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Diffusion-tensor imaging–guided tracking of fibers of the pyramidal tract combined with intraoperative cortical stimulation mapping in patients with gliomas

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Object. The goal of this study was to use diffusion-tensor (DT) magnetic resonance (MR) imaging to track fibers combined with cortical stimulation mapping to delineate descending motor pathways. Subcortical localization of motor pathways in relation to a glioma may provide critical information to guide tumor resection and prevent surgical morbidity.

Methods. Eleven adult patients harboring gliomas underwent MR imaging 1 day prior to image-guided intraoperative cortical motor mapping and tumor resection. Screens depicting 27 cortical motor sites on a surgical navigation system were saved to launch DT imaging of fiber tracks of descending motor pathways. The position and organization of motor tracts were visualized by fiber tracking. Tracks from 16 motor stimulation sites followed descending pathways from the precentral gyrus, through the corona radiata and internal capsule, and into the cerebral peduncle. These tracks were also observed on DT images to diverge along crossing white matter bundles (four patients) and to terminate or deviate in regions of peritumoral vasogenic edema (five patients).

Conclusions. The use of precise intraoperative cortical mapping information and DT images of fiber tracks can reveal the course of motor pathways beneath the cortex. The subcortical fiber tracks generated are consistent with the known anatomical course and somatotopic organization of the motor tract in relation to its cortical origins. Tracking fibers by using DT imaging in combination with functional localization has the potential to reduce surgical morbidity by revealing subcortical connections of the functional cortex.

KEY WORDS • diffusion-tensor imaging • fiber track • intraoperative stimulation mapping • neoplasm

REMOVING glial neoplasms within or adjacent to functional pathways serving motor functions carries with it a risk of injuring subcortical fibers emanating from the primary motor cortex. Before removing a lesion in this critical area, functional mapping with the aid of magnetic source imaging, functional MR imaging, or intraoperative electrical stimulation of the exposed cortex can be used to identify the rolandic cortex.[23–25] These mapping strategies provide a safety margin for the surgeon during radical tumor resection; however, localization is largely limited to the gray matter. Intraoperative stimulation mapping can be performed to identify subcortical motor pathways subserving the motor cortex, although this procedure is complex and time-consuming.[5,8,17] The ability to localize subcortical pathways preoperatively by using an imaging modality would be highly advantageous, especially if these data are incorporated into a navigational workstation to be used during tumor removal.

Magnetic resonance DT imaging is a noninvasive method of studying the structure of human neuronal fibers. Diffusion-tensor imaging captures the local water diffusion characteristics of tissue and models the 3D distribution of brownian motion as the diffusion tensor.[1,2] The diffusivity of water is affected by the orderly arrangement of neuronal fiber structures such as axonal membranes.[4] The three orthogonal principal directions of diffusion, termed the "eigenvectors," can be calculated from the diffusion tensor for each MR imaging voxel. The primary eigenvector and associated eigenvalue indicate, respectively, the direction and magnitude of greatest water diffusion. In highly collimated neuronal bundles with minimal fiber crossing, such as the internal capsule or corpus callosum, water diffusion will be anisotropic, with the primary eigenvector oriented parallel to the axons.[16,21]

Fiber tracking, or tractography, has emerged as a method of obtaining the primary eigenvector of the diffusion tensor to follow a neuronal tract in three dimensions from voxel to voxel through the human brain. Analysis of previous study data has demonstrated the ability to track pathways of interest in three dimensions by using DT imaging.[3,7,10,19] To delineate a specific neural pathway in the complex architecture of the brain requires some prior knowledge of the fiber tract origin. The purpose of this study was to use motor sites

Abbreviations used in this paper: DT = diffusion-tensor; FSE = fast–spin echo; MR = magnetic resonance; SLF = superior longitudinal fasciculus; SPGR = spoiled gradient–recalled acquisition; 3D = three-dimensional.

TABLE 1

*Summary of cases and tracking results**

Case No.	Age (yrs), Sex	Tumor Location & Type†	Motor Site & Type	Fiber Tracking Result
1	41, M	lt frontal Grade 2 gemistocytic astrocytoma	mouth 1	descends through CR & IC to CP
			mouth 2	descends through CR & IC to CP
			jaw	descends through motor gyrus to CR
2	32, F	lt parietooccipital Grade 2 oligodendroglioma	finger flexion	descends through motor gyrus & diverges posteriorly in region of edema
			hand, wrist, thumb, & finger flexion	descends through motor gyrus & terminates in region of edema
			wrist & finger flexion	descends through motor gyrus & diverges posteriorly in region of edema
3	33, F	lt temporal Grade 2 oligodendroglioma, recurrence of Grade 3 oligoastrocytoma	mouth 1	descends through CR & IC to CP
			mouth 2	descends through CR & IC to CP
4	44, F	lt frontal Grade 2 oligoastrocytoma	wrist flexion	descends through motor gyrus to SLF
			hip flexion	descends through CR & IC to CP
5	40, F	rt parietal Grade 4 GBM	jaw 1	descends through CR & IC to CP
			jaw 2	descends through CR & IC to CP
6	49, M	rt frontoparietal Grade 4 GBM	hand	descends through CR & IC to CP
			index finger	descends through CR & IC to CP
			forearm	descends through CR & IC to CP
7	46, M	lt insular Grade 4 GBM	mouth 1	descends through CR & IC to CP
			mouth 2	stimulation site proximal to tumor & edema, tracks diverted posteriorly
			jaw	stimulation site proximal to tumor & edema, tracks diverted posteriorly
8	36, F	lt frontal Grade 3 anaplastic astrocytoma	mouth 1	descends through CR & IC to CP
			mouth 2	descends through CR & IC to CP
9	22, M	lt pst frontal lobe Grade 2 astrocytoma	wrist	descends through CR & IC to CP
			forearm	descends through motor gyrus to SLF
			shoulder	descends through CR & IC to CP
10	65, M	rt pst frontal lobe Grade 3 anaplastic astrocytoma	hand 1	descends through motor gyrus to SLF
			hand 2	descends through motor gyrus to SLF
11	38, M	lt Grade 3 frontotemporal anaplastic astrocytoma	tongue 1	descends through CR & IC to CP
			tongue 2	descends through motor gyrus to CR

* Cases with two different cortical stimulation sites controlling similar motor responses are numbered. Abbreviations: CP = cerebral peduncle; CR = corona radiata; GBM = glioblastoma multiforme; IC = internal capsule; pst = posterior.

† Tumors are graded according to the World Health Organization Scale II (see Kleihues, et al.).

identified on intraoperative cortical stimulation to launch DT imaging–aided fiber tracking of the subcortical motor pathways.

Clinical Material and Methods

Magnetic Resonance Imaging

This study included 11 consecutive adult patients harboring gliomas who had undergone MR imaging 1 day before intraoperative cortical motor mapping and image-guided resection. The patients consisted of six men and five women with a mean age of 40.5 years. The mix of tumor grades and locations are summarized in Table 1. Magnetic resonance imaging was performed on a 1.5-tesla Signa scanner (General Electric Medical Systems, Milwaukee, WI). The institutional review board at our medical center approved our protocol. Diffusion-tensor imaging was performed using a single-shot multislice spin echo–echo planar sequence: diffusion sensitization 1000 seconds/mm^2, TR 10,000 msec, TE 100 msec, mean acquisitions four to six, slice thickness 2 to 2.3 mm, no gap between slices, and voxel volume 4.5 to 9 mm^3. Six diffusion gradient directions and one image set without diffusion weighting (b = 0 second/mm^2) were obtained. Acquisition coverage extended from the cerebral peduncle to the brain vertex. The diffusion tensor, eigenvectors, eigenvalues, and relative anisotropy were calculated using in-house software written in C, as described elsewhere.[1] Both T_2-weighted FSE and postcontrast T_1-weighted SPGR images were acquired for use with the image-guided surgical navigation system.

Cortical Stimulation and Stereotactic Registration

Stimulation was directly applied to the patient's exposed cortex to identify the cortical sites of motor function origin. Stimulation was performed using a 5-mm-wide bipolar electrode that produced a small electric current to depolarize cortical neurons. This elicited motor responses in muscle groups in the extremities, which we monitored through electromyographic recordings.[27] Motor points on the cortex were stereotactically identified on FSE or SPGR MR images during the operation but before resection with the aid of the StealthStation surgical navigation system (Medtronic, Broomfield, CO). The stereotactic probe was positioned on the stimulation site and viewed on the navigation system's screen (Fig. 1A). Screens from the navigation system showing axial, coronal, and oblique trajectory views of the stimulation point were saved for later use with DT imaging–guided fiber tracking.

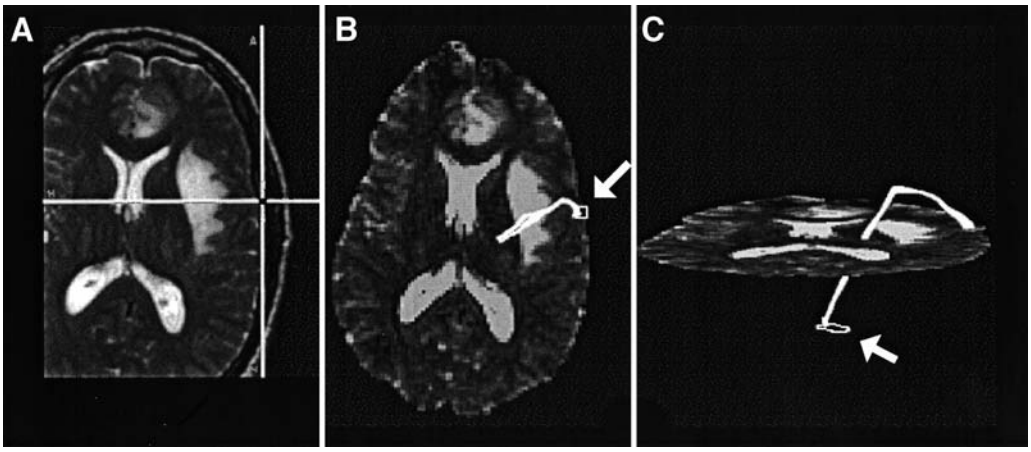

FIG. 1. Case 11. Fiber tracking from a stereotactically identified motor site. A: Surgical navigation screen demonstrating a tongue motor site in a patient. The center of the cross-hairs indicates the position of the stereotactic probe tip on T_2-weighted FSE MR images. B: Corresponding axial echo planar image from the DT imaging set revealing the square starting region *(arrow)* and 3D fiber tracks (white). C: Coronal projection of fiber tracks connecting the cortex with the cerebral peduncle. The outline of the regions drawn in the cerebral peduncle for filtering the fiber tracks is shown *(arrow)*.

Fiber Tracking

After completing the surgery, we downloaded from the navigation system screens showing the location of stimulation sites on FSE or SPGR images. Both the navigation and DT images were acquired during the same MR imaging study so that a common coordinate system existed. Stimulation points were transferred to the echo planar DT imaging volume by using the common coordinate system. The transferred stimulation sites were visually checked to ensure an accurate match between echo planar DT images and navigational image volumes. A 6×6–mm square drawn at the stimulation site on the echo planar image without diffusion weighting was used as the starting region for DT imaging–aided fiber tracking (Fig. 1B). Fiber tracking trajectories were launched from multiple points within every voxel in the starting region. Each voxel inside the starting region contained 64 evenly spaced starting points distributed in a $4 \times 4 \times 4$ cubic grid. Fiber tracks were generated from each individual starting point within the stimulation site.

Diffusion-tensor imaging–guided fiber-tracking software was written in Interactive Data Language (Research Systems, Inc., Boulder, CO) and run on a workstation (Sun-Blade 150; Sun Microsystems, Santa Clara, CA). The fiber tracking method was based on fiber assignment by continuous tracking.[19] An algorithm computed a 3D trajectory in continuous space by beginning at a user-defined starting point and running parallel to the principal eigenvector. When the 3D fiber track enters a different voxel, the fiber track's direction is altered to match the direction of the new voxel's primary eigenvector. The 3D fiber track is allowed to continue from voxel to voxel until it enters a region of relative anisotropy less than 0.014, turns an angle greater than 70°, or exits the brain. Generating such fiber tracks from a stimulation site required less than 1 minute of computer processing. The diffusion-tensor imaging fiber tracks were visualized in three dimensions by using Interactive Data Language and the 3D Slicer program (MIT Artificial Intelligence Laboratory and Surgical Planning Lab at Brigham & Women's Hopital, website: http://www.slicer.org).

In each case, the cerebral peduncle was identified and manually outlined on the echo planar images. If DT imaging–demonstrated fiber tracks reached the cerebral peduncle, false tracks not passing through the cerebral peduncle itself were excluded[7] (Fig. 1C). In cases in which no DT imaged fiber tracks reached the cerebral peduncle, all generated tracks were retained for analysis.

Results

A total of 28 cortical motor stimulation sites were identified in the 11 patients. A mean of 2.6 motor sites (range two–three motor sites) were found in each patient. Observed muscle responses included mouth, tongue, shoulder, arm, wrist, hand, finger, trunk, and leg motions. These intact motor responses were spread over the motor homunculus and represented both the corticospinal and corticobulbar tracts. One shoulder stimulation site could not be used for fiber tracking because it was at the extreme vertex of the brain, and the axial surgical navigation system image contained no brain landmarks such as sulci that could be located on the echo planar images. Figure 1 features a tongue motor stimulation site transferred from the surgical navigation system to the DT imaging set and the resulting fiber tracks connecting the cortex with the cerebral peduncle.

Four patients exhibited preoperative motor function impairments. The patients in Cases 2 and 5 exhibited motor weakness. The patient in Case 4 had upper-extremity shaking and the patient in Case 6 exhibited upper-extremity pronator drift. The remaining patients showed no motor deficit prior to surgery.

Motor Pathway With DT Imaging–Guided Fiber Tracking

Results of fiber tracking from each of the stimulation points are summarized in Table 1. Based on results of DT imaging studies, fiber tracks from 16 motor sites coursed from the cortex, into the corona radiata and the posterior limb of the internal capsule, and entered the cerebral pedun-

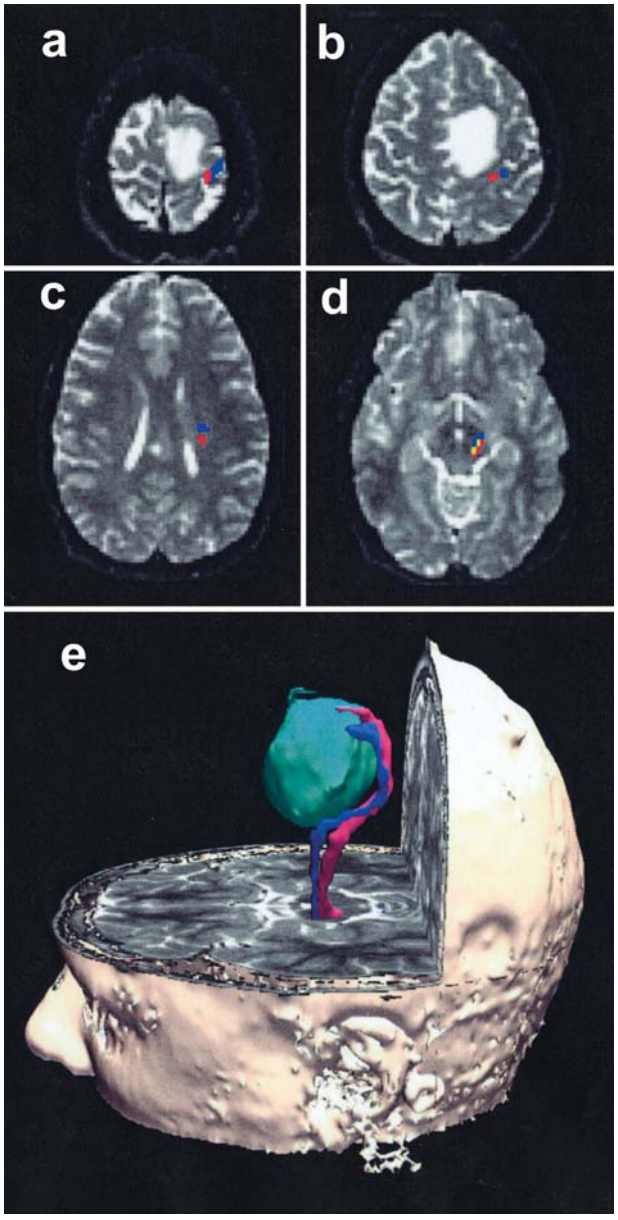

FIG. 2. Case 9. Subcortical organization of fiber tracks demonstrated on DT imaging. Fiber tracks are shown intersecting different axial levels. Tracks from shoulder (red) and wrist (blue) motor cortex stimulation sites descend to the cerebral peduncle. Overlapping voxels appear in yellow. a: Level of shoulder stimulation site. The wrist stimulation site was superior to the shoulder site. b: Motor tracks passing by the border of the tumor. The corticospinal tract is deviated posterolaterally by the tumor mass. c: Corticospinal tracts descend through the centrum semiovale. The DT imaging fiber tracks have rotated, with the shoulder track situated directly posterior to the wrist track. d: The shoulder track lies medial to the wrist track in the cerebral peduncle. e: Three-dimensional view of fiber tracks in relation to the tumor (green). The two tracks are seen twisting around each other as they descend through the internal capsule.

cle. Fiber tracks from two sites only reached the corona radiata. The pathway of the descending fiber tracks matched the known anatomical locations of the corticospinal and corticobulbar tracts.[18]

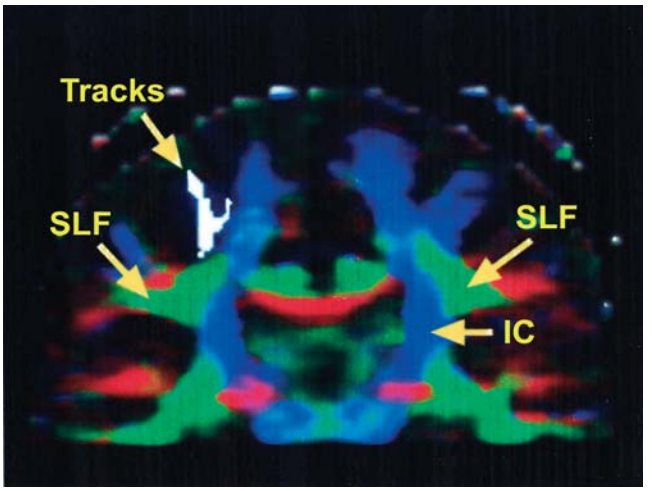

FIG. 3. Case 10. Coronal slice obtained through fiber tracks (white) terminating at the SLF. Directionality of the primary eigenvector is color coded: anteroposterior, green; left–right, red; and inferosuperior, blue. The anteroposteriorly directed fibers of the SLF appear as green triangular regions *(arrows)* in both the left and right hemispheres. The descending motor pathway tracks (hand no. 2, depicted in white) intersects or passes very closely to the SLF, preventing DT imaging–demonstrated fiber tracking from entering the internal capsule.

Fiber tracks descending from the precentral gyrus through the corona radiata were organized somatotopically, mirroring the cortical motor homunculus. The corticospinal tract is known to twist as it descends through the corona radiata and internal capsule.[18] In the patient in Case 9, this twisting was also observed in the DT imaged fiber tracks (Fig. 2). The motor cortex representation for the shoulder is superolateral to the wrist representation. As the DT imaging–demonstrated tracks enter the cerebral peduncle, the wrist and shoulder tracks have switched positions; the wrist track lies medial to the shoulder track.

Fiber Tracking and Crossing Neuronal Fibers

In four cases in which the fiber tracks did not connect the cortex with the internal capsule, the tracks diverged along the SLF. These tracks originated at wrist, forearm, and two hand motor stimulation sites. The SLF courses anteroposteriorly through the centrum semiovale and intersects or passes very closely to portions of the pyramidal tract, particularly those axonal tracts from the upper extremity. Fiber tracks in these four cases were observed coursing from the cortex, through the precentral gyrus along the pyramidal tract, and into the centrum semiovale (Fig. 3). Instead of descending into the internal capsule, however, these four tracks entered the SLF and were diverted either anteriorly or posteriorly.

Fiber Tracking and Edema

Five of the fiber tracks that did not reach the internal capsule diverged and terminated in regions of peritumoral vasogenic edema exhibiting low anisotropic diffusion. Figure 4 features a fiber track from a cortical site in a patient (Case 2) initiating wrist and finger flexion, which enters a region of edema anterior to the tumor. Tumor and edema infiltra-

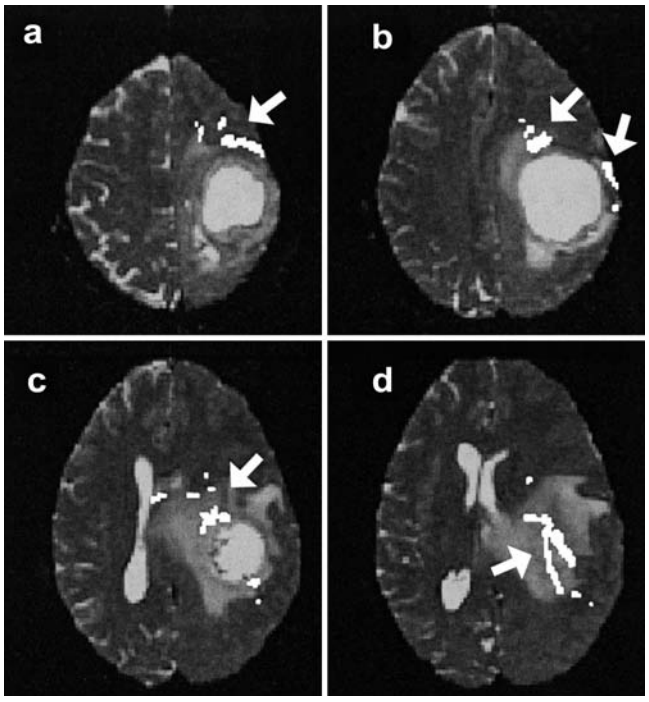

FIG. 4. Case 2. Diffusion-tensor MR images demonstrating fiber track divergence in regions of edema. a: Fiber tracks *(arrow)* from a wrist/finger motor site initially descend through the precentral gyrus. b: Fiber tracks *(arrows)* descend parallel to the tumor border and enter a hyperintense region of edema (c). d: The tracks *(arrow)* are deviated posteriorly and are not consistent with the known location of the pyramidal tract at this level.

tion of the pyramidal tracts is evident from decreased anisotropy and hyperintensity on T_2-weighted images. The fiber tracks initially descend through the precentral gyrus and corona radiata anterior to the tumor. As the track proceeds through the regions of edema, it fragments and courses posteriorly.

Discussion

Diffusion-tensor imaging–demonstrated fiber tracks originated at the motor cortex stimulation sites and revealed the subcortical connectivity of the pyramidal tract. The rostral segment of the subcortical motor tract was delineated in all cases.

Analysis of the results indicates that the DT imaging–demonstrated fiber tracks maintain some degree of functional specificity. The descending tracks were not observed on DT imaging to diverge greatly or to encompass the entire pyramidal tract. The human motor cortex homunculus is topographically organized by function, as observed through cortical stimulation.[22] The underlying architecture of the subcortical white matter is an extension of the organization of the cortex. The motor tracts form a converging sheet as they descend into the internal capsule. The organization of this sheet by function was observed with DT imaging–demonstrated fiber tracking. The motor tracts spiral as they descend from the cortex to the cerebral peduncle. In one case, fiber tracks from two stimulation points were observed to twist around each other in the corona radiata and internal capsule. The tracks were consistent with the known structure and somatotopic organization of the motor functions associated with the cortical origins of the track.[18]

In previous studies investigators have used DT anisotropy maps and directional color-coded images to determine the relationship of tumor to surrounding white matter.[14,26] Tracking neuronal fibers based on DT imaging can supplement other techniques by extending functional knowledge of the cortex to subcortical regions. Because a large tumor can distort the surrounding brain anatomy, it may be unclear which gyrus contains the descending motor pathway. By following white matter fasciculi from known motor points on the cortex, the position of the pyramidal tract at the level of the tumor can be elucidated. Even if it is not possible to follow the pyramidal tract completely to the midbrain, fiber tracking with the aid of DT imaging may still be valuable in delineating the motor pathway near the borders of a tumor.

Fiber tracks that entered regions of edema or tumor were prone to be misrepresented on DT imaging because of low anisotropy indicating uncertainty of the primary eigenvector direction. Edema increases the isotropic characteristic of diffusion and degrades the ability of DT imaging to reveal white matter tracts. Thus, fiber tracks entering regions of edema could be misdirected by eigenvectors not accurately representing the directionality of axonal bundles. Even though the fiber tracks sometimes terminated or diverged in regions of edema, it was demonstrated through motor stimulation that the pyramidal tract was functionally intact within these regions. Thus, in cases in which DT imaging does not reveal neuronal pathways in a lesion, no immediate conclusion can be made about whether the tracts are destroyed or functionally intact.

The error in fiber tracking trajectories are known to accumulate as a function of distance, step size, algorithm, signal-to-noise ratio data, track geometry, and ambient white matter architecture.[15,20] Our results demonstrate a high degree of precision, which is partly due to tracking a convergent pathway from the cortex to the midbrain. Conversely, tracking from the midbrain to the cortex would produce more errors in the final destination of the tracks. Therefore, cortical localization of functional regions enables association of function with structural connectivity and is optimal in terms of delineating fiber tracts that converge subcortically.

Four DT imaging–demonstrated fiber tracks from upper-extremity motor sites were observed to deviate from the pyramidal tract when encountering fiber crossings. Portions of the pyramidal tract can intersect the SLF at the level of the centrum semiovale. When white matter bundles intersect or pass very close to one another, the directionality of the primary eigenvector can be ambiguous and DT imaging–guided fiber tracking can indicate false connectivity. Only fiber tracks from upper-extremity motor sites were observed entering the SLF. The section of the motor cortex controlling upper extremities is superior and lateral to the SLF. The descending white matter pathways from this region of cortex curve inferiorly and medially through the corona radiata and can intersect the SLF. Motor skills of the hand and arm are important to preserve during resection, and the limitation caused by interference from the SLF must be considered when following tracks from these motor sites. To prevent tracks from being diverted from the pyramidal tract, the SLF can be segmented and DT imaging–demonstrated tracks terminated prior to encountering the

SLF. Even though fiber tracking would be halted, the pyramidal tract between the cortex and SLF could still be delineated and could be useful for surgical planning.

The dominant factors affecting the validity of DT imaging–guided fiber tracking in following the motor tract are crossing fibers and lesion location. Crossing fibers in the centrum semiovale are expected to complicate fiber tracking of upper-extremity motor pathways in all patients. Nonetheless, the location and geometric configuration of lesions differ in each case. Factors such as preoperative functional deficit, tumor grade, and patient age were not observed to affect the ability to delineate motor pathways. From the results of previous studies, one can infer that DT imaging–guided fiber tracking can be performed to delineate motor pathways in patients with congenital hemiparesis.[9] It was found that motor pathways affected by hemiparesis exhibited lower anisotropy than those in contralateral tracts; however, fiber tracking was successful in both motor pathways.

The technique described herein—fiber tracking beginning at cortical stimulation sites—may be implemented in the operating room.[6,12] Although motor mapping by cortical stimulation is performed after the surgical procedure has begun, DT imaging–guided fiber tracking could be completed in approximately 30 minutes, which is rapid enough to be of use during the subcortical resection. The necessary steps include translating motor points from the 3D volumetric MR images on the surgical navigation system to the 3D DT images, performing the DT imaging–guided fiber tracking, and then overlaying the pathway back on the 3D volumetric images. A process involving these tasks in the operating room would enable the neurosurgeon to identify the subcortical position of specific motor functions in relation to the border of the resection cavity. Further validation of pathways delineated by DT imaging–guided fiber tracking is required for the technique to be relied on for determining the extent of tumor resection.[16] Nonetheless, fiber tracking can currently be used to reduce surgical time and patient morbidity by guiding subcortical stimulation mapping of resection margins.

An analysis of the extent of the usefulness of DT imaging–guided fiber tracking is currently under way with the aid of preoperative magnetic source imaging or functional MR image localization to generate tracks for subsequent use during image-guided surgery. In addition, fiber tracking is also being used to examine the subcortical connectivity of the somatosensory pathways and language pathways.[11]

Conclusions

Identifying the position of the pyramidal tract relative to all tumor borders is critical to preserve motor function during surgery to remove the lesion. The combination of precise intraoperative cortical mapping information and DT imaging–guided fiber tracking can reveal the course of motor pathways beneath the cortex. The subcortical fiber tracks generated are consistent with the known anatomical course and somatotopic organization of the pyramidal tract. Motor pathways displaced by the tumor mass were readily observed. Nonetheless, the brain tumor and its surrounding vasogenic edema can alter the diffusion characteristics of functional white matter, thus interfering with the ability of DT imaging–guided fiber tracking to delineate a white matter pathway fully. Crossing white matter fibers can also divert DT imaging–demonstrated fiber tracks from portions of the descending motor tract to another pathway such as the SLF. Within these limitations, this new imaging technique allows functional cortical localization to be extended to the subcortical white matter pathways.

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