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Diffusion tensor imaging to evaluate commissural disconnection after corpus callosotomy

Asim F. Choudhri · Matthew T. Whitehead · Amy L. McGregor · Stephanie L. Einhaus · Frederick A. Boop · James W. Wheless

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Abstract
Introduction Corpus callosum transection can prevent propagation of epileptic discharges. If seizures persist after surgery, assessment of the efficacy of the transection requires knowledge that the commissural fibers have been disrupted. We evaluated whether diffusion tensor imaging (DTI) and diffusion tensor fiber tracking can assess the degree of callosal transection and determine which white matter pathways remain intact.
Methods This HIPAA-compliant retrospective study was performed after Institutional Review Board approval. Patients who underwent corpus callosotomy with postoperative magnetic resonance imaging (MRI) that included DTI were identified. Axial DTI was performed with either 15 or 25 noncollinear directions of encoding. MRI and DTI were reviewed by two board-certified neuroradiologists to evaluate commissural disconnection.
Results One hundred eleven patients underwent corpus callosotomy with postoperative MRI, of which 32 had postoperative DTI. Of these 32, there were 16 males and 16 females, with a mean age of 12.2±6.3 years (range 0.24 to 32.8 years, median 12.3). Eighteen patients had undergone complete callosal transection and 14 patients had partial callosal transection. Seventeen of 18 patients undergoing complete callosal transection had structural and diffusion tensor fiber tracking (DT-FT) evidence of complete transection. The forceps major was intact in all patients undergoing partial transection. At least some commissural fibers originating from the precuneus, postcentral gyrus, and posterior cingulate were intact in all six partial transections which spared the callosal isthmus.
Conclusion DTI and DT-FT aid in the postoperative characterization in patients with callosal transection for seizure control. This can confirm whether the intended fibers have been disconnected, helping in the planning for possible further surgical intervention versus other therapies.

Keywords Seizure · Diffusion tensor imaging · Corpus callosum · MRI · Epilepsy

Abbreviations

DT-FT	Diffusion tensor fiber tracking
DE-FA	Directionally encoded fractional anisotropy
FA	Fractional anisotropy

A. F. Choudhri · M. T. Whitehead
Department of Radiology, University of Tennessee Health Science Center, Memphis, TN, USA

M. T. Whitehead · A. L. McGregor · S. L. Einhaus · F. A. Boop · J. W. Wheless
Le Bonheur Neuroscience Institute, Le Bonheur Children's Hospital, Memphis, TN, USA

A. L. McGregor · J. W. Wheless
Department of Pediatrics–Neurology, University of Tennessee Health Science Center, Memphis, TN, USA

S. L. Einhaus · F. A. Boop
Department of Neurosurgery, University of Tennessee Health Science Center, Memphis, TN, USA

A. F. Choudhri (✉)
Department of Radiology, Le Bonheur Neuroscience Institute, Le Bonheur Children's Hospital, 848 Adams Ave-G216, Memphis, TN 38103, USA
e-mail: achoudhri@uthsc.edu

Introduction

The corpus callosum is a white matter tract which serves as the largest forebrain commissure in placental mammals [1]. The fibers within the corpus callosum largely provide homotopic connections, where an area of the cortex is connected to a homologous area in the contralateral hemisphere. The corpus callosum transmits electrical impulses between the hemispheres and can also serve as a conduit for neoplastic spread. As the dominant forebrain commissure, the corpus callosum can result in the propagation of epileptic discharges between cerebral hemispheres.

Corpus callosum transection has been used as a means of preventing propagation of epileptic discharges [2–5]; however, the procedure can be difficult to perform due to adjacent vasculature and the deep location of the corpus. If seizures persist after surgery, assessment of the efficacy of the transection requires knowledge that the commissural fibers have been disrupted.

Diffusion tensor imaging (DTI) is a technique that evaluates white matter integrity, and diffusion tensor fiber tracking (DT-FT) evaluates the expected integrity of axonal tracts within the central nervous system [6–10]. Prior work has looked at DTI after callosotomy in a small series [11] and after radiosurgical callosotomy [1, 12], including studies focusing more on myelin changes [2–5, 13]; however, no prior study has used DTI and DT-FT to confirm and characterize the extent of callosal transection or identify the origin of the remaining fibers. We evaluated whether DTI and DT-FT can be used to assess the degree of callosal transection and determine which white matter pathways remain intact.

Methods

This HIPAA-compliant study was performed after Institutional Review Board approval. A search of the electronic medical record and surgical database at a single academic pediatric hospital was performed to identify patients who had undergone corpus callosotomy, including those who underwent functional hemispherectomy. All patients who had preoperative and postoperative magnetic resonance imaging (MRI) were identified. Patients who had postoperative MRI with DTI were analyzed. The timing of the MRI relative to the surgical procedure was recorded.

The etiology and preoperative severity of the patients' seizures were evaluated. Clinic notes and operative reports were reviewed to determine the intended extent of commissural disconnection.

Anatomic MRI analysis

Preoperative sagittal T1-weighted images were evaluated to determine the morphology of the corpus callosum and anterior–posterior dimension. Postoperative sagittal T1-weighted images were evaluated to determine the extent of the callosotomy. Individual segments evaluated include the rostrum, genu, anterior body, midbody, posterior body, isthmus, and splenium.

Diffusion tensor analysis

Studies were performed on either a 1.5- or 3-T MRI scanner (Signa HDxt, General Electric, Milwaukee, WI) with an eight-channel head coil. DTI was performed in the axial plane with 4 mm slice thickness and either 15 or 25 directions of encoding with a 128×128 matrix, a *b* value of 1,000 ms, and a single b0 image. Vendor-provided software (Functool, General Electric, Milwaukee, WI) was used for distortion correction and processing of fractional anisotropy (FA), directionally encoded fractional anisotropy maps (DE-FA), and DT-FT overlays at the time of clinical interpretation. DT-FT was subsequently evaluated using a dedicated workstation (Dynasuite Neuro 3.0, InVivo Corp, Pewaukee, WI). All DT-FT processing was performed using a deterministic fiber assignment by continuous tracking algorithm algorithm (FACT) with an FA threshold of 0.2 [6–10]. All DTI data was processed by one of two board-certified neuroradiologists at the time of clinical interpretation. DTI data and structural images were interpreted for the purposes of this study in consensus by two board-certified neuroradiologists blinded to the clinical status of the patient. Both neuroradiologists had greater than 3 years of clinical experience after board certification. Region of interest (ROI) seeds for DT-FT were typically placed in four separate locations in each cerebral hemisphere (Fig. 1), and screen captures were performed of the DT-FT results (Fig. 2). Neuroradiologist discretion was used to determine if additional ROIs were required for a specific case.

Comparison between DT-FT and structural images

Each segment of the corpus callosum, including the rostrum, genu, body, isthmus, and splenium, was rated as either intact or transected on conventional images and on DT-FT images. This was performed separately for structural images and for DT-FT, with subsequent unblinded consensus comparison. DT-FT analysis from axial and coronal DTI acquisitions was evaluated independently. The presence of artifact which was felt to possibly interfere with analysis and interpretation was recorded, as well as suspected origin including susceptibility artifact from postoperative pneumocephalus and blood products.

Results

One hundred eleven patients were identified who underwent corpus callosotomy, of which 32 had postoperative MRI which included DTI. Thirty-two patients (16 M, 16 F; age 12.2±6.3, range 0.24 to 32.8 years, median 12.3 years) who underwent prior corpus callosotomy were evaluated with DT-FT. DTI was obtained in the axial plane using 15 directions of

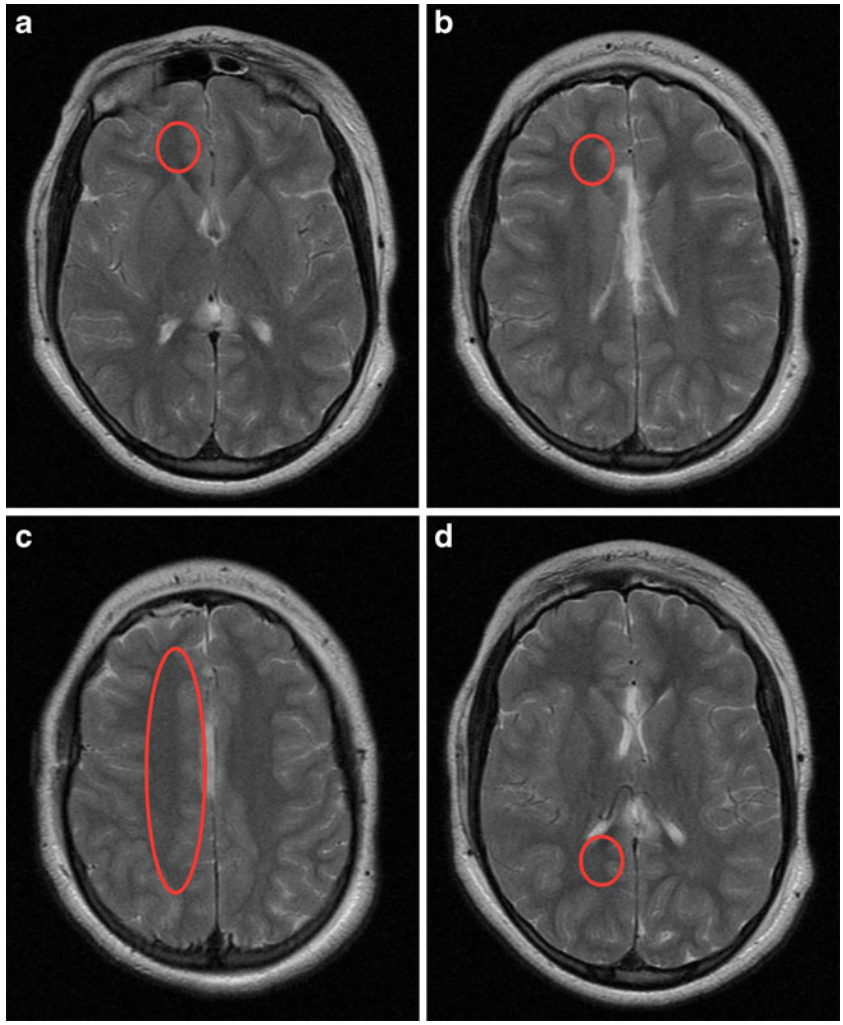

Fig. 1 Multiple axial T2W images showing location of DT-FT ROI placement. ROI in the inferior frontal white matter (**a**) evaluates the rostrum of the corpus callosum. ROI in the white matter of the frontal pole (**b**) evaluates the genu and anterior body of the corpus callosum. ROI in the frontoparietal deep white matter (**c**) evaluates the body and isthmus of the corpus callosum. ROI placed in the occipital white matter (**d**) evaluates the splenium and posterior isthmus of the corpus callosum

encoding ($n=26$) and 25 directions of encoding ($n=6$), with additional coronal plane 25 direction DTI performed in 8 patients. Eighteen patients had undergone complete callosal transection, including 4 with functional hemispherectomy. Fourteen patients had partial callosal transection with preservation of the splenium alone ($n=8$) and the splenium and isthmus ($n=6$).

Seventeen of 18 patients undergoing complete callosal transection had structural and DT-FT evidence of complete transection, and 1 patient had a small quantity of intact forceps minor fibers within the rostrum on DT-FT with transection of the remainder of the corpus callosum (Fig. 3). As there was appropriate seizure control, no further transection was performed. In an additional patient who underwent functional hemispherectomy for hemimegalencephaly (Fig. 4a) where structural images from the immediate postoperative MRI were equivocal regarding the completeness of the callosotomy (Fig. 4b, c), DT-FT was able to confirm complete callosotomy (Fig. 4d). Subsequent MR examinations showed both conventional MR and DTI evidence of commissural disconnection.

In patients undergoing partial transection, the forceps major was intact in all patients. At least some commissural fibers originating from the precuneus, postcentral gyrus, and posterior cingulate gyrus were intact in all six patients undergoing partial transections with sparing of the callosal isthmus.

Of the eight patients who had both axial and coronal DTI acquisitions, no differences were noted in determining the presence of intact commissural fibers traversing the midline throughout various portions of the corpus callosum. No differences were seen in the parenchyma area of origin of the fibers which traversed the remaining intact portions of the corpus callosum.

Of the 32 patients with postoperative DTI, 24 had a single post-callosotomy MRI with DTI, 6 had two post-callosotomy MRI scans with DTI, and 2 patients had three post-callosotomy MRIs with DTI available. The first postoperative scan was performed within the first two postoperative days in 12 patients, representing the 12 most recently performed surgical procedures in our series (median postop day 1). For

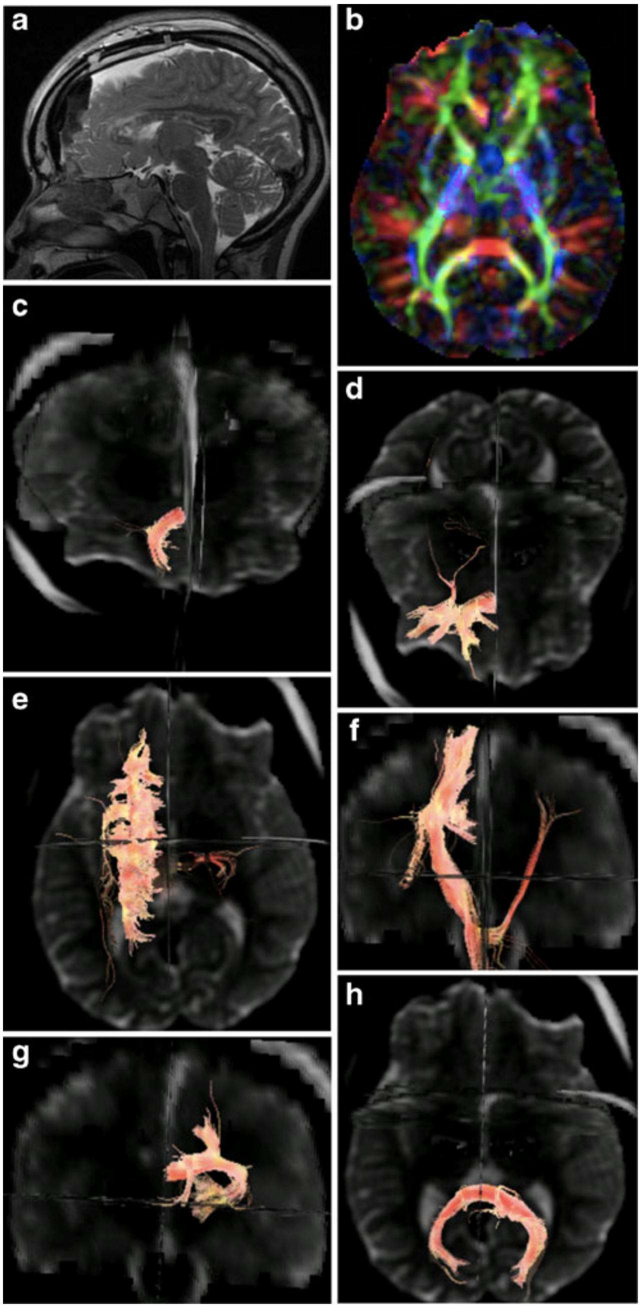

Fig. 2 Sagittal T2W image after a splenium-sparing corpus callosotomy (**a**). Directionally encoded FA map through the level of the genu and splenium of the corpus callosum (**b**) shows disruption of fibers at the midline within the genu of the corpus callosum; however, there was preservation of the splenium. Anterior oblique views of DT-FT performed with ROI placed in the inferior frontal lobe (**c**) and frontopolar deep white matter (**d**). Superior (**e**) and anterior (**f**) views of DT-FT performed with ROI in the frontoparietal deep white matter. Posterior projection of DT-FT performed with ROI in the white matter of the precuneus shows transection of the isthmus of the corpus callosum (**g**). Superior projection of DT-FT performed with ROI in the white matter of the occipital pole (**h**) shows intact fibers of the forceps major

the remaining 20 patients, the initial postoperative scan ranged from 1 to 124 months after callosotomy.

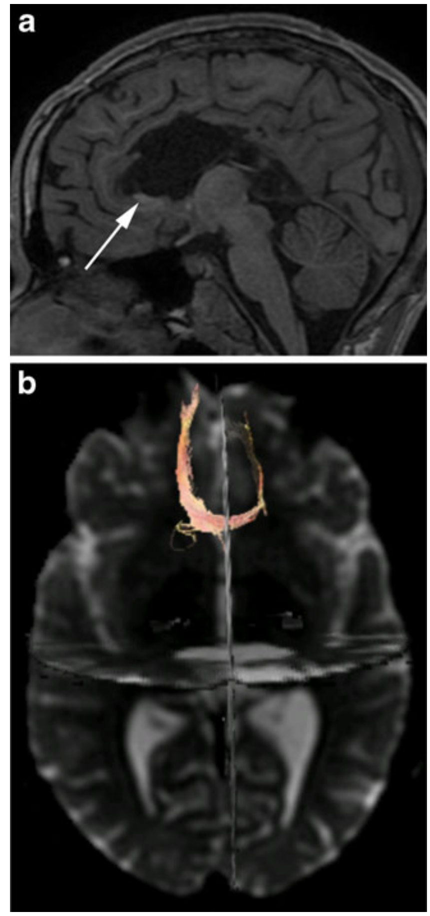

Fig. 3 Sagittal T1WI after complete callosotomy (**a**) shows a small intact portion of the callosal rostrum, which was identified after reviewing DT-FT with ROI placed in the inferior frontal white matter (**b**) that showed commissural fibers traversing the midline through the rostrum

In eight patients who had more than one postoperative MRI that included DTI, no change was seen in the extent of structural or DT-FT extent of callosal transection on the subsequent studies. Of these patients, six had their initial postoperative DTI study within the first week of post-callosotomy. For these six patients, the interval between their first and most recent post-callosotomy MRI scan with DTI was 238± 252 days (median 192 days). No difference in the results of DTI analysis of callosal integrity was seen between the initial immediate postoperative scan and the delayed MRI scan. In particular, the late postoperative scans showed similar extent of fibers extending to the transection margin, suggesting that decreased FA in the adjacent fibers did not impair FACT DT-FT analysis.

Discussion

Postoperative DTI can aid in the characterization of commissural disconnection in patients undergoing corpus callosotomy. DT-FT images provide an easy to understand overview of the

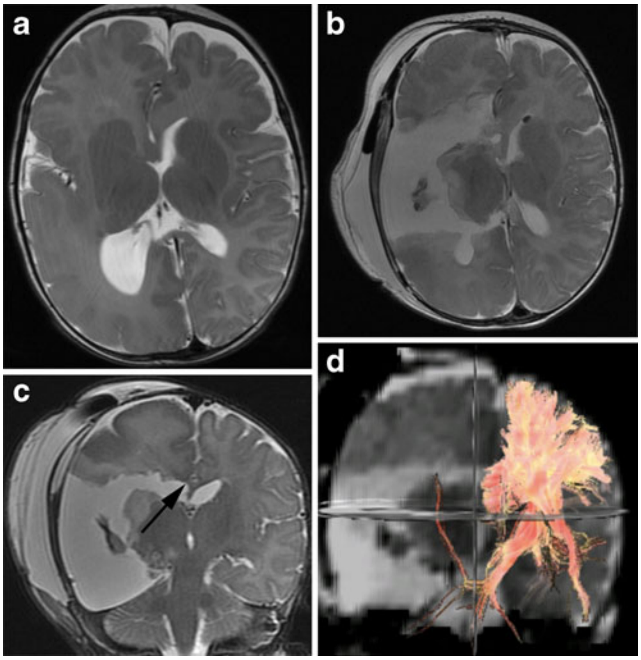

Fig. 4 Axial T2-weighted image in a patient with right-sided hemimegalencephaly prior to (**a**) and after (**b**) functional hemispherectomy. Coronal STIR on the postoperative study showed close apposition of the margins of the callosotomy in the midbody of the corpus callosum (**c**); however, DT-FT with ROI placed in the frontoparietal deep white matter of the left cerebral hemisphere showed no evidence of intact commissural fibers traversing the midline (**d**)

impact of the surgical procedure to the surgeons, epileptologists as well as to patients and their families. This information can be used to guide treatment planning for patients with persistent seizure propagation post-callosotomy.

DT-FT ROI placement in the inferior-most white matter of the frontal lobes is required to evaluate possible integrity of the rostrum of the corpus callosum when using axial source images, as evidenced in one of the cases in this series (Fig. 3) where the frontopolar deep white matter ROI did not identify the persistent intact rostral fibers. Accordingly, we feel that at least four ROIs in three separate transaxial planes are required for each hemisphere. Coronal DTI acquisition produced similar results as axial acquisition in the cases in this series where both were available. Sagittal ROIs were not performed on a prospective clinical basis due to limitations in the clinical software used; however, sagittal ROI analysis of the axial DTI data was performed in a retrospective manner on a separate workstation, and a single parasagittal ROI may be able to appropriately evaluate the entirety of the corpus callosum. In cases whether there is severe parenchymal abnormality such as encephalomalacia, the ROI placement in the less diseased hemisphere is typically easier to place to depict commissural tracts.

Approximately 70 patients in our series did not have postoperative MRI which included DTI, typically those with callosotomy performed prior to 2010 who did not have follow-up studies since instituting DTI at our center on specific cases (2010) and on all cases (2011). Going forward, nearly all patients undergoing callosotomy at our institution will have preoperative and postoperative DTI available for comparison. Additionally, some of the earlier patients in our series who underwent callosotomy prior to instituting DTI may return for follow-up MRI. In patients where there is preoperative and more than one postoperative MRI with DTI available, it will be possible to perform serial evaluation of FA in the deep white matter to quantify changes that would be expected due to Wallerian degeneration [11, 13–15].

Wallerian degeneration is known to decrease FA. It is possible that on a voxel level, Wallerian degeneration may decrease FA below the chosen deterministic FACT threshold. This could artifactually result in DT-FT truncation of fibers, preventing detection of intact fibers. DT-FT performed late after callosotomy, at which time there were changes of Wallerian degeneration evident, showed fiber tracts extending to the margin of the callosotomy, suggesting that this may not prevent detection of intact commissural fibers. This could be due to the very high FA within the corpus callosum to begin with, which may remain above clinically relevant FACT thresholds even after Wallerian degeneration.

Eight of 32 patients with post-callosotomy DTI had more than one MRI with DTI examination. Of these, six of eight had their initial study in the immediate postoperative period; however, no differences were seen in the structural or DT-FT extent of callosal transection. This suggests that early postoperative DTI may be able to be reliably performed without concern about susceptibility artifact from blood products and pneumocephalus degrading the results. Evaluation of DTI source data should be performed as a quality control to ensure that there is no artifactual signal degradation at the site of the callosal transection.

Appropriate analysis of commissural disconnection requires an understanding of commissural anatomy and topography. Detailed studies and reviews exist in the literature [1, 16]; however, a brief review is worthwhile. The fibers of the corpus callosum carry homotopic commissural fibers between the cerebral hemispheres. The genu and rostrum contain fibers connecting the frontal poles, including the fibers of the forceps minor. The body of the corpus callosum largely contains fibers arising from the frontal lobes. The isthmus of the corpus callosum, often overlooked as a discrete subsegment, contains fibers arising from the perirolandic cortex. The splenium of the corpus callosum has at least two distinct subsets of fibers [1]. There are fibers arising from the precuneus and the occipital lobes, including those fibers of the forceps major, and there are hippocampal commissural fibers which have a distinct developmental origin from the remainder of the corpus callosum.

Not all patients in this series had preoperative DTI; however, this is not a major limitation on this qualitative analysis as structural imaging showed an intact corpus callosum in all cases. The corpus callosum has an organized topographic orientation [16], which has a high FA due to parallel fibers [17]. There are known structural and DTI changes that occur after callosotomy [11, 15]. Future work on quantitative analysis of deep white matter FA, as well as axial and radial diffusivity, would benefit from preoperative DTI and multiple time points of postoperative DTI to quantify the microstructural changes that occur after transection with the goal of improving DT-FT processing thresholds.

Technical limitations include DTI acquisition parameters, including voxel size and number of encoding directions, as well as DT-FT deterministic thresholds; however, these are inherent to all DTI studies which are collectively being validated on clinical and experiential grounds given difficulty in establishing a true gold standard for confirmation. The parameters used in this study have been used extensively in other clinical and research studies, predominantly related to brain tumors [10, 18] and traumatic brain injury [19–21], and are felt to be clinically reliable. Future advances in diffusion spectrum imaging and diffusion kurtosis imaging may further improve detailed characterization. Susceptibility effect related to postoperative hemorrhage in the surgical bed and cytotoxic edema along the margins of the transection could pose a potential problem for DT-FT in some cases. In our patient subset, no substantial limitations on the grounds of hemorrhagic artifact were present, and findings from early and late postoperative images were concordant in patients where both were available. Seizure outcome was not analyzed for the purpose of this retrospective analysis.

In the modern world, patients and families move frequently, requiring re-establishment of care for the patient with refractory epilepsy (the group undergoing callosotomy). In addition, the patient may transition from a pediatric to an adult neurologist for ongoing epilepsy care as they age. Often, the family or caregiver may not know the extent of the prior corpus callosum section. While this can be estimated from an anatomic MRI, using DTI and DT-FT is helpful to document the extent of the operative commissural disconnection in patients who previously underwent corpus callosotomy. This information will facilitate better decision making in this group of patients with refractory generalized epilepsies, who likely will have the need for ongoing treatment of their epilepsy.

Conclusion

Diffusion tensor fiber tracking is a robust method to evaluate the extent of commissural transection after corpus callosotomy. Residual white matter tract integrity can be a clinically significant discovery that may alter the therapeutic plan in patients with persistent generalized seizures. It provides early feedback to the neurosurgeon, which may improve the technique. It also allows the epileptologist to more accurately predict response to the surgery in the immediate postoperative period, providing a more informed prognosis for families.

Conflict of interest We declare that we have no conflict of interest.

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