Tracking the language pathways in edema patients: Preliminary results.

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Abstract: The tractability and integrity of fiber tracts within an edema, and the functional roles of long-range fiber tracts during language processing are discussed controversially. We studied the dorsal and ventral language fiber tracts of patients initially presenting with a peritumoral edema in both their pre- and postoperative states. Here, we report preliminary results of three patients. Diffusion tensor imaging (DTI)-based fiber tracking was performed. We were successful in locating the tracts in the presence of edema by lowering the fractional anisotropy (FA) threshold for streamline tractography. Moreover, the affected tracts demonstrated recovery after edema treatment and neurosurgery, both in terms of tractability and cognitive function.

1 Introduction

In recent years, diffusion tensor imaging (DTI)-based tractography of language fiber tracts has emerged as a valuable tool for presurgical planning of tumor resections [e.g., Be08, Mo02, Ni05, Pa11, Yu05; see Bi09 for an overview], for intraoperative mapping of fiber tracts in order to achieve maximally safe tumor resection while preserving cognitive functions [Be08, Ku12, Ni05], for postoperative assessment [e.g., Yu05], and for the investigation of language deficits in tumor patients [e.g., Bi12]. Little is known, however, about the application of DTI-based tractography in edema patients.

In the present study, we therefore aimed to clarify the impact of pre- and postoperative DTI-based tractography in edema patients. We hypothesized that a postoperatively tractable tract is also existent and intact preoperatively, and should be tractable by using an appropriate tracking algorithm combined with a reduced fractional anisotropy (FA) value as threshold. This would have direct implications for the presurgical planning, the advisable extent of the tumor resection, and the prognosis of the patient. We were specifically interested in the dorsal (arcuate fascicle, superior longitudinal fascicle) and ventral (uncinate fascicle, inferior fronto-occipital fascicle/extreme capsule fiber system) fiber tracts that are known to be important for language processing [Fr11].

Up to now, we studied three patients with peritumoral edemas pre- and postoperatively. Both DTI-based fiber tracking and a battery of clinical tests and behavioral language experiments were conducted pre- and postoperatively. In the present manuscript, we provide preliminary results.

2 Material and Methods

2.1 Patients and participants

We studied three patients (Pat01, Pat02, Pat03) pre- and postoperatively who showed a vasogenic edema around a brain tumor. Whereas 62-year old Pat01 and 46-year old Pat03 suffered from brain metastases, 65-year old Pat02 suffered from a high-grade glioma (WHO IV). The tumor of Pat01was located in the left anterior temporal lobe, and the tumors of Pat02 and Pat03 were located in the left parietal lobe. All patients presented with pronounced vasogenic edema around the tumor which was treated with dexamethasone directly after admittance to the hospital. All patients reported problems in recalling words, Pat01 additionally loss of appetite and disorientation, Pat02 problems with his working memory, and Pat03 problems of arm coordination. All patients were male, right-handed, and German native speakers who did not acquire a second language.

The patients were included into the study and tested first on average 46 hours (range: 37-53h) after admittance to the hospital. All patients underwent neurosurgery 8 (Pat01), 12 (Pat02), and 14 days (Pat03) after admittance to the hospital. The patients were resubmitted to the neuropsychological testing 3-4 weeks after surgery (Pat01: 21days; Pat02: 23d, Pat03: 28d). Each testing session lasted approximately two hours, during which the clinical and language tests were conducted. The order of behavioral tests was adjusted to the patients' ability. Additionally, anatomical brain scans were acquired before or after each session.

All patients or adequate family members gave their written informed consent to participate in the study. The study was approved by the local ethical committee (University of Leipzig).

2.2 MR Data acquisition and preprocessing

T1-weighted structural MPRAGE scans (TI = 650 ms; TR = 1300 ms; TR,A = 10 ms; TE = 3.5 ms; alpha = 10°; FOV = 256 x 240 mm²; 176 sagittal slices; spatial resolution = 1 x 1 x 1 mm³) and diffusion MRI (dMRI) scans (TE = 100 ms; TR = 12.9 s; 128 x 128 image matrix; FOV = 220 x 220 mm²; 88 axial slices (no gap); spatial resolution: 1.7 x 1.7 x 1.7 mm³, GRAPPA acceleration factor 2) were acquired on a whole-body 3 Tesla Siemens Verio magnetic resonance (MR) scanner (Siemens, Erlangen, Germany) equipped with an 32-channel head array coil. The diffusion sequence provided 60 diffusion-encoding gradient directions with a b-value of 1000 s/mm². Seven images without any diffusion weighting (b0) were obtained: one at the beginning of the scanning sequence and one after each block of 10 diffusion-weighted images as anatomical reference for offline motion correction.

The postoperative structural scan was reoriented to the sagittal intercommissural plane and brain was segmented. The b0 images were used to estimate motion correction parameters of the dMRI sequence using the rigid-body registration [Je02], implemented in FSL (FMRIB Software Library, University of Oxford, http://www.fmrib.ox.ac.uk/fsl/). We combined the motion correction for the dMRI data with the global registration to the T1 anatomy, corrected the gradient direction for each volume with the rotation parameters, and resampled the registered images to an isotropic voxel resolution of 1.7 mm. Finally, we computed the diffusion tensor, the three eigenvectors, and the FA value for each voxel [BML94]. The preoperative structural image was matched to the postoperative brain volume using rigid-body registration, and the diffusion data was processed in the same way as the postoperative measurement.

2.3 Fiber tracking and edema analysis

The fiber tracking algorithm was modeled on an advection-diffusion based propagation method [WKL99]. Depending on the extent of the edema or degree of impairment, it was necessary to adjust the tracking parameters to prevent premature termination, specifically, the FA cutoff was lowered and ω, the puncture parameter, was increased. This parameter adds weight to the incoming vector in the determination of the resultant propagation vector, and can thereby aid tracking through local regions of reduced anisotropy.

Mask regions were selected appropriate to the tract in question. Each tract requires spatially distinct masks at two characteristic locations along the tract. For the arcuate fascicle, one mask was placed in the temporal lobe near the temporoparietal junction and the second mask in the posterior frontal lobe. For the inferior fronto-occipital fascicle, one mask was placed in the mid frontal lobe and the other in the occipital lobe, and for the uncinate fascicle, one mask was in the rostral temporal lobe and the other in the inferior frontal lobe. The fiber tracking searched for all fibers that extend to or through both masks. Those fibers which followed tortuous routes or visually extended far outside the anatomical pathway were discarded, and fibers which continued far beyond the region of interest were truncated.

The fibers resulting from the tracking algorithm were considered to belong to a bundle or tract. They were then grouped together in a manner similar to the distance map method described by O'Donnell [OWG09]. Our approach can be described in the following manner: A seed point, directional point and reference (or end-)point is manually placed on the tract in question. Each fiber is searched for its voxel of nearest approach to the seed point and tested against a given maximum allowed radius (between 2-10 voxels). If the fiber approaches the seed point within the inclusion radius and its propagation vector does not differ by more than 60 degrees from the propagation direction, the fiber's voxel parameters are included in the bundle. (The proximal tract's end propagation direction is defined by the difference vector between the manually placed directional and start points). The arithmetic average of the FA of the resulting voxels is calculated, and the propagation vectors are summed and normalized after opposed fibers have their propagation vectors reversed. The result is added to the bundle, and the bundle is propagated by one step in the direction of the average propagation vector. The voxel found by propagation becomes the new seed point and the process is repeated until the reference point is reached or proves unreachable. It should be noted that at any given step, those fibers which do not meet the inclusion criteria are not included in the bundle.

The edema was manually segmented for each patient in the pre- and post-interventional datasets using the T2 weighted B0 volumes, and analyzed for volume. Preoperatively, also the average FA within the edema was calculated by finding the arithmetic average of the FA of all voxels within the edema mask. .

3 Results

3.1 Edema development

For each segmented edema region, the volume and preoperative average FA were calculated. Postoperatively, in all cases the volume of the edema was significantly reduced (see table 1).

	Preoperative FA (std. dev.)	**Preoperative Vol [mm³]**	**Postoperative Vol [mm³]**	**% Volume Reduction**
Pat01	0.195 (0.1)	11665	2015	83%
Pat02	0.13 (0.07)	32441	6388	80%
Pat03	0.157 (0.09)	23015	3308	85%

Table 1: Preoperative average FA over edema region, and development of edema volume in the three patients studied.

3.2 Tracking results

We report the pre- and postoperative FA progression along the tract (fig. 1), as well as the number of fibers and the average FA within the bundled tracts (fig. 4). 3D projections of the lesions and tracts, as well as color-coded FA-maps are shown in fig. 2; fig. 3 shows a pre- and postoperative interactive three-dimensional (3D) model of Pat03.

Pat01: In this patient, the uncinate fascicle (UF) and the inferior fronto-occipital fascicle (IFOF) were studied, as the localization of the tumor in the left anterior temporal lobe was most likely to affect these tracts. UF: The number of fibers that could be demasked increased by 127 %, from 11 to 25, accompanied by an increase in FA of 39 %, from 0.23 (SD: 0.06) to 0.32 (SD: 0.07). The bundle was in close proximity with the tumor for most of its length, and in this extended region there was a visible difference in the FA of the bundle, which showed an improvement at the second data point. See fig. 1a and fig. 4. IFOF: This tract was separated from the tumor by a greater distance as compared to the UF. At both the pre- and postoperative data points, the same number of fibers (17) was bundled. However, the postoperative bundle had, on average, a 19 % higher FA. The preoperative FA was 0.31 (SD: 0.06), postoperatively it increased to 0.37 (SD: 0.09), which equals a 19 % improvement. See fig. 1b and fig. 4.

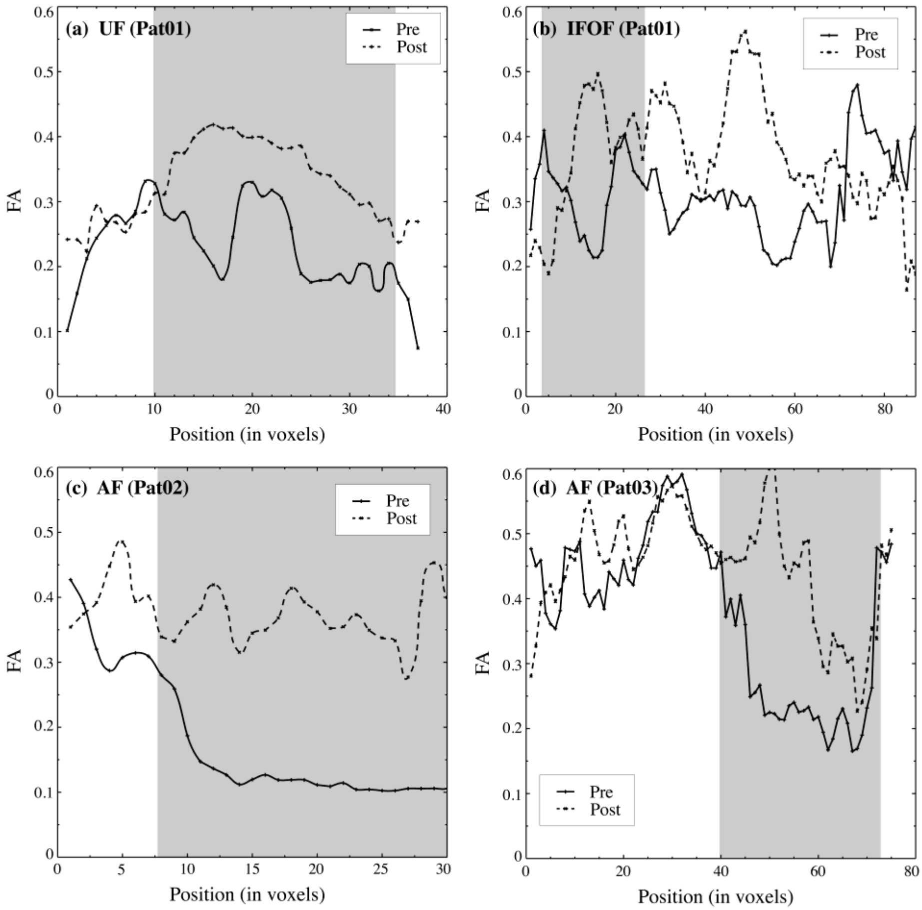

Figure 1: Progression of FA values along the tracked fibers. Pre- (red) versus postoperative (green) bundles are shown. The bundles begin (x = 0) in the temporal lobe and progress ventrally to the frontal lobe (UF), or dorsally to the parietal/frontal lobe (AF). The IFOF bundles begin (x = 0) in the frontal lobe and progress ventrally to the occipital lobe. The shaded region indicates the region of the edema. a) UF (Pat01): The fibers in the shaded region showed a quantitative improvement in the postoperative measurement. b) IFOF (Pat01): In general, the postoperative curve has a higher FA, but it is not obvious where the edema lies by looking at the progression curves. At the frontal and occipital terminations, the preoperative FA has higher values. c) AF (Pat02): The postoperative FA is significantly increased, as are the number of fibers that could be demasked. d) AF (Pat03): A postoperative improvement can be seen. However, a depression in the postoperative curve within the edema remains, with approx. 30 % less FA than the remainder of the curve.

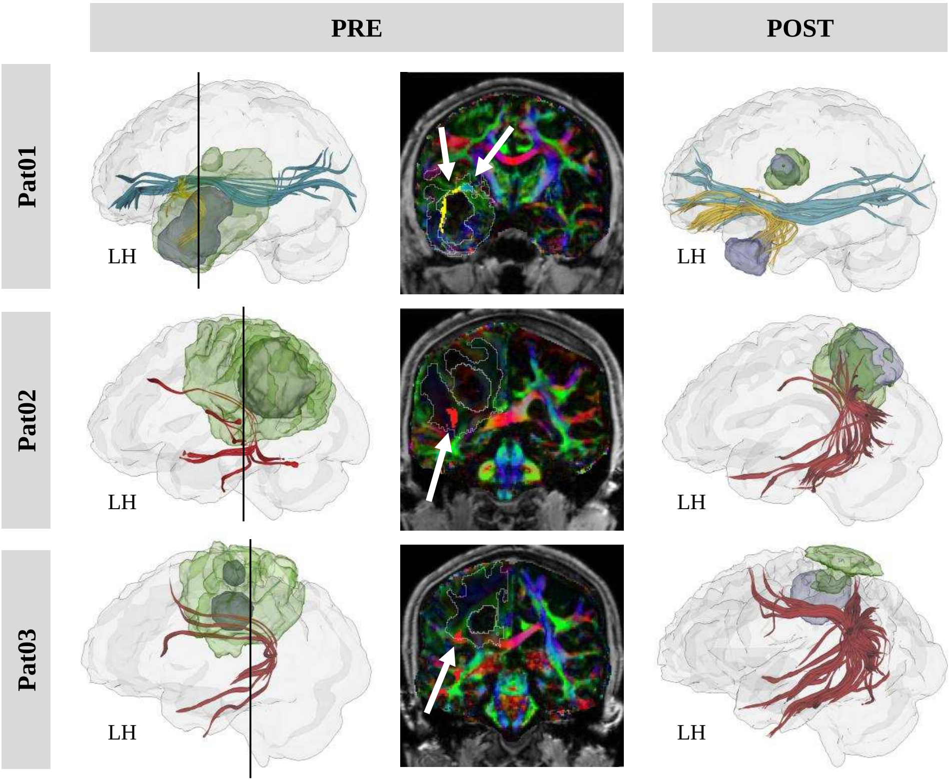

Figure 2: Results of pre- and postoperative fiber tracking per patient. Fibers are displayed in 3D figures as streamtubes with FA dependent radii. Edema is shown in green; in blue preoperatively tumor is shown, postoperatively the resection cavities. Segmentation is preliminary, as it is based on T1 weighted images only which does not allow a precise delineation of the boundaries. FA-color maps indicate how much the fiber tracts of interest (white arrows) are affected by the edema (contour drawn in white). The selected slices are indicated as vertical lines in the 3D figure. Pat01: Both, the turquoise tract (IFOF) and the yellow tract (UF) run through the edema, the UF reaching the tumor. Pat02: The tract lies completely within the edema. Pat03: The tract is only partly, i.e., in its superior part, affected by the edema. LH = left hemisphere.

Pat02: In this patient, the arcuate fascicle (AF), respectively superior longitudinal fascicle (SLF), was studied. Comparing the results from pre- and postoperative tracking, an improvement could be measured, both in terms of the number of fibers which could be demasked (4 versus 10, a 150 % improvement), as well as in the average FA of said fibers (0.17 (SD: 0.10) versus 0.38 (SD: 0.04), a 123 % improvement). See fig. 1c and fig. 4.

Pat03: In this patient, the arcuate fascicle was also studied. This patient shows the most significant improvement in the number of fibers which could be demasked and bundled

compared to the other patients (6 versus 48). However, the FA only improved by a modest 13 %, from 0.39 (SD: 0.12) to 0.45 (SD: 0.83). See fig. 1d and fig. 4.

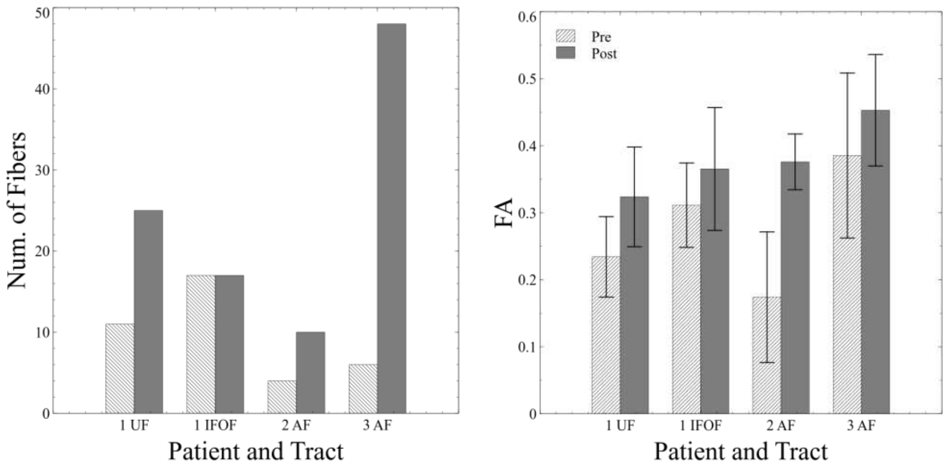

Figure 4: Difference of number of fibers and mean FA per tract per patient. Error bars indicate SD.

4 Discussion

In the present study, we examined pre- and postoperative fiber tractography in edema patients to investigate the tractability and amount of fiber recovery within an edema. We hypothesized that a postoperatively tractable fiber pathway is also existent and anatomically intact preoperatively, and should be traced by using an appropriate tracking algorithm combined with a reduced FA value as threshold. If this were the case, this would have direct implications for the presurgical planning and the amount of resection during neurosurgery.

Our data indeed show that it is possible to do reasonably robust fiber tracking through an edema. A similar approach was used earlier for tractography through tumor tissue [Ak05]. The long-range fiber tracts that proved present postoperatively could be traced preoperatively when lowering the FA threshold to 0.10 and using an advection-diffusion based tractography algorithm in the three patients. Thus, it is highly recommended to lower the FA threshold in the process of presurgical planning. Doing this, the neurosurgeon could be saved from resecting white matter which may regain function again after intervention. An alternative method for fiber tracking in edema was proposed by free water elimination using a multiple compartments model [Pa09]. This approach produces increased FA values in the edema but needs additional constraints to stabilize this process and is less robust than the single tensor fit. Lowering the FA threshold might result in false positive tractography results as shown in [Pa09]. The tracking result must be interpreted with caution. In our application we interpreted only the central part of the pathway which appears to be more robust.

Second, our data furthermore indicate that the white matter may recover through edema treatment. In all patients, the number of fibers and the average FA of the fiber bundles that passed through the edema increased postoperatively after reduction of the edema volume by around 80-85 %. This improvement was accompanied by an improvement of the cognitive behavior suggesting that the recovered white matter has regained function.

Interestingly, in Pat03 the investigated tract was only partly affected by the edema, which correlated with a good performance on the language experiments and other clinical tests. In Pat02 on the contrary, the core faculty of the investigated tract was effectively terminated by the edema. Congruently, he demonstrated an inability to perform any task preoperatively. Postoperatively, the tract mainly recovered and Pat02 was now able to perform most of the tasks. We therefore conclude that the edema is suppressing the function of the tract as far as it is covering and hitting the tract, and that the tract may regain function again after treatment. (Details of the different performance of the patients will be reported later.)

Reasons for the recovered white matter function after neurosurgery could be, apart from a mild improvement in the general state of health, both reduced pressure as result of the resection of the tumor, as well as reduced edema volume as result of the edema management. Moreover, it might occur to one that not the respective tract but other parts of the brain have taken over the functional role within the scope of plasticity processes, thus explaining the functional improvements. However, it is rather unlikely that plasticity takes place within four to six weeks without special training [cf., Du06]. The high potential for the recovery of white matter through neurosurgery and edema treatment is an important argument for retaining as much of the white matter as possible during resection.

In conclusion, we demonstrated that it is possible to trace a fiber tract preoperatively in edema patients. Both, the diffusivity values and the cognitive behavior of the patients improved through edema treatment and neurosurgery: the more the tract was affected by the edema preoperatively, the more the cognitive ability improved through treatment. Our preliminary analysis is based on three patients only, thus requires further investigation.

5 Acknowledgments

We gratefully thank the neurosurgeons of the University Clinic Leipzig for the successful collaboration and supplying the patient data, and Silvia Born of the Innovation Center Computer Assisted Surgery (ICCAS) Leipzig for the 3D visualizations.

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