NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 25 (2005) 424–429

Fiber-tracking does not accurately estimate size of fiber bundle in pathological condition: initial neurosurgical experience using neuronavigation and subcortical white matter stimulation

Manabu Kinoshita,[a] Kei Yamada,[b,1] Naoya Hashimoto,[a,*] Amami Kato,[a] Shuichi Izumoto,[a] Takahito Baba,[a] Motohiko Maruno,[a] Tsunehiko Nishimura,[b,1] and Toshiki Yoshimine[a]

[a]Department of Neurosurgery, Osaka University Medical School, Yamadaoka, 2-2, Suita, Osaka 565-0871, Japan
[b]Department of Radiology, Kyoto Prefectural University of Medicine, Kajii-cho, Kawaramachi Hirokoji Agaru, Kamigyo-ku, Kyoto City, Kyoto 602-8566, Japan

Received 19 April 2004; revised 21 June 2004; accepted 29 July 2004

The fiber-tracking method enables in vivo visualization of the white matter tracts of the brain using a diffusion tensor MR imaging technique. While this method represents a promising tool in the field of neurosurgery, especially when confronted with brain tumors in eloquent areas, its reliability remains unknown. We present here our preliminary validation of tractography in human subjects harboring brain tumors by comparing the results produced by neuronavigation and electrical white matter stimulation in two patients with gliomas in the eloquent area. Although we were able to visualize the pyramidal tract with the fiber-tracking technique, the images failed to present the actual size of the fiber bundles. Here we discuss the advantages and limitations of fiber-tracking in the field of neurosurgery.

Keywords: Diffusion tensor imaging; DTI; Fiber-tracking; Eloquent area brain tumors; Neuronavigation system; Electrical white matter stimulation

Introduction

Surgery of brain tumors involving the so-called "eloquent areas" remains challenging. Awake surgery, intraoperative navigation systems, and intraoperative electrical and chronic intracranial electrical stimulation with grid or strip electrodes have been proposed as efficient tools for such procedure (Duffau et al., 2003; Kato et al., 1991). Recently, not only the preservation of cortical functions but also of the subcortical functions has been emphasized for better operative results. With the advent of MR imaging, it is now possible to visualize the white matter fibers of the brain with diffusion tensor images (DTI), and this technique is known as "fiber-tracking" or "tractography" (Conturo et al., 1999; Gossl et al., 2002; Mori et al., 1999; Witwer et al., 2002; Yamada et al., 2003b). Use of this technique, anisotropy, and orientation of water molecule diffusion properties in the brain can be recorded, and the obtained orientation information can be used to delineate the white matter tracts. While fiber-tracking images have been used for neurosurgical planning (Coenen et al., 2001, 2003; Hendler et al., 2003; Holodny et al., 2001; Wieshmann et al., 2000), the validity of this technique remains to be confirmed. In this two case series, we attempted a validation of fiber-tracking images used for neurosurgical planning of gliomas located at the eloquent areas of the brain, combined with intraoperative navigation and cortical and subcortical white matter electrical stimulation. We present our findings on the reliability, limitations, and pitfalls of this new imaging technique.

Materials and methods

Case presentation

Case 1 (Figs. 1–3): This 66-year-old woman with a right frontal brain tumor was referred to our facility for treatment. MRI study showed a ring-enhanced mass in the right frontal lobe that involved part of the precentral gyrus. She underwent preoperative fiber-tracking of sensory and motor tracts and the tumor was completely resected with the aid of intraoperative neuronavigation and electrical subcortical stimulation.

Case 2 (Figs. 2 and 4): This 11-year-old girl presented with a recurrent anaplastic ependymoma in the right parietal lobe that contained a cystic component and involved the primary motor cortex. She also underwent preoperative fiber-tracking of sensory and motor tracts and the tumor was completely resected with the aid of intraoperative neuronavigation and electrical subcortical stimulation.

* Corresponding author. Fax: +81 6 6879 3659.
E-mail address: nhashimoto@nsurg.med.osaka-u.ac.jp (N. Hashimoto).
[1] Fax: +81 75 251 5840.
Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2004.07.076

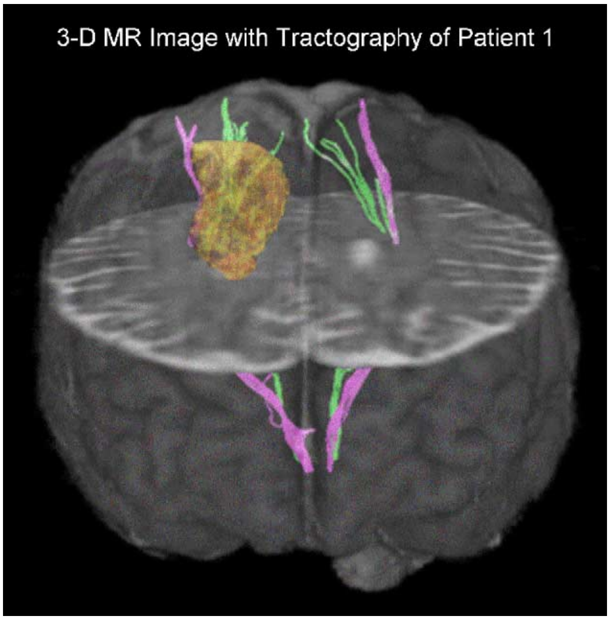

Fig. 1. (Patient 1) Three-dimensional reconstruction of the MR image with tractography. The tumor involving the right frontal lobe is colored in orange, the pyramidal (corticospinal) tract in purple, and the sensory tract in green. The tumor posteriorly compresses both the pyramidal and sensory tract.

MRI data acquisition for fiber-tracking

MR imaging was performed as previously described (Yamada et al., 2003a). In both patients, preoperative MR images for fiber-tracking were obtained with a 1.5-T whole-body scanner (Gyroscan *Intera*, Philips Medical Systems) with a gradient strength of 30 mT/m. A single-shot echo-planar imaging technique was used for DTI (repetition time / echo time = 6000/88 ms) with a motion-probing gradients in 32 orientations, a field of view of 230 mm, b values of 0 and 800 s/mm^2, and image averaging of 2 times. The recorded data points were 128 × 53 with the parallel-imaging technique. The true resolution of the acquired images was equivalent to 128 × 106. A total of 36 slices were obtained with a thickness of 3 mm without interslice gaps.

Fiber-tracking technique

We transferred the DTI data to an off-line workstation for analysis. Data were analyzed with Philips Research Integrated Development Environment (PRIDE) software written in Interactive Data Language (IDL™). Diffusion tensor elements, including vectors and anisotropy at each voxel, were calculated using a previously described method (Yamada et al., 2003b). Translation of eigenvectors into neuronal trajectories was achieved by a technique known as Fiber Assignment by Continuous Tracking (FACT) method, which was first described by Mori et al. (1999).

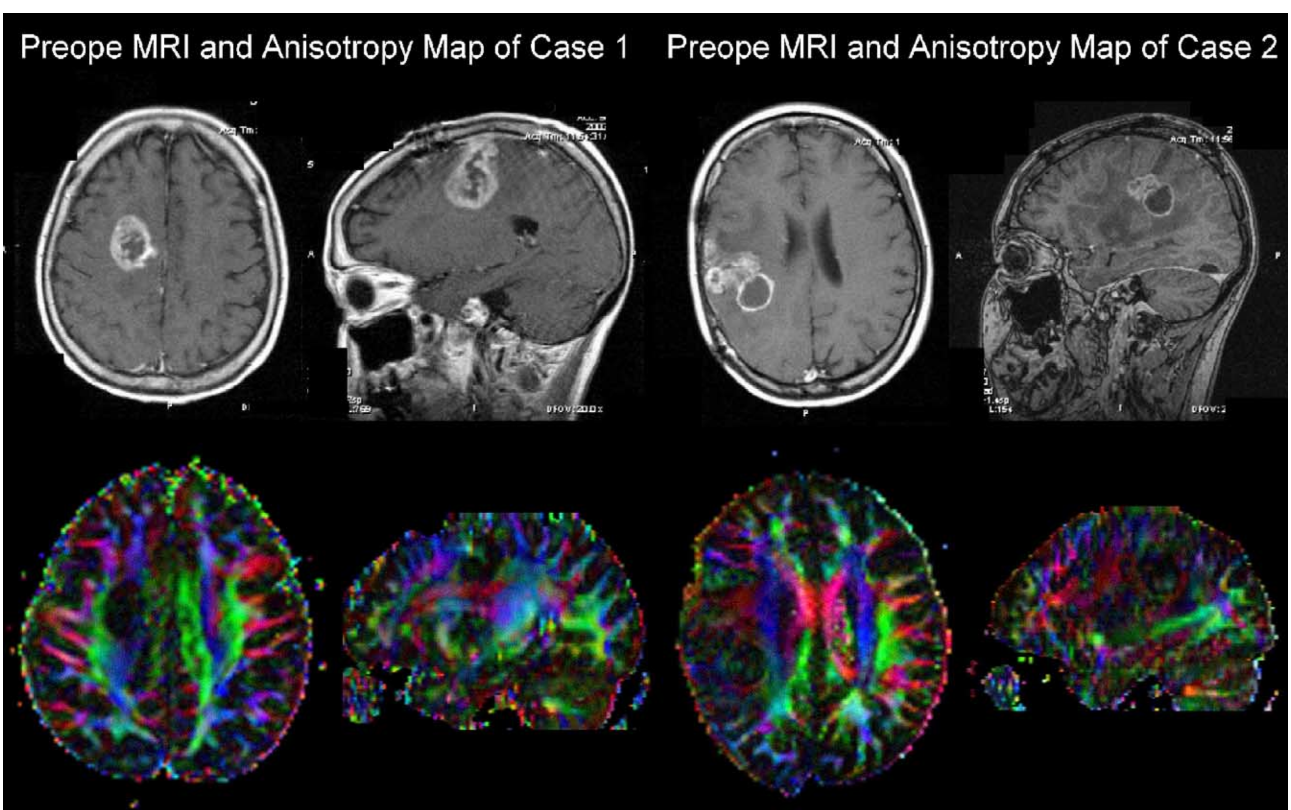

Fig. 2. Preoperative sagittal and axial Gd-enhanced MR images (upper rows) and relative anisotropy maps (lower rows) of both case 1 (left two rows) and case 2 (right two rows). Each color of the anisotropy map indicates the principal eigenvector (green: anterior–posterior; red: right–left; and blue: inferior–superior). The intensity of the color correlates with the relative anisotropy.

The procedure for mapping neural connections was started by designating two arbitrary regions of interest (ROI) in the 3-dimensional (3D) space on PRIDE software. Tracking was terminated when it reached a pixel with low fractional anisotropy (FA < 0.3) and/or a predetermined trajectory curvature between two contiguous vectors (inner product <0.85). Fiber tracts that passed through both ROIs were designated as the final tract of interest. The traced fiber tracts in this study included the motor and sensory pathways. ROIs for depicting the motor tract were placed at the ventral pons and motor cortex. Likewise, ROIs for the sensory tract were placed at the dorsal pons and sensory cortex.

Intraoperative neuronavigation system

In case 1, we used a magnetic field (CANS: Shimadzu, Kyoto, Japan), and in case 2, an optical neuronavigation system (EVANS: Tomiki, Ishikawa, Japan). In both cases, 1.4 mm thin-slice sagittally sectioned MR images were used for navigation.

Intraoperative electrical cortical and subcortical stimulation

For intraoperative direct electrical motor cortex and subcortical stimulation, an evoked-potential measuring system (Neuropack 8; Nihon-Kohden, Tokyo, Japan) was used. We delivered a standard train of 50 stimuli at 480 Hz stimulation frequency. Stimulation with a maximum of 10 mA and duration of 0.2 ms was applied to both the motor cortex and the subcortical white matter via a bipolar stimulation electrode. Motor responses were recorded with epidermally placed dish electrodes from the musculi biceps brachii, m. tricipitis brachii, m. flexor carpi ulnaris, m. extensor carpi ulnaris, and m. flexor pollicis brevis of the upper extremity, and the m. quadriceps femoris, m. biceps femoris, m. tibialis anterior, and m. gastrocnemius of the lower extremity. To record the motor response, where necessary, stimulation was incrementally increased at 1 mA from 5 to 10 mA. Recording was possible from either the upper or lower extremities. After anatomically identifying the precentral gyrus by neuronavigation just after dural opening and by referring to the fiber-tracking images, cortical stimulation was applied and the precentral gyrus was functionally confirmed. In both patients there was a match of anatomical and functional identification. During tumor resection, white matter subcortical stimulation was delivered at points where, based on fiber-tracking images, the pyramidal tract was considered to be close.

Operation and results

In case 1, the precentral gyrus was successfully identified, both anatomically and functionally. Movement of the upper and lower extremities was confirmed by electrical motor cortex stimulation. The contrast-enhanced parts of the tumor depicted on the monitor of the neuronavigation system were uneventfully removed. The histological diagnosis of intraoperative frozen sections was glioblastoma multiforme. At the deepest site of the tumor, where the pyramidal tract was considered closest according to the fiber-tracking images, we applied electrical subcortical white matter stimulation. At 10 mA, but not at 5 mA stimulation, movement of the upper and lower extremities was elicited (Fig. 3). Although stimulation at the maximum amplitude elicited a response, on the fiber-tracking images there still appeared to be some distance from the pyramidal tract and because residual tumor was strongly suggested from the texture of the site, we decided to remove a small amount of the residual tumor. Subsequently, the motor-evoked potential (MEP) elicited by motor cortex stimulation was reduced dramatically. Although we succeeded in resecting the entire tumor and comparison of preoperative fiber-tracking and postoperative MR images showed that the pyramidal tract was intact (Fig. 3), this patient experienced worsening of left-sided hemiparesis following surgery.

In case 2, the precentral gyrus was also anatomically and functionally identified and the tumor was totally resected with the aid of the neuronavigation system. Histologically, the neoplasm was an anaplastic ependymoma. In this case, with 8 mA stimulation movement of the left hand was identified by subcortical white matter stimulation at the deepest surgical field (Fig. 4). As the intraoperatively identified cystic portion of the tumor matched its location on the navigation system, declination by brain shift was considered minimal. Considering our experience with case 1, we left this area untouched in case 2. Postoperative MRI confirmed complete tumor removal and the patient is free of motor weakness or other neurological defects (Fig. 4).

Discussion

Brain tumors, especially gliomas, can involve both the cortex and white matter tracts. Their surgical resection requires detailed preoperative assessment of the adjacent functional anatomy, especially when the tumors are located in eloquent areas where motor, sensory, speech, and cognitive functions reside. To improve the treatment outcomes in patients with these lesions, full neuro-radiological study, neuronavigation, intraoperative cortical and subcortical electrical mapping, chronic intracranial electrical mapping, and, in some cases, awake surgery have been proposed (Duffau et al., 2003; Kato et al., 1991). Despite technical advances in the visualization of cortical functions by conventional MR imaging, functional MR (fMR) imaging, positron emission tomography (PET), and magnetoencephalography (MEG), it has remained impossible to visualize the subcortical white matter tracts. Recent advances in MR imaging techniques have made it possible to visualize white matter tracts on diffusion tensor images (DTI) and fiber-tracking images (Basser et al., 2000; Conturo et al., 1999; Gossl et al., 2002; Mori et al., 2002; Witwer et al., 2002; Yamada et al., 2003b). The usefulness of fiber-tracking for neurosurgical planning in patients with brain tumors in eloquent areas has been reported (Coenen et al., 2001, 2003; Hendler et al., 2003; Holodny et al., 2001; Wieshmann et al., 2000; Witwer et al., 2002). Coenen et al. have integrated DTI in a neuronavigation system during brain tumor surgery and reported its usefulness (Coenen et al., 2001) and Hendler et al. have combined fMR and fiber-tracking for neurosurgical planning (Hendler et al., 2003). Although there are many such studies that have emphasized its clinical usefulness, there has been no study that attempted a true validation of the obtained tractography.

We combined fiber-tracking, neuronavigation, and electrical subcortical white matter electrical stimulation in two patients operated for gliomas involving the primary motor cortex and pyramidal tract. We attempted a retrospective validation of the fiber-tracking technique by comparing preoperative tractographic

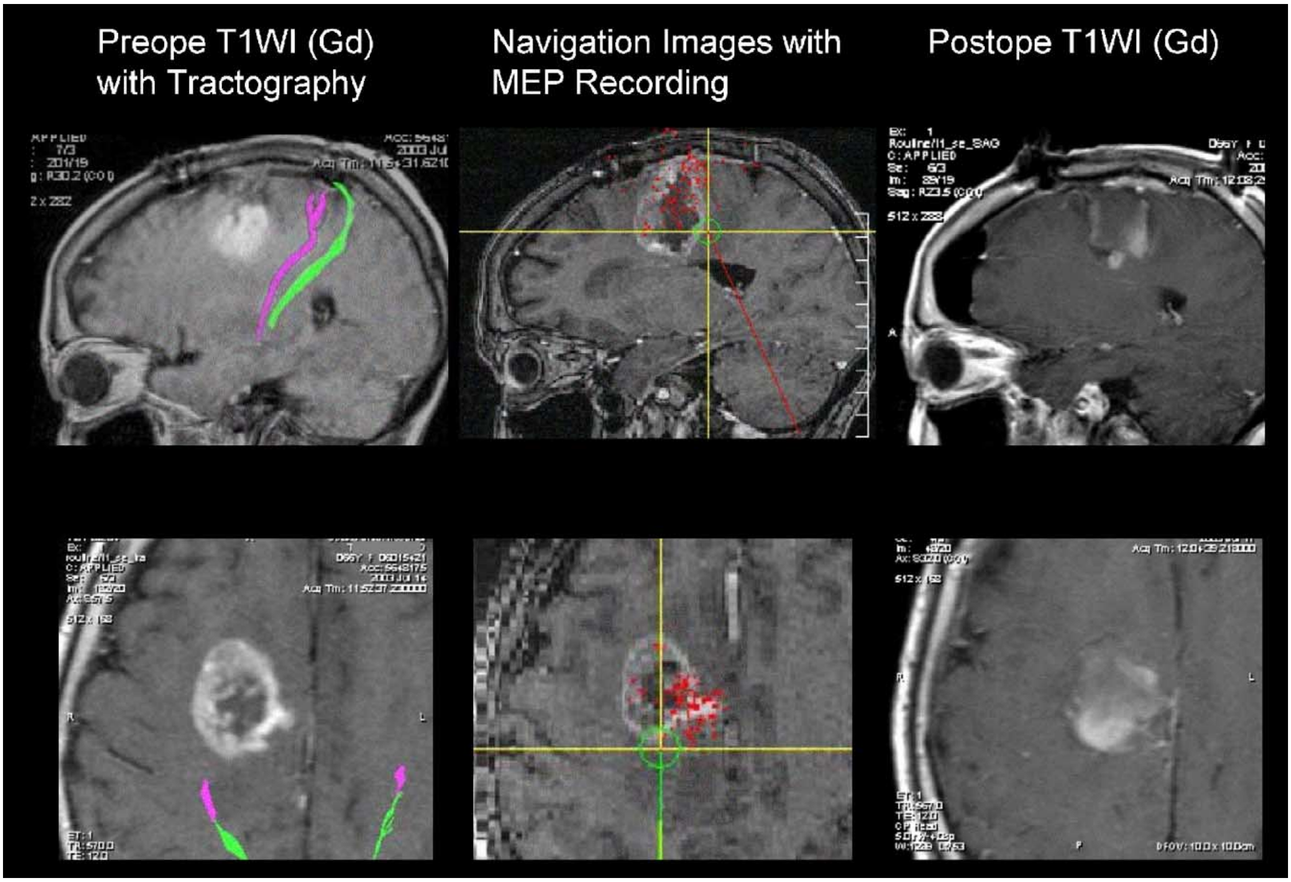

Fig. 3. (Patient 1) MR images. Left row: preoperative sagittal and axial Gd-enhanced MR images with tractography. A ring-enhanced mass is identified at the right frontal lobe. Purple and green lines represent the pyramidal and sensory tract, respectively. Both appear to be located far behind the tumor. Middle row: images obtained intraoperatively with the CANS neuronavigation system. At the target, the intersection of the yellow lines, subcortical electrical stimulation elicited a positive response. Red spots show the track of the suction tube tip and identify the areas removed during surgery. Compared to the fiber-tracking images, the site where MEP was first recorded appears far anterior to the depicted pyramidal tract. Removal of a small amount of tissue from this area resulted in a dramatic reduction in the MEP response to electrical stimulation of the motor cortex. Right row: postoperative MRI confirming complete resection of the tumor. Reference to the fiber-tracking images suggests that there is sufficient distance from the pyramidal tract. However, this patient's left-sided hemiparesis worsened after surgery.

images with the results of intraoperative electrical white matter stimulation, postoperative MR images, and surgical outcomes.

In case 1, the fiber-tracking images helped us understand the anatomical relationship between the tumor and the pyramidal tract. By comparing the fiber-tracking images with images of the tumor depicted on the neuronavigation system, the direction of the pyramidal tract was easily recognized during surgery. Our ability to limit electrophysiological testing to areas where it seemed necessary contributed to shortening the time required for the operative procedure. Although we made a serious effort to preserve the motor function, we went slightly past the point at which we recorded the first MEP in patient 1; consequently, she suffered postoperative hemiparesis.

When we compared this patient's pre- and postoperative MR- and fiber-tracking images, we found that there was sufficient distance between the pyramidal tract and the margin of surgical resection. We concluded that while tractography can visualize the direction of the fibers, it is less informative with respect to the actual size of the fiber bundle.

In case 2, we took this experience into consideration and kept in mind that on tractographs, the actual size of the motor tract is underestimated. The pyramidal tract was electrophysiologically identified near the depicted tractography and this area was not touched during surgery. This patient manifested no neurological deficits after complete tumor resection.

While DTI-based tractography is considered to be a promising technique for neurosurgery, it entails many limitations. First, technical factors such as poor spatial resolution and low signal-to-noise ratio (SNR) of the acquired image will lead to poor DTI and tracking of fibers. Lin et al., who validated the accuracy of the principal eigenvector by comparing Mn^{2+}-enhanced optic tracts and DT-MRI, reported that its accuracy depends on the SNR (Lin et al., 2001).

Second, fiber-tracking is a user-defined process, and the results are dependent on the size and location of the seed ROIs (Clark et al., 2003), thresholding of fractional anisotropy, and the algorithm used. In most cases, including ours, the selection of seed ROIs is based on anatomical landmarks. When tracking the fibers of patients harboring space-occupying brain lesions, it is desirable to choose ROI based on both anatomical and functional information. Therefore, an automated method or standard protocol for fiber-tracking is required to avoid bias. Furthermore, information obtained from functional evaluations such as fMR and MEG may be able to facilitate the design of a more objective post-processing protocol.

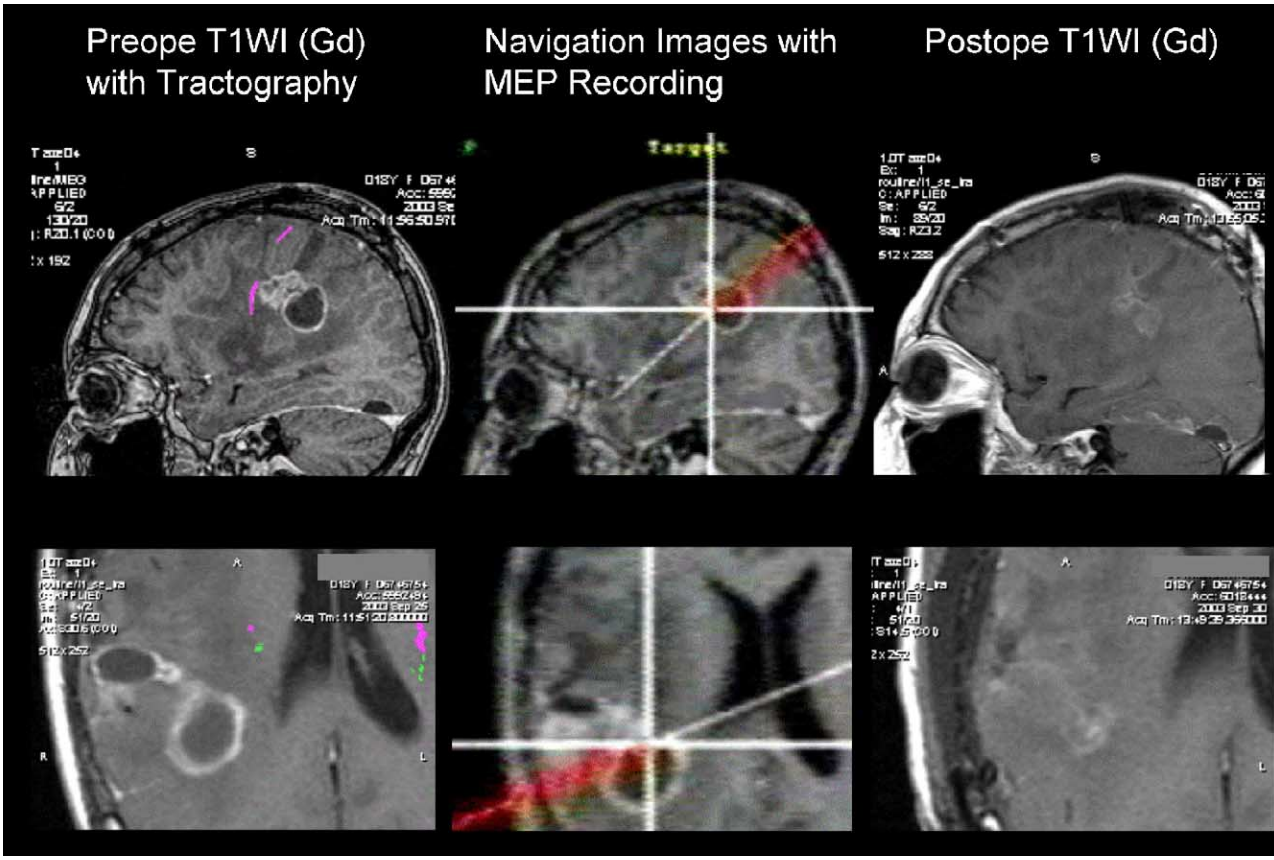

Fig. 4. (Patient 2) MR images. Left row: preoperative sagittal and axial Gd-enhanced MR images with tractograph traces. Note the ring-enhanced mass with a cystic component in the right parietal lobe. The purple and green lines represent the pyramidal and sensory tracts, respectively. Both appear to be far anterior and medial to the cystic tumor component. Middle row: images obtained intraoperatively with the EVANS neuronavigation system. At the target, the intersection of the white lines, subcortical electrical stimulation elicited a positive response. Compared to the fiber-tracking images, its location is much posterior and lateral to the depicted pyramidal tract. This portion, considered to be the wall of the cystic component, was not touched. Right row: postoperative MRI confirming complete resection of the tumor. This patient experienced no neurological sequelae.

As to the algorithm of fiber-tracking, no "gold standard" method exists at present. However, besides the conventional streamline algorithm, new and modified algorithms have been reported, e.g., the "Fast Marching Tractography (FMT)" algorithm of Parker et al. (2002) and the probabilistic tractography algorithm of Behrens et al. (2003). The FMT algorithm that presents connectivity metrics of white matter fibers produced excellent results in the tracking of fibers in areas where the fiber density changes, for example, in areas past the point where branching or fanning of fibers occurs. The probabilistic tractography algorithm reveals fiber connectivity that progresses into the gray matter; conventional streamlined algorithms failed to yield acceptable results. One of the reasons we failed to depict the entire motor tract may be related to the chosen algorithm. Comparison and evaluation of different algorithms may identify the method that is most suitable for clinical use.

A third limitation is the problem of crossing fibers and multiple principal directions of the eigenvector. Motor tracts of the brain should have a fan-shaped configuration at the level of the centrum semiovale. However, the fiber-tracking technique can only depict the fibers traveling to the vertex of the brain (Fig. 1). This is attributable to the existence of multiple crossing fibers at the level of the centrum semiovale which leads to inaccuracy in the estimation of the direction of anisotropy in these areas. The development of new models and methods seeks to provide solutions for these problems. Tuch et al. successfully reconstructed multitensors and resolved multiple intravoxel fibers (Tuch et al., 2002) and Jones (Jones, 2003) estimated the uncertainty of the eigenvector and succeeded in the simultaneous presentation of both fiber orientation and uncertainty. These new techniques may improve the reproducibility of fiber-tracking and solve the crossing fiber problem. Besides these physiological factors, under pathological conditions, in addition to the above-mentioned physiological factors, other factors such as edema can also affect the principal directions and cannot be overlooked in the presence of brain tumors. Bulk flow within the edematous areas may override anisotropy, lead to errors in fiber-tracking, and result in serious mistakes in neurosurgical planning. However, the successful application of motor (Clark et al., 2003) and even language fiber-tracking (Henry et al., 2004) in surgical cases has been reported.

Lastly and perhaps most importantly, the fiber-tracking technique has not yet been fully validated and its true clinical efficacy remains to be confirmed, although attempts at validation using different strategies have been made (Ciccarelli et al., 2003; Lin et al., 2001; Parker et al., 2002). Most of these efforts are based on comparisons of fiber-tracking images and known neuroanatomy. We evaluated fiber-tracking images from a more functional perspective and offer our intraoperative electrophysiological results as another step toward the validation of fiber-tracking.

Ours is one of the first reports to document that fiber-tracking cannot depict the entire motor tract, especially under pathological conditions. Due to the above caveats and our preliminary experience, the incorporation of fiber-tracking information in neurosurgical decision making must proceed with caution. Further validation of fiber-tracking images and the improvement and optimization of the fiber-tracking technique are required. For current neurosurgical planning, fiber-tracking must continue to be combined with electrophysiological and functional image guidance.

References

Basser, P.J., Pajevic, S., Pierpaoli, C., Duda, J., Aldroubi, A., 2000. In vivo fiber tractography using DT-MRI data. Magn. Reson. Med. 44, 625–632.

Behrens, T.E., Johansen-Berg, H., Woolrich, M.W., Smith, S.M., Wheeler-Kingshott, C.A., Boulby, P.A., Barker, G.J., Sillery, E.L., Sheehan, K., Ciccarelli, O., Thompson, A.J., Brady, J.M., Matthews, P.M., 2003. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nat. Neurosci. 6, 750–757.

Ciccarelli, O., Toosy, A.T., Parker, G.J., Wheeler-Kingshott, C.A., Barker, G.J., Miller, D.H., Thompson, A.J., 2003. Diffusion tractography based group mapping of major white-matter pathways in the human brain. NeuroImage 19, 1545–1555.

Clark, C.A., Barrick, T.R., Murphy, M.M., Bell, B.A., 2003. White matter fiber tracking in patients with space-occupying lesions of the brain: a new technique for neurosurgical planning? NeuroImage 20, 1601–1608.

Coenen, V.A., Krings, T., Mayfrank, L., Polin, R.S., Reinges, M.H., Thron, A., Gilsbach, J.M., 2001. Three-dimensional visualization of the pyramidal tract in a neuronavigation system during brain tumor surgery: first experiences and technical note. Neurosurgery 49, 86–92 (discussion 92-83).

Coenen, V.A., Krings, T., Axer, H., Weidemann, J., Kranzlein, H., Hans, F.J., Thron, A., Gilsbach, J.M., Rohde, V., 2003. Intraoperative three-dimensional visualization of the pyramidal tract in a neuronavigation system (PTV) reliably predicts true position of principal motor pathways. Surg. Neurol. 60, 381–390 (discussion 390).

Conturo, T.E., Lori, N.F., Cull, T.S., Akbudak, E., Snyder, A.Z., Shimony, J.S., McKinstry, R.C., Burton, H., Raichle, M.E., 1999. Tracking neuronal fiber pathways in the living human brain. Proc. Natl. Acad. Sci. U. S. A. 96, 10422–10427.

Duffau, H., Capelle, L., Denvil, D., Sichez, N., Gatignol, P., Taillandier, L., Lopes, M., Mitchell, M.C., Roche, S., Muller, J.C., Bitar, A., Sichez, J.P., van Effenterre, R., 2003. Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: functional results in a consecutive series of 103 patients. J. Neurosurg. 98, 764–778.

Gossl, C., Fahrmeir, L., Putz, B., Auer, L.M., Auer, D.P., 2002. Fiber tracking from DTI using linear state space models: detectability of the pyramidal tract. NeuroImage 16, 378–388.

Hendler, T., Pianka, P., Sigal, M., Kafri, M., Ben-Bashat, D., Constantini, S., Graif, M., Fried, I., Assaf, Y., 2003. Delineating gray and white matter involvement in brain lesions: three-dimensional alignment of functional magnetic resonance and diffusion-tensor imaging. J. Neurosurg. 99, 1018–1027.

Henry, R.G., Berman, J.I., Nagarajan, S.S., Mukherjee, P., Berger, M.S., 2004. Subcortical pathways serving cortical language sites: initial experience with diffusion tensor imaging fiber tracking combined with intraoperative language mapping. NeuroImage 21, 616–622.

Holodny, A.I., Schwartz, T.H., Ollenschleger, M., Liu, W.C., Schulder, M., 2001. Tumor involvement of the corticospinal tract: diffusion magnetic resonance tractography with intraoperative correlation. J. Neurosurg. 95, 1082.

Jones, D.K., 2003. Determining and visualizing uncertainty in estimates of fiber orientation from diffusion tensor MRI. Magn. Reson. Med. 49, 7–12.

Kato, A., Yoshimine, T., Hayakawa, T., Tomita, Y., Ikeda, T., Mitomo, M., Harada, K., Mogami, H., 1991. A frameless, armless navigational system for computer-assisted neurosurgery. Technical note. J. Neurosurg. 74, 845–849.

Lin, C.P., Tseng, W.Y., Cheng, H.C., Chen, J.H., 2001. Validation of diffusion tensor magnetic resonance axonal fiber imaging with registered manganese-enhanced optic tracts. NeuroImage 14, 1035–1047.

Mori, S., Crain, B.J., Chacko, V.P., van Zijl, P.C., 1999. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann. Neurol. 45, 265–269.

Mori, S., Frederiksen, K., van Zijl, P.C., Stieltjes, B., Kraut, M.A., Solaiyappan, M., Pomper, M.G., 2002. Brain white matter anatomy of tumor patients evaluated with diffusion tensor imaging. Ann. Neurol. 51, 377–380.

Parker, G.J., Stephan, K.E., Barker, G.J., Rowe, J.B., MacManus, D.G., Wheeler-Kingshott, C.A., Ciccarelli, O., Passingham, R.E., Spinks, R.L., Lemon, R.N., Turner, R., 2002. Initial demonstration of in vivo tracing of axonal projections in the macaque brain and comparison with the human brain using diffusion tensor imaging and fast marching tractography. NeuroImage 15, 797–809.

Tuch, D.S., Reese, T.G., Wiegell, M.R., Makris, N., Belliveau, J.W., Wedeen, V.J., 2002. High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity. Magn. Reson. Med. 48, 577–582.

Wieshmann, U.C., Symms, M.R., Parker, G.J., Clark, C.A., Lemieux, L., Barker, G.J., Shorvon, S.D., 2000. Diffusion tensor imaging demonstrates deviation of fibres in normal appearing white matter adjacent to a brain tumour. J. Neurol. Neurosurg. Psychiatry 68, 501–503.

Witwer, B.P., Moftakhar, R., Hasan, K.M., Deshmukh, P., Haughton, V., Field, A., Arfanakis, K., Noyes, J., Moritz, C.H., Meyerand, M.E., Rowley, H.A., Alexander, A.L., Badie, B., 2002. Diffusion-tensor imaging of white matter tracts in patients with cerebral neoplasm. J. Neurosurg. 97, 568–575.

Yamada, K., Mori, S., Nakamura, H., Ito, H., Kizu, O., Shiga, K., Yoshikawa, K., Makino, M., Yuen, S., Kubota, T., Tanaka, O., Nishimura, T., 2003a. Fiber-tracking method reveals sensorimotor pathway involvement in stroke patients. Stroke 34, E159–E162.

Yamada, K., Kizu, O., Mori, S., Ito, H., Nakamura, H., Yuen, S., Kubota, T., Tanaka, O., Akada, W., Sasajima, H., Mineura, K., Nishimura, T., 2003b. Brain fiber tracking with clinically feasible diffusion-tensor MR imaging: initial experience. Radiology 227, 295–301.