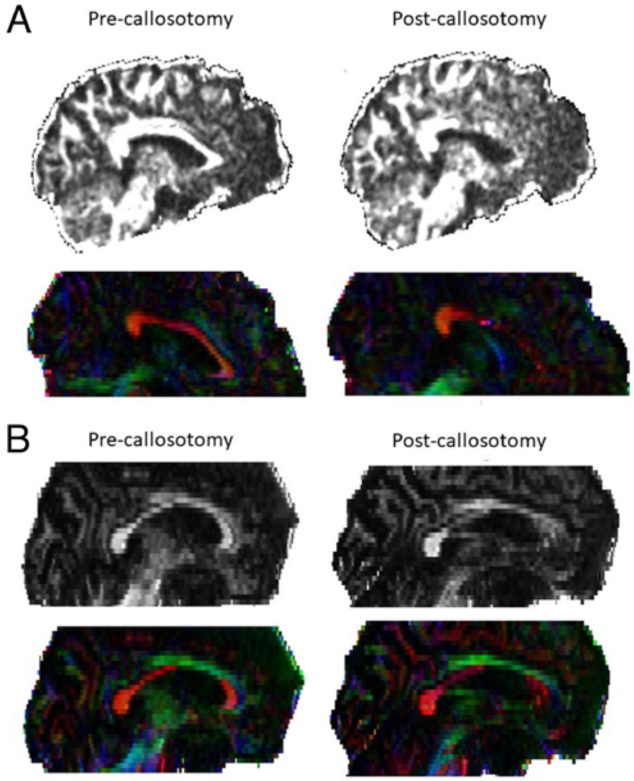

FIG. 2. DTI obtained in case 1 (**A**) and case 2 (**B**) demonstrating a large decrease in fractional anisotropy within the corpus callosum postcallosotomy. High FA is illustrated by *white* regions in the first row and *red* regions in the second row. Left-right direction was shown with *red*, anteroposterior with *green*, and "z" direction (top to bottom) with *blue*. Figure is available in color online only.

fiber assembly is placed using frame-based stereotaxy, in which CT angiogram and postcontrast MR image fusion (Integra) are used. In contrast to Singh et al., who used the Neuroblate system for callostomy, we found that the anatomy of the corpus callosum in our patients prevented a standardized approach.[39] Probe trajectories were plotted using planning software. Entry points targeted the genu and posterior body (anterior parasagittal) and anterior body (posterior parasagittal) (Fig. 1B) based on known safe entry points sufficiently anterior or posterior to the coronal suture to avoid the presumed location of the motor strip. Fibers entered through the nondominant lobe, with targets located within the corpus callosum prior to divergence of fibers (within 2 cm of midline).

The patient in case 1 required the placement of 3 fibers, 1 due to a missed target as described below. The patient in case 2 required a posterior fiber targeting the anterior body and an anterior fiber targeting the genu and rostrum due to a partial callosotomy from a prior surgical procedure. The patient in case 3 required the placement of a posterior fiber for the genu and rostrum and an anterior fiber for the remaining body. The patient in case 4 had partial agenesis of the corpus callosum and required the placement of a single posterior fiber targeting the genu and body. Finally, the patient in case 5 required the placement of 2 fibers—a low-lying parietooccipital fiber for coverage of the body and another posterior parasagittal fiber for the genu and rostrum.

The LITT procedure was conducted under thermometry guidance in the MRI suite after resuming medications and performing electrical stimulation mapping. The Visualase LITT procedures involve placement of low and high safety markers to automatically terminate treatment at a thermometric calculation of 45°C and 90°C. Treatment was performed while monitoring axial and sagittal planes. Low safety markers were placed over the adjacent cingulum and at sites close to electrode contacts that were visible on the MRI sections used for thermometry guidance. High safety markers were placed near the diffuser tip in the callosum. To further minimize possible thermal induction at the electrode contacts, MR scanning protocols were performed for less than 3 minutes at a time, with breaks lasting at least 2 minutes. A notable difference when concomitant SEEG electrodes were in place involved the use of a receive-only coil (as opposed to a transmit/receive coil). The use of depth electrodes in MRI with these protocols has been shown to be safe in multiple studies.[7,24]

From 1 to 3 lesions were performed for each device in all patients. When multiple lesions were performed, the device was withdrawn 5–8 mm at each step to cover the length of the corpus callosum traversed by the fiber. Notably, due to the optical properties of the white matter of the callosum, a faster-than-expected time to reach therapeutic thermal injury was noted. Maximum energy delivered was 7.5 W (50% of maximum), typically using 4–5 W for 1–2 minutes. The area of the callosum showing contrast enhancement is shown in Fig. 1C. This contrast enhancement and DTI results shown in Fig. 2 demonstrate anatomical disconnection of the anterior callosum by using LITT. The LITT devices were removed immediately after the procedure, and patients were monitored overnight.

Of note, a few general principles should be used with trajectory planning. It is of paramount importance to avoid pericallosal arteries, which reduces the risk of infarction. The lateral ventricles should also be avoided so as not to provide a tract for CSF leakage, and to avoid the effects of CSF as a heat sink. Entry points should avoid the motor strip and primary sensory cortex, the sagittal and transverse sinus, and, when possible, fibers should enter gyri rather than sulci to decrease the risk of venous damage.

Complications

The course of the patient in case 1 was complicated by inaccurate placement of 2 of the LITT fibers (Fig. 3). She was taken back to the operating room for completion of the anterior callosotomy with a second LITT procedure 5 days later. Following the second procedure, the patient developed a mild supplementary motor area (SMA) syndrome that resolved within 1 week. The patient in case 5 had an 8-mm hemorrhage associated with placement of the catheter and LITT fiber at the parietal surface. His postoperative course was complicated by frequent seizures over the first postoperative week. No disconnection syndrome was observed in any patient. There were no

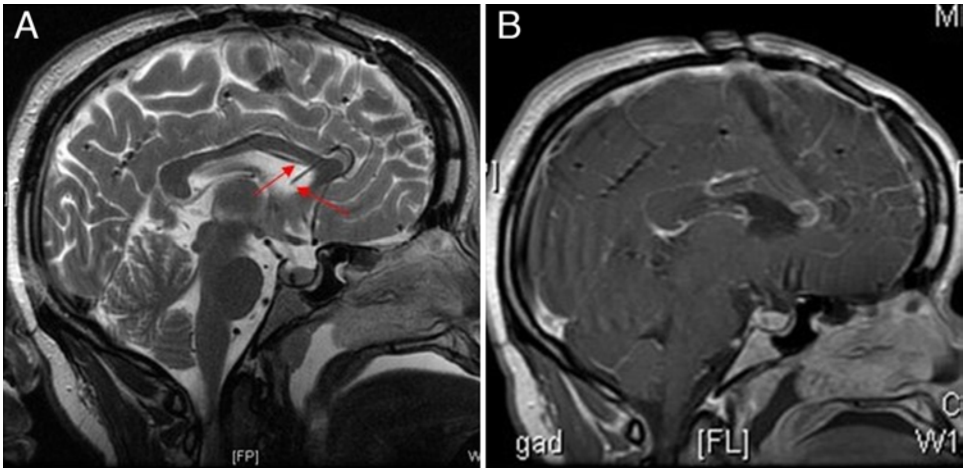

FIG. 3. A: Sagittal intraoperative MRI study demonstrating misplaced fiber in case 1 (*red arrows*). **B:** Postprocedural T1-weighted MRI study obtained with contrast demonstrating incomplete callosotomy. Figure is available in color online only.

nonneurological complications associated with long-term placement of electrodes, including deep vein thrombosis, pulmonary embolism, and myocardial infarction.

Seizure and Functional Outcomes

The patients in cases 1–4 showed a decrease in generalized seizure frequency following anterior two-thirds CC. Specifically, the patients in cases 1, 3, and 4 showed a 100% reduction in generalized seizures (Table 2). The patient in case 2 had 2 GTC seizures during an 18-month follow-up, resulting in an 83% decrease in generalized seizure frequency. Drop seizures were eliminated in the patient in case 4. All patients continued to have CPS following the callosotomy, but the frequency and duration of their CPS was reduced.

Lateralization of the seizure onset focus and interictal discharges was observed on SEEG recordings in cases 2 and 3 immediately after callosotomy and in case 1 immediately after the second LITT procedure (Fig. 4A, representative image). The patients in cases 1 and 3 elected to proceed with focal resection of the right frontal seizure-onset zone, resulting in seizure freedom at last follow-up. The patient in case 2 refused any surgical intervention involving craniotomy. The patient in case 5 did not obtain meaningful seizure reduction from the callosotomy, with little change in noninvasive electrographic monitoring.

Improved social function was noted in the patients in cases 1–4 per the individuals or their caregivers. The patients in cases 1 and 2 are currently holding full-time employment (cashier and salesperson). Two of the other patients remain on disability (cases 3 and 4), but their caregivers note overall improvement in quality of life. No patient has had an emergency department visit due to seizures, fractures, or soft-tissue injury since the LITT procedure.

Functional Connectivity Measures

Functional connectivity may be used to identify the physiological consequences of CC. Figure 5 shows rfMRI connectivity results using a seed placed for correlation analysis in homologous right and left frontal regions in cases 1 and 3. Robust interhemispheric connectivity is demonstrated prior to the LITT callosotomy procedure. Postcallosotomy, interhemispheric connectivity is greatly reduced while intrahemispheric connectivity is largely maintained, indicating disconnection of the cerebral hemispheres. More formal analysis of these data is being

TABLE 2. Outcomes of patients undergoing MRI-guided LITT for CC

Case No.	Length of FU (mos)	% Reduction of Generalized Szs	SEEG Postcallosotomy	Drop Attacks Postcallosotomy	% Callosum Ablation	Postcallosotomy Procedures & Outcome
1	24	100	Lateralization of interictal discharges & SOZ	No	79	Rt frontal lobectomy resulting in Sz freedom
2	24	83	Lateralization of interictal discharges & SOZ	No	56	None
3	24	100	Lateralization of interictal discharges & SOZ	No	62	Rt frontal lobectomy resulting in Sz freedom
4	24	100	NA	No	100	None
5	1	0	NA	Yes	81	None

FU = follow-up; NA = not applicable; SOZ = seizure onset zone.

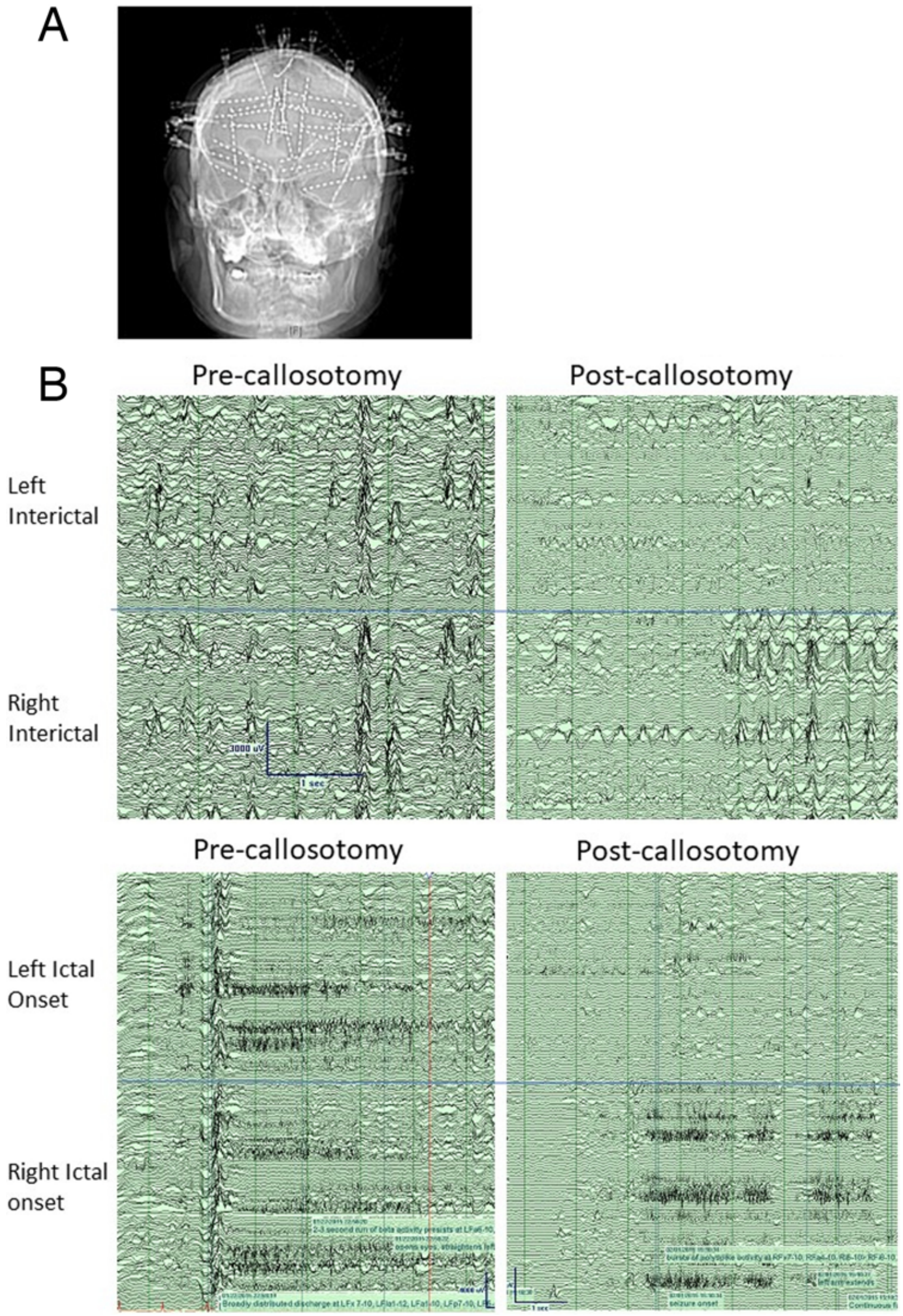

FIG. 4. A: Representative anteroposterior skull radiograph obtained in case 1, showing placement of SEEG depth electrodes. **B:** Interictal and ictal EEG obtained in case 1 showing rapid generalized seizure activity precallosotomy and lateralization of the seizure to the right hemisphere postcallosotomy. Figure is available in color online only.

conducted, but is beyond the scope of this paper. The presurgical anatomy of the other patients prevents generalizability of our results to the normal MNI brain space and would make comparison between patients difficult. Figure 4B shows the results of resting ECoG analysis pre- and postcallosotomy—analogous to the case for rfMRI results, frontal electrodes demonstrate decreased interhemispheric connectivity after callosotomy. CCEPs infer connectivity relying on oligosynaptic connections via pulse stimulation at a pair of intracranial electrodes, with recording at other electrodes.[12,29] Figure 6B and 6F show examples of reduced CCEPs in 2 patients after callosotomy, providing additional evidence of functional disconnection of the hemispheres.

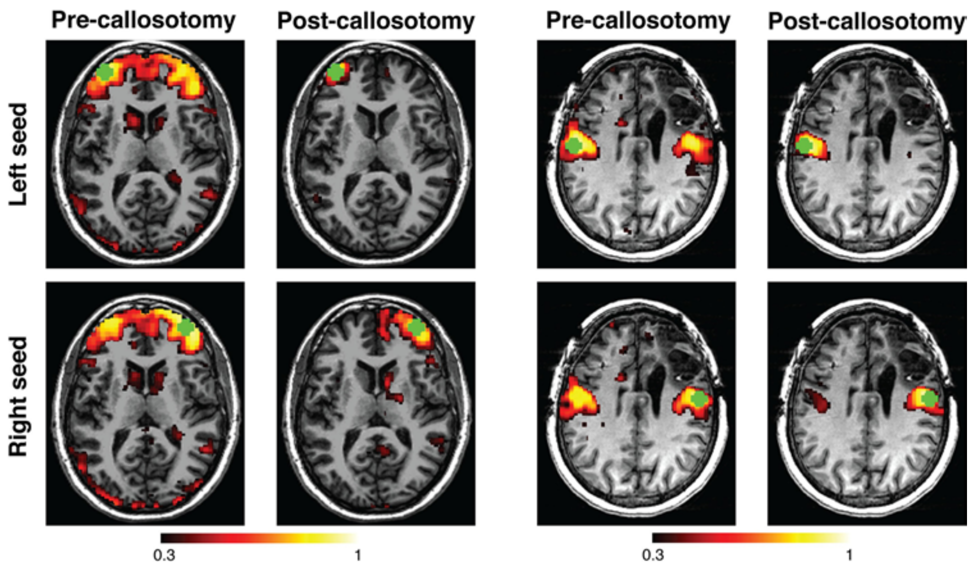

FIG. 5. Representative rfMRI sequences obtained in cases 1 (left-hand set of 4 images) and 3 (right-hand set of 4 images) pre- and postcallosotomy. A significant decrease in contralateral BOLD signal correlation is observed following callosotomy for both right and left hemisphere seed regions, demonstrating a decrease in resting state interhemispheric connectivity. Figure is available in color online only.

Discussion

Until now, there has only been a single case study that has examined the utility of LITT for ablation of the splenium in a case of intractable epilepsy.[21] Here for the first time, we report the successful ablation of the anterior corpus callosum achieved using LITT. In our series, 4 of 5 patients demonstrated a meaningful decrease in frequency of generalized seizures. Seizure lateralization following CC has been shown previously;[9,15,30] however, results following focal resection after callosotomy are mixed.[38] Three of our patients had lateralization of their seizures postcallosotomy, and 2 of those 3 elected subsequent resection of the focus, resulting in seizure freedom. Although we demonstrate the effectiveness of this approach, our results are based on a much smaller series of patients. Patient selection is likely to play a major role in outcome, with a consistent seizure semiology and/or lesion on MRI being major factors. Concurrent use of perioperative SEEG and the less invasive LITT procedure may allow for better detection of lateralization of seizure focus compared to an open callosotomy and intracranial EEG monitoring done sequentially. This is probably because electrodes may shift in position following open callosotomy, making pre- and postcallosotomy assessment of physiology more difficult.

Traditional CC typically requires a large scalp incision and craniotomy, with risk of injury to the sagittal sinus, draining veins, pericallosal arteries, and the cingulum. Intraoperative assessment of the exact extent of the callosotomy may be facilitated by image guidance.[42] Less invasive methods in which endoscopy and CO_2 lasers were used have also been completed successfully, but these approaches also require an interhemispheric approach with its associated risks.[8,13,19] Radiosurgical approaches to CC performed using stereotactic radiosurgery (SRS) involve even lower levels of invasiveness than LITT; however, latency of effect and potential risks of radiation necrosis are notable disadvantages.[11,14] Other radiosurgical approaches including focused ultrasound and radiofrequency ablation have not been reported.

MRI-guided LITT CC offers numerous advantages compared to traditional callosotomy. A substantial proportion of patients with intractable epilepsy (e.g., case 2) are reluctant to undergo surgical intervention due to fear of invasive brain procedures.[1,41] Although the efficacy of LITT for mesial temporal lobe epilepsy appears to approach that of open surgery, LITT provides a viable alternative in those patients for whom open surgical treatment is not an option.[18] Open CC may also have higher risks in patients with prior interhemispheric procedures, such as cases 1 and 3 in our series.

Although the LITT approach is minimally invasive, it is not risk free. Risks associated with LITT include catheter malposition, hemorrhage, neurological dysfunction related to thermal injury, and equipment malfunction.[37] The complications seen in our series may be minimized by decreasing the overall number of devices used. When possible, we recommend placing the device that is most likely to deflect last. In our case 1, one of the misdirected devices might have been avoided by placing the anterior entry point targeted to the genu of the callosum prior to placement of the posterior entry site targeted to the anterior callosum. Of note, the transient SMA syndrome observed in case 1 appears to be secondary to the effects of callosotomy as opposed to injury to the SMA, because no diffusion restriction was noted in the region of the SMA.

The cost of the LITT devices represents another barrier to gaining widespread acceptance. The "C" shape of the corpus callosum in most patients requires placement of 3 devices: 1 in the genu, 1 in the anterior body, and 1 in the posterior body. Atypical callosal anatomy (cases 3

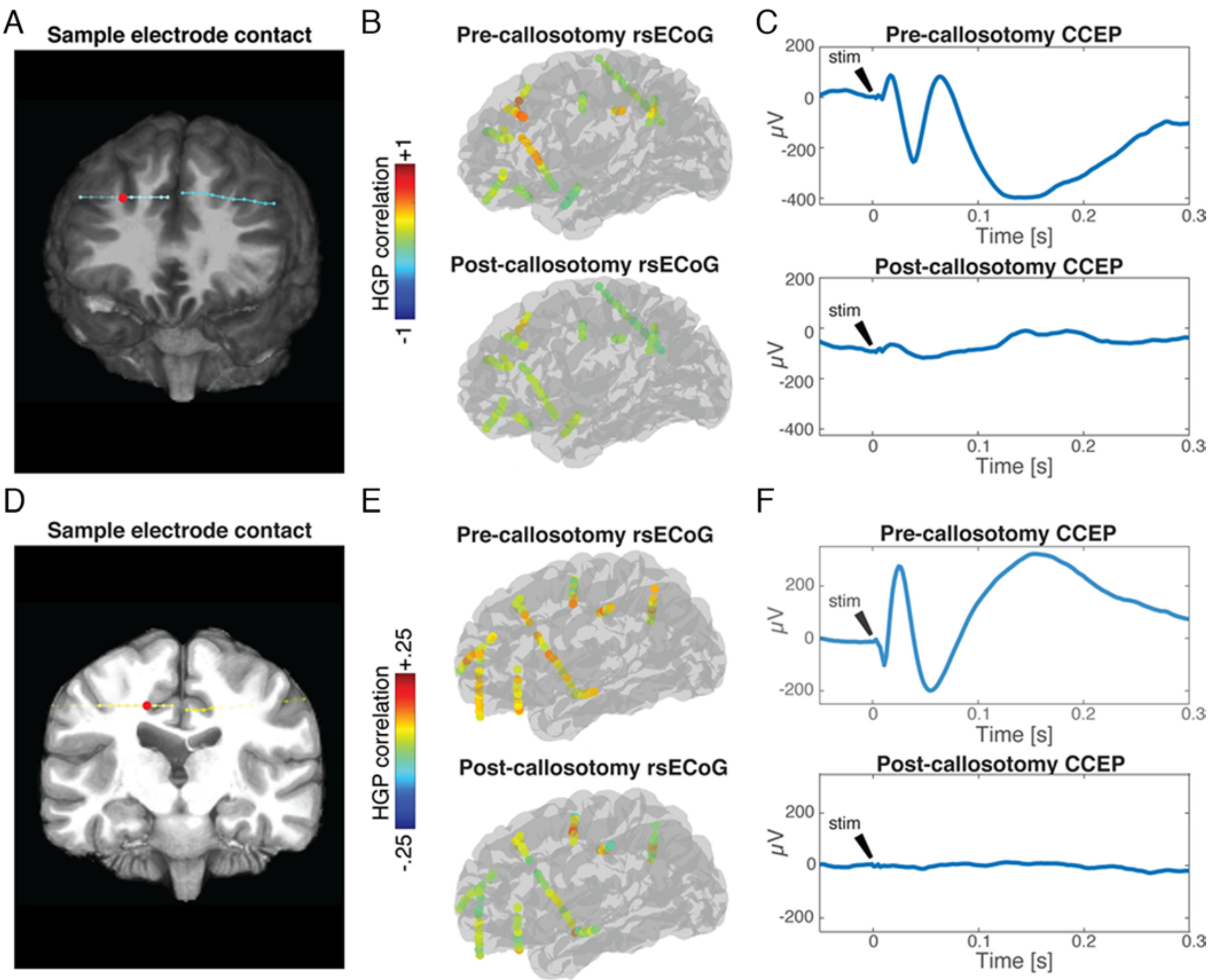

FIG. 6. Sample electrode contact for CCEP located in the right hemisphere (*red dot*) for cases 1 (**A**) and 3 (**D**). HGP correlation of resting state ECoG (rsECoG) recorded in the left hemisphere pre- and postcallosotomy in cases 1 (**B**) and 3 (**E**), using sample electrode as seed. A decrease in HGP correlation is observed in diffuse frontoparietal locations. Representative mean CCEP recorded from electrode in left frontal lobe during stimulation of sample electrodes in right frontal lobe in cases 1 (**C**) and 3 (**F**), pre- and postcallosotomy. In both patients the characteristic CCEP implying direct functional connectivity between the 2 regions was abolished following callosotomy. Figure is available in color online only.

and 4) can result in the need to use fewer devices, resulting in lower costs and reduced chances for malposition; indeed, the presurgical anatomy of the corpus callosum dictates the number of devices necessary. Whereas the upfront cost of LITT may be greater than that of SRS, no study has looked at the cost of the delayed effects of SRS such as continued seizures or radiation necrosis, making comparison of the cost-effectiveness of these procedures impossible at this time.

The adequacy of LITT callosotomy was assessed using invasive EEG, MRI, DTI, and functional connectivity methods. Postcontrast MRI showed contrast enhancement restricted to the targeted callosal region and DTI showed disruption of the targeted white matter tracts. rfMRI reliably infers brain connectivity by using correlated low-frequency fluctuations of the blood oxygen level–dependent (BOLD) MRI signal[4]—and reduced interhemispheric connectivity following open callosotomy has previously been demonstrated.[36] With intracranial electrodes, analogous connectivity measures may be derived from the ECoG data.[20,33] Such recordings provide an advantageous direct electrophysiological measurement of neuronal activity, as opposed to neuroimaging methods using second-order derivations that link neuronal activity to the BOLD signal.[26]

CCEPs have also been used to investigate functional connectivity between brain regions.[27] CCEPs allow for direct measurement of the propagation of neuronal firing across brain networks at a spatiotemporal resolution exceeding commonly used neuroimaging methods, providing a reproducible method for more precise localization of the seizure onset zone and the network associated with a seizure compared to SEEG recordings.[43] Our data demonstrate that CC abolishes CCEPs measured between homotopic brain regions, implying disruption of direct connections between those areas via corpus callosum. When combined with the neuroimaging and intracranial EEG data, a convincing picture emerges showing the disruption of a rapidly propagating interhemispheric seizure network via CC performed with MRI-guided LITT.

Conclusions

We have demonstrated here, for the first time, successful CC using MRI-guided LITT for the treatment of refractory epilepsy in 5 patients without major side effects or adverse events. Although further experience will be needed to replicate these results and to examine longer-term outcomes and side effects associated with LITT, initial findings using anatomical and functional connectivity methods suggest results that would compare favorably with those of open procedures. Based on these initial findings, we believe that LITT is a viable alternative for CC in patients hesitant to undergo an open procedure and in those needing immediate relief of seizures, which SRS would not be able to offer.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Mehta. Acquisition of data: Mehta, Lehner, Yeagle, Argyelan, Du, Megevand, Hwang. Analysis and interpretation of data: all authors. Drafting the article: Mehta, Lehner, Yeagle, Klimaj. Critically revising the article: Mehta, Lehner, Hwang. Reviewed submitted version of manuscript: Mehta, Lehner, Yeagle, Argyelan, Megevand, Hwang. Approved the final version of the manuscript on behalf of all authors: Mehta. Administrative/technical/material support: Lehner. Study supervision: Mehta, Lehner.

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