

FUNCTIONAL MONITORING FOR VISUAL PATHWAY USING REAL-TIME VISUAL EVOKED POTENTIALS AND OPTIC-RADIATION TRACTOGRAPHY

Kyousuke Kamada, M.D., Ph.D.

Department of Neurosurgery,
University of Tokyo, Tokyo, Japan

Tomoki Todo, M.D., Ph.D.

Department of Neurosurgery,
University of Tokyo, Tokyo, Japan

Akio Morita, M.D., Ph.D.

Department of Neurosurgery,
University of Tokyo, Tokyo, Japan

Yoshitaka Masutani, Ph.D.

Department of Radiology,
University of Tokyo, Tokyo, Japan

Shigeki Aoki, M.D., Ph.D.

Department of Radiology,
University of Tokyo, Tokyo, Japan

Kenji Ino, R.T.

Department of Radiology,
University of Tokyo, Tokyo, Japan

Kensuke Kawai, M.D., Ph.D.

Department of Neurosurgery,
University of Tokyo, Tokyo, Japan

Takaaki Kirino, M.D., Ph.D.

Department of Neurosurgery,
University of Tokyo, Tokyo, Japan

Reprint requests:

Kyousuke Kamada, M.D.,
Department of Neurosurgery,
University of Tokyo,
Bunkyo-ku, 7-3-1 Hongo,
Tokyo 113-8655, Japan.
Email: kamady-k@umin.ac.jp

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OBJECTIVE: It has been difficult to obtain anatomic and functional information about the visual pathway during neurosurgical operations. The aim of this study was to combine the information of the visual evoked potentials (VEPs) and the anatomic navigation of the optic radiation by diffusion tensor imaging-based tractography for functional monitoring of the visual pathway.

METHODS: The subjects were two patients with brain lesions adjacent to the visual pathway. Diffusion tensor imaging-based tractography of the optic radiation was performed by selecting appropriate regions of interest and by fractional anisotropy. During surgery, cortical VEPs were recorded continuously under general anesthesia with sevoflurane. In Patient 2, the results of optic radiation tractography were imported to a neuronavigation system to better understand the spatial relationships between the lesions and the visual pathway (functional neuronavigation).

RESULTS: In Patient 1, the lesion did not seem to be attached to the optic radiation, and VEP profiles remained stable during resection. In Patient 2, who had a lesion adjacent to the posterior horn of the lateral ventricle, VEPs suddenly diminished when resection reached the optic radiation as illustrated on the neuronavigation system. As a result, complete left hemianopia developed after surgery in Patient 2.

CONCLUSION: We confirmed functional correlations of the results of diffusion tensor imaging-based tractography by monitoring intraoperative VEPs. The combination of continuous VEP and optic-radiation tractography is reliable to monitor the visual function and is helpful in performing neurosurgical planning near the visual pathway.

KEY WORDS: Diffusion tensor imaging, Functional neuronavigation, Optic radiation, Tractography, Visual evoked potentials

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Tumor resection in functional areas involving eloquent subcortical fibers presents a high risk of neurological impairments, despite preservation of eloquent cortical areas. Sparing the components of the visual pathway, such as the optic radiation, during surgery is not always possible, because electrophysiological monitoring of the visual pathway is technically more difficult than that of other pathways.

Intraoperative neurophysiological monitoring, such as somatosensory and motor evoked potentials, plays important roles in preserving sensory and motor functions during neurosurgery (8, 12). In addition, intraoperative fiber stimulation of the corticospinal tract may be a reliable way to directly identify subcortical mo-

tor connections (6, 7). However, identification and monitoring of the visual pathway have not been widely applied clinically. Visual evoked potentials (VEPs) reflect the activity of the area centralis of the retina, to which particularly large areas of the visual cortex respond. Although there have been a few reports about the intraoperative usefulness of flash VEPs recorded via scalp electrodes, the results obtained exhibited marked variability in latency and amplitude and little correlation with operative outcomes (1, 5, 16). Curatolo et al. (5) have reported that VEP recordings with subdural electrodes revealed sufficient amplitude and consistent profiles throughout epileptogenic lesionectomy. Because they found no visual field deficits after

surgery, Curatolo et al. concluded that their method of recording VEPs enabled intraoperative monitoring of visual connections and might avoid visual morbidity in some cases.

Diffusion tensor imaging (DTI)-based tractography is a promising technique capable of tracing white matter tracts *in vivo*. This technique has been used to visualize the corticospinal tract and recently, to elucidate the three-dimensional structure of the visual pathways in the temporo-occipital region (3, 13). A central assumption of DTI-based tractography, however, is that the measured diffusion characteristics of tissue water are faithful representations of the underlying axonal microstructure (2, 15). This assumption, however, has not yet been verified electrophysiologically.

In this study, we used DTI-based tractography to visualize the spatial relation between brain lesions and the nearby optic radiation in two patients and confirmed functional connections of the illustrated optic radiation by recording VEPs. We describe the reliability of DTI-based tractography for the visual pathway using intraoperative VEP monitoring and the usefulness of the combination of two techniques.

PATIENTS AND METHODS

Patients

We studied two patients in whom brain lesions were near the optic radiation, one with cortical dysplasia and one with glioblastoma. This study was approved by our institutional review board, and written informed consent was obtained from the subject or a family member or both before participation.

Magnetic Resonance Protocols

All magnetic resonance imaging (MRI) studies were performed as a single MRI experiment on a 1.5-T whole-body MRI scanner with echo-planar capabilities (Signa, Echosped; General Electric, Milwaukee, WI).

DTI Acquisition

We used a single-shot spin-echo echo-planar sequence (TR, 5000 ms; TE, 96 ms) to acquire 32 interleaved, contiguous 3-mm-thick axial images with no cardiac triggering. A data matrix of 128×128 over a field of view of 240×240 mm was obtained, acquiring 128 echoes per excitation. Diffusion gradients were applied in 12 noncollinear independent axes, using b -values of 0 and 1000 s/mm^2 . A single echo-planar imaging (EPI) set required 25 seconds and was repeated five times to increase the signal-to-noise ratio, and compensation for eddy-current-induced morphing was performed. Realignment of these 13 DTI sets and compensation for eddy-current-induced morphing were performed on the basis of the T2-weighted EPI set ($b = 0$) on an equipped workstation with the MRI scanner. This compensation was performed by maximizing the mutual information between T2-weighted EPI and other EPI data sets with diffusion gradients. Three-dimensional anatomic MRI data of each patient's head were obtained, consisting of 128 sequential, 1.5-mm-thick axial slices with a resolution of 256×256 pixels over a field of view of 240 mm with three-dimensional spoiled, gradient-recalled

acquisition in steady state sequence. Their heads were immobilized with foam cushions during all entire MRI examinations.

Diffusion Tensor Calculation and DTI-based Fiber Tracking

The DTI data sets and anatomic MRI scans were analyzed with software for diffusion tensor analysis and fiber tracking (VOLUME-ONE and dTV; available at <http://volume-one.org> and <http://www.ut-radiology.umin.jp/people/masutani/dTV.htm>). Three eigenvalues and three eigenvectors of anisotropic components for each pixel were determined by the software (14, 15). An eigenvector (e_1) associated with the largest eigenvalue (λ_1) was assumed to represent the local fiber direction. Fiber tracking was started from a manually selected start point "seed area," from which lines were propagated in both the anterograde and retrograde directions according to e_1 at each pixel (Fig. 1). The seed area for the optic radiation was placed near the lateral geniculate nucleus, containing the optic radiation at the apex of the arc (suspected Meyer's loop) on key slices on the anisotropic maps where the transition from the posterior limb of the internal capsule to the cerebral peduncle was visible. The final destination of fiber propagation was determined by selecting cortical regions of interest (target areas). The target areas for the visual pathways were carefully placed in the occipital pole, including the calcarine fissure (Fig. 1). Tracking was terminated when it reached a pixel with a fractional anisotropy of less than 0.15.

Because DTI tractography of Patient 2 revealed that the tumor involved the optic radiation, we integrated the tract information

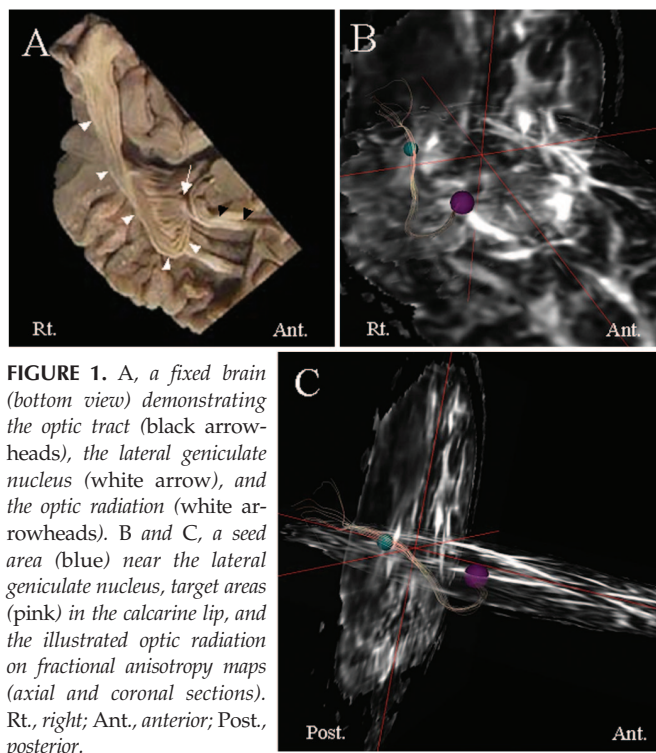


FIGURE 1. A, a fixed brain (bottom view) demonstrating the optic tract (black arrowheads), the lateral geniculate nucleus (white arrow), and the optic radiation (white arrowheads). B and C, a seed area (blue) near the lateral geniculate nucleus, target areas (pink) in the calcarine lip, and the illustrated optic radiation on fractional anisotropy maps (axial and coronal sections). Rt., right; Ant., anterior; Post., posterior.

with our routine neuronavigation system. The additional processes for image integration are described below.

Voxelization, Image Registration, and Data Fusion

After fiber tracking of the optic radiation, voxels containing tract fibers were marked in a volume data of which the matrix size was the same as the DTI, i.e., voxelization of tracking lines was performed. For coregistration of the voxelized tracts and anatomic MRI scans, coregistration between T2-weighted EPI data and anatomic MRI data were performed first, on the basis of maximization of mutual information and by affine transformation of the EPI data (4, 15). Because the voxelized optic radiation was in the same coordinate system as the EPI data, the volume data of the voxelized tracts were also transformed along with the EPI data. After the registration process, the results were visually evaluated by at least two radiologists and one neurosurgeon. Finally, the voxelized optic radiation and the anatomic MRI scans were simply fused and resliced (128 slices) with the Digital Imaging and Communications in Medicine (DICOM) format according to the original anatomic MRI header information.

Functional Neuronavigation

The resliced anatomic MRI scans with the tract information were transferred via fast Ethernet to a neuronavigation system (StealthStation; Medtronic Sofamor Danek, Memphis, TN). A program integrated with the neuronavigation system segmented the tract information by setting the signal thresholds and colored the optic radiation and the tumor purple and yellow, respectively. The procedures of the functional neuronavigation are summarized in a flowchart (Fig. 2).

Cortical VEPs

Each patient underwent craniotomy with general anesthesia with sevoflurane and muscle relaxants. The anesthesia was maintained with a 2.5% end-tidal sevoflurane concentration. Light-proof goggles (Nihon Koden, Tokyo, Japan) with flashing-light-emitting diodes for visual stimulation were placed over each eye. Flashing stimulation was made with the goggles through closed eyelids at a rate of 1 Hz. A subdural electrode strip with four channels was placed on the superior occipital pole. Low-pass and high-pass filters were set to 70 Hz and 1 Hz, respectively, with a notch filter of 50 Hz and a sensitivity of 20 μ V per division. A needle electrode was placed subdermally at the nasion for reference. Averaging runs of 10 stimuli were adequate to generate clear responses. The cortical VEPs were monitored constantly every 2 minutes.

RESULTS

Patient 1

Patient 1 was a 28-year-old man who had experienced intractable epilepsy for more than 15 years. The seizure attacks were

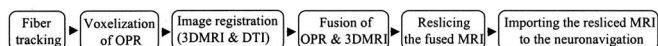


FIGURE 2. Flowchart showing the procedures of functional neuronavigation. 3DMRI, anatomic MRI data; OPR, optic radiation tractography.

poorly controlled despite attempted treatment with many anti-epileptic medications. The results of physical and neurological examinations, including examination of the visual fields, were normal. T1-weighted MRI scans showed a low-intensity area with no gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA) enhancement in the left parietal lobe. The lesion showed a slightly high intensity with little mass effect on T2-weighted MRI scans (Fig. 3). Subdural electrodes implanted over the left parietal region revealed epileptic activity arising predominantly from three contact points. DTI-based tractography showed that the optic radiation ran beneath the lesion and had not been deformed or invaded by the lesion in the inferior parietal lobe (Fig. 4A). Intraoperative cortical VEPs revealed stable negative waves peaking at 125 milliseconds after the flash stimuli (Fig. 4B). The VEP profiles were preserved until the epileptogenic lesion had been resected (Fig. 4, C and D). Postoperative MRI scans showed that the optic radiation had been spared, and the patient had no visual field deficit. The pathological diagnosis of the resected lesion was cortical dysplasia.

Patient 2

Patient 2 was a 52-year-old, right-handed woman who had had severe headaches for more than 1 year. High-grade glioma of the right posterior temporal lobe was diagnosed and was treated by radiotherapy (30 Gy) followed by partial resection at another hospital. Although the lesion had increased in size after 3 months, it caused no additional symptoms, such as visual field deficits. The patient was referred to our hospital for further treatment. Routine MRI scans showed a heterogeneous, high-intensity lesion in the posterior temporal area on T2-weighted images and ring-like Gd-DTPA enhancement on T1-weighted images (Fig. 3), suggesting a

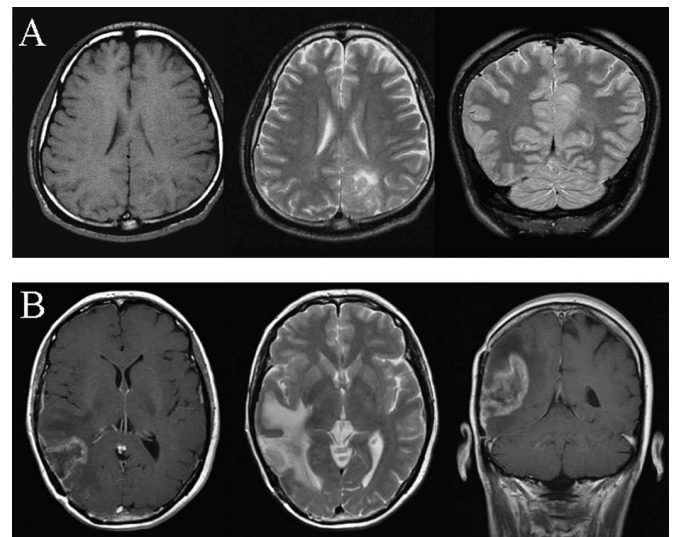


FIGURE 3. A, Patient 1. MRI scans revealing cortical dysplasia in the left parietal lobe. There are no clear borders between gray and white matter on T1- and T2-weighted MRI. B, Patient 2. MRI scans showing a mass lesion with ring-like enhancement on T1-weighted MRI and with marked peritumoral edema on T2-weighted MRI.

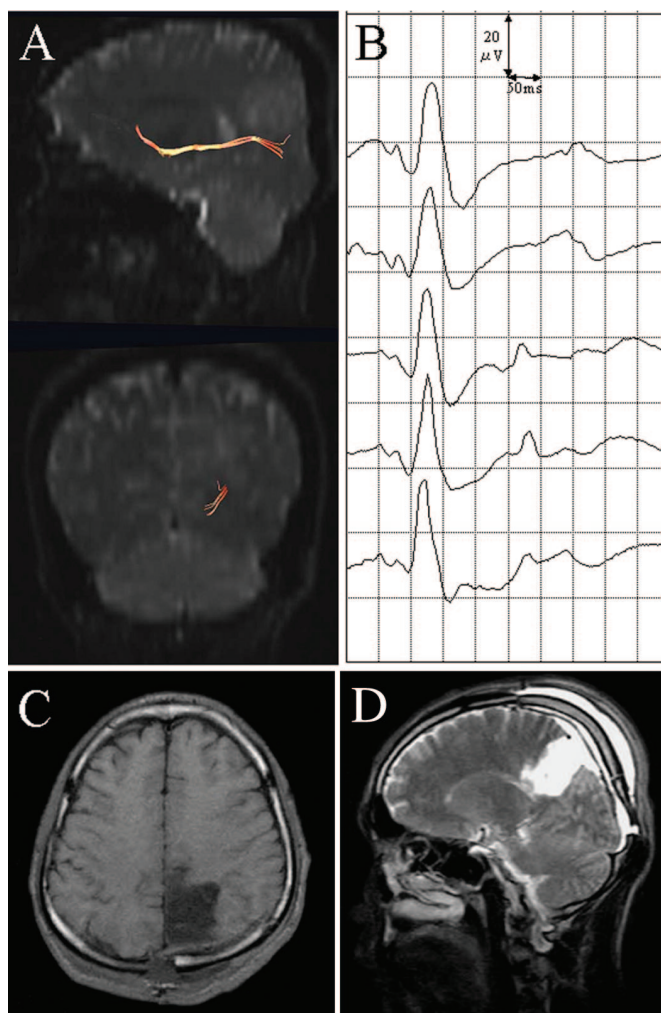


FIGURE 4. Patient 1. A, DTI-based tractography showing the optic radiation below the cortical dysplasia. B, tracings showing intraoperative monitoring of the VEPs, demonstrating negative deflections peaking at 125 milliseconds with consistent amplitudes during resection. C and D, post-operative MRI scans showing complete removal of the epileptogenic lesion.

recurrent high-grade glioma. DTI-based tractography revealed that the optic radiation was compressed medially and partially involved by the lesion, suggesting its invasion by the tumor despite a lack of neurological deficits. After image fusion, three-dimensionally reconstructed MRI scans on the neuronavigation system demonstrated the spatial relationship of the optic radiation (purple) and the tumor (yellow) (Fig. 5).

During the initial phase of resection, we observed no changes in the amplitude or latency of the cortical VEPs, which consistently peaked at approximately 125 milliseconds (Fig. 6A). After extirpating the tumor, we found degenerative tissue beneath the area of resection, which was tightly adherent to the ventricular wall. Although the neuronavigation indicated that the operative point was close to the illustrated optic radiation, the amplitude and latency of the VEPs were preserved. The VEPs, however, suddenly decreased

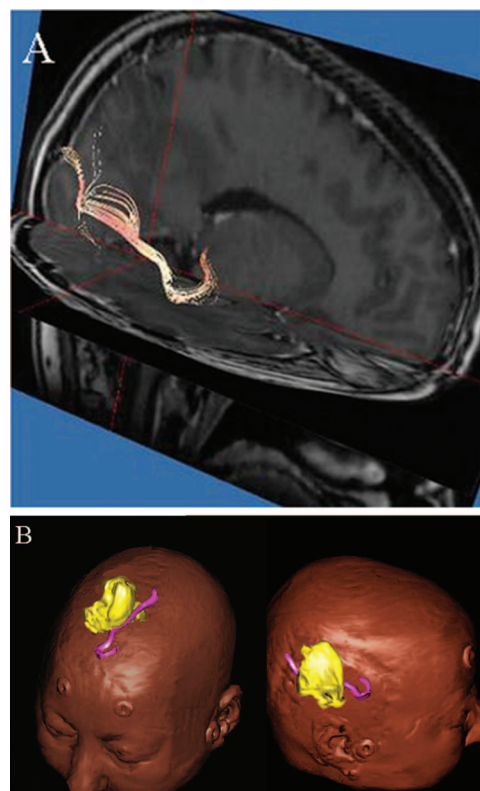


FIGURE 5. Patient 2. A, results of anatomic MRI fused with DTI-based tractography showing inferomedial shifting of the optic radiation by the tumor. B, three-dimensionally reconstructed whole-head MRI data on neuronavigation showing the optic radiation (purple) and the tumor (yellow).

when the posterior horn of the lateral ventricle was opened. We confirmed with the neuronavigation that the resection had finally reached the optic radiation, which might now have been damaged. The VEPs had not recovered within 1 hour after this event (Fig. 6A). The pathological diagnosis of the resected lesion was glioblastoma multiforme. A computed tomographic scan acquired just after surgery revealed little brain shifting, and postoperative MRI scans demonstrated extensive removal of the tumor and partial resection of the wall of the lateral ventricle (Fig. 7, A and B). Because the patient had left hemianopia after surgery, we concluded that intraoperative VEP monitoring accurately reflected the postoperative neurological deficit and that DTI-based tractography most likely demonstrated the actual anatomic optic radiation (Fig. 7C).

DISCUSSION

There is a continuing interest in the monitoring of visual function during surgery around the visual pathways. The present study demonstrates that optical stimulation under general anesthesia with sevoflurane evoked reproducible VEPs that could be monitored continuously. Because the VEPs were acquired within 10 seconds, they were frequently rechecked during resection, and the VEP monitoring has become

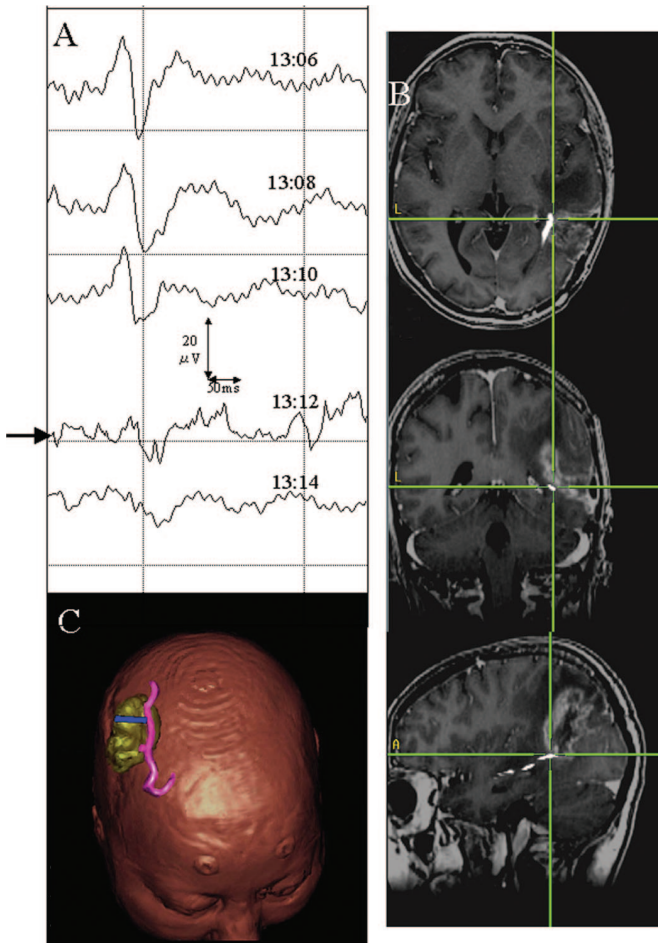


FIGURE 6. Patient 2. A, consecutive changes in the VEPs during tumor resection. VEPs became undetectable when the optic radiation was damaged at 13:12 (black arrow). B, two-dimensional MRI scans on neuronavigation demonstrating that resection had reached the ventricular wall, where the optic radiation was embedded. C, three-dimensionally reconstructed whole-head MRI data on neuronavigation showing the optic radiation (purple), the tumor (yellow), and the navigation probe (blue bar).

a potential functional indicator for the visual pathway. Moreover, DTI-based tractography with the two regions of interest method extracted the optic radiation, which seemed to accurately reflect the actual visual pathways, because the VEP abruptly decreased in Patient 2 when the surgical procedure reached this area. Postoperative visual field testing showed preserved central vision in Patient 1 and complete right hemianopia in Patient 2. The electrophysiological validation strongly supports our conclusion that DTI-based tractography provides us with accurate functional information about the white matter representation. We believe that the combination of these techniques would be useful for preserving visual function

There have been few reports of intraoperative VEP monitoring. Harding et al. (9) recorded VEPs with scalp electrodes

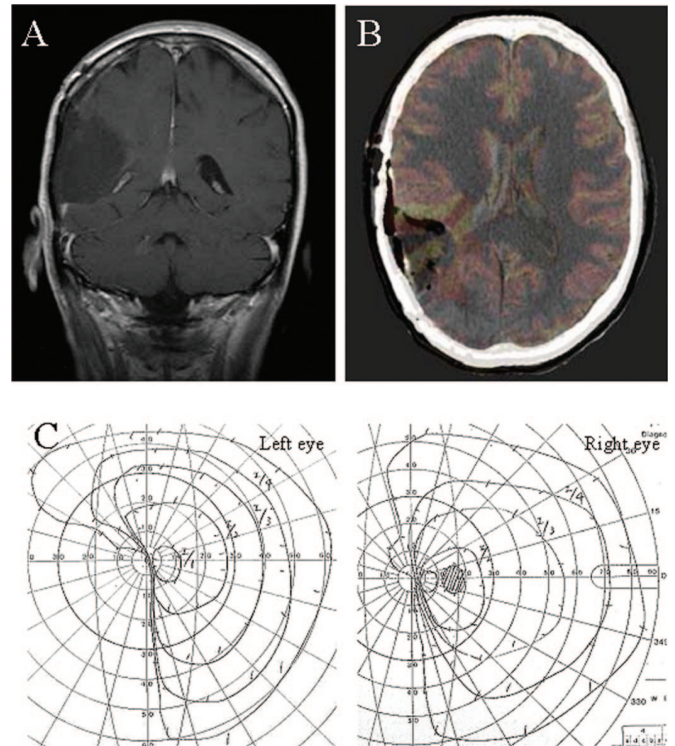


FIGURE 7. Patient 2. A, postoperative T1-weighted MRI scan with Gd-DTPA enhancement showing complete removal of the tumor and partial resection of the ventricular wall. B, superimposed transverse images of preoperative MRI (white-orange) and postoperative computed tomographic scan acquired just after surgery, demonstrating little brain shifting. C, postoperative visual field testing demonstrating complete left hemianopia.

under general anesthesia with enflurane (1%) and nitrous oxide. They suggested that the absence of VEPs for 4 minutes should prompt a search for a remediable cause of damage to the optic pathway. However, few studies have used their monitoring method because of low signal-to-noise ratio of the VEPs and filter effects of skin, cranium, and cerebrospinal fluid. For successful acquisition of intraoperative VEPs, the effects of anesthetics should be evaluated carefully. Volatile anesthetics suppress the background electroencephalography (EEG) and facilitate the extraction of evoked potentials (11). During isoflurane-induced burst suppression, somatosensory, photic, and auditory stimuli readily evoke burst-like activity in EEG investigations (10). Jantti et al. (11) have reported that a striking increase in the early components of somatosensory evoked potentials was observed consistently during sevoflurane-induced EEG suppression. Owing to the extremely low amplitude of ongoing EEG and the lack of electromyography, intraoperative VEP became consistently visible after only 10 stimuli by use of subdural electrodes. The subdural electrodes might be able to directly detect the cortical activity of limited areas as near-field potentials. The VEPs peaking at approximately 125 milliseconds should be representative of negative deflections, which are usually designated

N100 and originate from the central occipital region. The VEP amplitude was therefore used to quantify the function of the visual cortex and provided valuable prognostic information and immediate feedback to surgeons.

Fibers of the optic radiations leave the lateral geniculate nucleus and assemble into thick, compact lamina, which bend posteriorly toward the occipital pole (the temporal loop). The loop describes a sharp arc around the temporal horn of the lateral ventricle and terminates in the calcarine lip. In our study, the illustrated optic radiation probably followed its anatomic characteristics, because the seed and target areas had been placed in the appropriate areas, such as the temporal loop and the calcarine lip, respectively. We carefully verified that our findings with DTI-based tractography corroborated the classic anatomy of the visual pathways. In support of this, the continuous VEP recording in Patient 2 seemed to accurately monitor the visual function. Thus, the illustrated optic radiation was verified electrophysiologically by the VEP monitoring.

Like any other MRI technique, tractography provides anatomic information at only a macroscopic level. Specifically, the fiber orientation reflects the average orientation of axonal fibers for each pixel and is susceptible to tissue heterogeneity. Within a pixel, numerous fibers may be crossing, or a small portion of fibers may be oriented differently from the dominant fibers. It is therefore indispensable to validate the results obtained by this technique. In the near future, several new techniques for improving tractography should become available. These techniques include high angular sampling of the *k*-space, interpolation or regularization of tensor fields, and parallel imaging. And with these technical additions, various clinically important white matter tracts should be reliably illustrated. In addition, a critical issue with this technique is the geometric distortion induced by magnetic field heterogeneity and a motion-probing gradient. There have been several techniques to minimize the scanning artifact, which include homogenization of the static magnetic field and a morphing compensation. However, it is still important to address this issue of image distortion more carefully by developing a better shielding system and new sequences, such as parallel imaging.

A major practical problem of neuronavigation is supposedly the shifting of brain structures during surgery. In Patient 2, the neuronavigation accurately indicated that the surgical field was at the ventricular wall just after the posterior horn was opened, and a postoperative computed tomographic scan revealed little brain shifting. We therefore believe that this case might not be affected by the brain shifting. If an intraoperative MRI scanner with high magnetic fields (>1.5 T) is available in the near future, it would facilitate the practice of real-time DTI-based tractography with compensation of brain shifting. In the actual situation, we believe that the combination of these techniques that we have described might be the best way to preserve the visual function.

CONCLUSION

In conclusion, the combination of continuous VEP recording and functional neuronavigation with DTI-based tractography has en-

abled us to monitor visual function intraoperatively. Although this new method awaits a larger series of patients to ascertain its reliability and implementation, the present cases demonstrate its feasibility and potential usefulness for neurosurgical intraoperative monitoring. Furthermore, the illustrated tracts were verified electrophysiologically and potentially created an accurate map of the visual pathway. This validation strongly encourages clinical and basic neuroscientists to identify the white matter connections by use of DTI-based tractography. Moreover, this combination of techniques may be applied to other neuronal tracts, such as those for motor and language functions.

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COMMENTS

Kamada et al. report on the combination of intraoperative functional monitoring and preoperative tractography for the visual pathway, which they performed in two patients. Their setup allows a certain indirect verification of the results of optic-radiation tractography, because the loss of visual evoked potentials correlated well with the damaging of the visualized structures (i.e., the optic-radiation) in one patient. This report presents the potential benefit of the described techniques.

Integration of tractography data into a navigational setup is a major add-on to functional neuronavigation if intraoperative morphological changes, i.e., brain shift, is considered. Intraoperative visualization of the pyramidal tract allows preserving motor function in tumors located near the pyramidal tract. Comparing pre- and intraoperative tractography, using a high-field magnetic resonance scanner for intraoperative imaging, confirmed the marked shifting of major white matter tracts during neurosurgical procedures (Patients 1 and 2). Intraoperative tractography is a possibility to compensate for the effects of brain shift, when integrating tractography into functional neuronavigation. However, besides brain shift, the spatial distortion of the echo planar images also has to be considered if tractography data are registered with anatomical data for advanced functional neuronavigation. Furthermore, the inability to visualize major white matter tracts after surgery, or even during surgery, does not exclude neurological recovery in the postoperative course, and revisualized tracts do not necessarily mean a restoration of neurological function.

Christopher Nimsky
Rudolf Fahlbusch
Erlangen, Germany

The authors describe their fascinating experience with two patients in whom they resected lesions near the optic pathway radiations. They had diffusion tensor imaging (DTI) information on the optic pathways inserted their navigational workstation, and they did this all

with intraoperative visual evoked potentials (VEP). This is probably the first report that confirms that the VEP recordings correlate precisely with the DTI pathways. This is a very important observation because VEP monitoring during surgery is not trivial, and if one could rely on the DTI data to define the optic radiations in relationship to a lesion using navigation, this could potentially affect the course of surgery and change the morbidity rate during removal of lesions abutting the optic pathway. This study confirms that this is possible, and it also demonstrates something that a number of investigators have pointed out recently: that the deeper the resection, the less likely the shift using navigation, and thus DTI is quite reliable at this level. This is a very important contribution, and despite the fact that it only represents two patients, it confirms a very important finding: that DTI can be relied upon in conjunction with navigation to depict the functional as well as the anatomic component of the optic pathway.

Mitchel S. Berger
San Francisco, California

The authors address their initial experience with functional tractography during resection of lesions bordering visual pathways and demonstrate reasonable accuracy with postoperative visual function. This is an interesting technique and, while the results are not surprising, they do show where this technique is headed and how it can be used. This raises a problem for the surgeon. Is the impairment of a visual field loss worth the value of more aggressive tumor resection? I suspect the answer is not the same for all patients. In addition, surgery for infiltrative lesions is more likely to cause a deficit than well-demarcated tumors. As techniques improve, the use of tractography will also increase. This can potentially make surgery safer for selected patients and provide the surgeon with more information regarding potential postsurgical impairment.

Joseph M. Piepmeier
New Haven, Connecticut



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