CLINICAL ARTICLE

Diffusion tensor imaging fiber tracking using navigated brain stimulation—a feasibility study

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Abstract

Background Navigated brain stimulation (NBS) is a newly evolving technique. In addition to its supposed purpose, e.g., preoperative mapping of the central region, little is known about its further use in neurosurgery. We evaluated the usefulness of diffusion tensor imaging fiber tracking (DTI-FT) based on NBS compared to conventional characterization of the seed region.

Methods We examined 30 patients with tumors in or close to the corticospinal tract (CST) using NBS with the Nexstim eXimia system. NBS was performed for motor cortex mapping, and DTI-FT was performed by three different clinicians using BrainLAB iPlan® Cranial 3.0.1 at two time points. Number of fibers, tract volume, aberrant tracts, and proximity to the tumor were compared between the two methods.

Results We recognized a higher number of fibers (1,298± 1,279 vs. 916±986 fibers; p<0.01), tract volume (23.0±15.3 vs. 18.3±14.0 cm³; p<0.01), and aberrant tracts (0.6±0.5 vs.

0.3±0.5 aberrant tracts/tracked CST; p<0.001) when the seed region was defined conventionally, while proximity of the tracts to the tumor did not differ. While NBS-based DTI-FT is independent of the planning clinician, conventional outlining of the seed region shows generally higher variability between investigators.

Conclusions Conventional DTI-FT showed significant differences between the two modalities, most likely because of the more specific definition of the seed region when DTI-FT is based on NBS. Moreover, NBS-aided DTI fiber tracking is user-independent and, therefore, a method for further standardization of DTI fiber tracking.

Keywords DTI · Fiber tracking · Navigated brain stimulation · Neurophysiology · Preoperative monitoring

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Introduction

The resection of tumors within motor-eloquent areas, particularly the precentral gyrus and the corticospinal tract (CST), is always a compromise between the extent of resection and preserving motor function.

Especially in gliomas, surgical tumor reduction has a significant impact on survival and, thus, has to be as extensive as possible [13, 25]. On the other hand, motor function has to be preserved to secure quality of life for the patient. To achieve both of these goals, neurosurgeons employ various modalities to examine, visualize, and monitor motor function and anatomy before and during the resection of such tumors.

For preoperative mapping of the rolandic region, navigated transcranial magnetic stimulation (nTMS), also known as navigated brain stimulation (NBS), has gained increasing influence in neurosurgery and neuroscience in

the last 2 years [22]. Moreover, good concordance between preoperative NBS mapping and intraoperative DCS mapping during surgery was shown in our own but also in other series [9, 23].

Intraoperatively, several techniques allow the identification of CST, including neuronavigation, motor-evoked potentials (MEPs), and subcortical mapping. While electrophysiological monitoring and mapping via subcortical stimulation are the gold standard during the resection of tumors within or adjacent to the CST [5, 14, 19, 22, 25], MRI-based diffusion tensor imaging fiber tracking (DTI-FT) is a recent method used for presurgical planning and intraoperative localization of white matter tracts [6, 7, 11–13, 21]. Based on DTI and the concept of anisotropic water diffusion, specific white matter tracts such as the CST can be visualized; used for surgical planning, including three-dimensional (3D) reconstruction; and imported into the neuronavigation system [18]. Various studies have compared DTI-FT with intraoperative subcortical mapping during the surgical removal of tumors and attested to good accuracy [1, 2].

In reconstructing white matter fibers by DTI-FT, the definition of a functionally significant seed region is crucial for initializing the tracking process. Especially when tumors compromise the rolandic region, functional as well as structural neuroanatomy is considerably deranged, and the definition of seed areas can be severely hampered.

NBS provides specific information where the monosynaptic motor-evoked potential (MEP) is elicited in the precentral gyrus, which is supposed to be equivalent to the primary motor cortex. Thus, this study was designed to prospectively evaluate the value and feasibility of DTI fiber tracking based on NBS data as the seed region in patients with tumors within or close to the CST.

Methods

Patients

From May to December 2010, we performed preoperative mapping in 30 patients with tumors in or adjacent to the subcortical white matter motor tract using navigated brain stimulation.

The mean age was 57.2 ± 16.5 years (range 18.7–78.8 years); 16 patients (53%) were female, and 14 (47%) were male. Seventeen patients (57%) had a history of seizures, while 14 (47%) were on antiepileptic medication. Mild preoperative motor deficit occurred in 12 cases (40%), but there were no severe preoperative motor deficits. Seventeen tumors (57%) were in the dominant hemisphere.

Of 30 cases, there were 15 GBMs, 2 anaplastic astrocytomas, 3 diffuse WHO grade II astrocytomas, 1 WHO grade I DNET, 1 grade I meningioma, 1 AVM, and 7 metastases.

Preoperative magnetic resonance imaging

All patients underwent a preoperative MRI scan, which assessed the topographic association between the tumor and corticospinal tract or rolandic cortex, and eligible patients were recruited for this study. Informed consent was obtained.

A whole-body 3-T imaging system (Philips Achieva, Philips Electronics, Amsterdam, The Netherlands) with an eight-channel head coil was used, and 3D imaging was performed by continuous sagittal images using a T1-weighted 3D gradient echo sequence with isotropic voxels of 1 mm in length after intravenous administration of 0.1 mmol/kg of gadopentetate dimeglumine. Moreover, diffusion tensor imaging (DTI) sequences were performed with a single-shot spin echo EPI (TR/TE=7,571/55 ms) with b values of 0 and 800 and six orthogonal diffusion directions. Using parallel imaging (sensitivity encoding factor 2), two averages of 73 contiguous 2-mm slices with a matrix of 112°-112 mm covering the whole brain were acquired within 2 min 15 s. The DTI data were then interpolated to a matrix of 224°-224, resulting in a voxel size of 0.88°-0.88°-2 mm^3. In addition, data were corrected for motion artifacts by using the software installed on the scanner. For navigation, a 3D fastfield echo sequence was chosen with TR/TE= 9/4 ms and a flip angle of 8°. A sense factor of 1.5 and a turbo factor of 164 allowed the covering of the whole head in an isotropic resolution of 1 mm^3.

The 3D data set was then transferred to the NBS system (Nexstim eXimia, Helsinki, Finland) and to a BrainLAB iPlan® Net server (BrainLab, Feldkirchen, Germany) using the DICOM standard.

Navigated brain stimulation

The NBS system (Nexstim eXimia 3.2, Helsinki, Finland) includes a magnetic stimulator with two biphasic figure-of-eight TMS coils with a mean radius of 50 mm. The device also includes a navigation system that orients individual 3D MR images to the patient's head by infrared tracking (Polaris Spectra, Waterloo, Ontario, Canada), as previously reported [9, 23].

While performing stimulation with TMS, EMG was monitored continuously with four channels for the upper extremities and two channels for the lower extremities (Nexstim eXimia, Helsinki, Finland). For mapping of the upper extremities, we used electrodes on the abductor pollicis brevis (APB), abductor digit minimi (ADM), flexor carpi radialis (FCR), and biceps brachii (BCS) muscle. For mapping of the lower extremities, we used electrodes over the skin of the tibialis anterior (TA) and gastrocnemius (GCN) muscle. The reference electrode was placed at the elbow above the tendon of the BCS. Mapping of the primary motor

cortex, including determination of the resting motor threshold (rMT), was performed as shown by our group and others [9, 23]. For final mapping, a stimulator output of 110% rMT was used. It started at the hot spot and proceeded over the complete precentral gyrus, the tumor, and adjacent gyri until no CMAP was detected anymore. For mapping of the lower extremities, stimulation intensity was increased until CMAP was recorded at up to 130% of the stimulator output.

In the upper as well as in the lower extremities, CMAP above 50 μV was considered significant if latency was within the commonly known latency range of MEPs for each muscle.

After finishing the mapping, every stimulation point was assessed for its correctness, and data were exported via the DICOM standard and imported into the neuronavigation planning system (BrainLAB iPlan® Net, BrainLAB AG, Feldkirchen, Germany).

Neuronavigation and fiber tracking

NBS mapping was imported to the neuronavigation planning system (BrainLAB iPlan® Cranial 3.0.1, BrainLAB AG, Feldkirchen, Germany) and fused with continuous sagittal images of the T1-weighted 3D gradient echo sequence, T2 FLAIR, and DTI data. The white matter tracts were computed from the DTI data set as previously described using BrainLAB iPlan® Cranial 3.0.1 [20]. Seeding was performed using two regions of interest (ROI) for each fiber tracking. One ROI was set in the ipsilateral brain stem at the level of the tentorium; the second ROI was placed over the ipsilateral primary motor cortex.

Positioning of the ROI within the primary motor cortex was performed in two different ways. Primarily, the seed region was traditionally outlined by the investigator according to anatomical landmarks, e.g., the hand knob, on multiple axial slices, creating a 3D volume of the precentral gyrus as ROI. Second, the seed region of the primary motor cortex was generated from the NBS points of positive eliciting of MEPs as described above. To do so, an additional rim of two millimeters was calculated for each positive stimulation point, and the whole volume was defined as ROI.

The fractional anisotropy (FA) threshold and minimum fiber length were individually defined for each patient, remained constant for each patient, and were all below 0.2 and around 100 mm, respectively. The iteration was started and continued until certain stop criteria, such as FA value and fiber angulation (>30°), were reached. Finally, tracked white matter fibers were included as an object in the 3D T1 anatomic MR data set; i.e., fibers were enveloped within one contour.

Fiber tracking using the free hand and NBS seed regions was performed by three different investigators using BrainLAB iPlan® Cranial 3.0.1 (BrainLAB AG, Feldkirchen, Germany) at two different time points. The number of tracked fibers, CST volume, aberrant tracts, and proximity of the tracts to the tumor were compared for the two different seed regions and three observers, and intra- and interobserver differences were evaluated. Proximity of the tracts to the tumor was evaluated on axial MRI slices by BrainLAB iPlan® Cranial 3.0.1 (BrainLAB AG, Feldkirchen, Germany). Depending on the kind of lesion, gadolinium-enhanced T1-weighted or contrast-free T2-weighted sequences were used.

Ethical standard

The study was conducted in accordance with ethical standards of the Technical University of Munich, the local ethics committee (registration no.: 2793/10), and the Declaration of Helsinki.

Statistical analysis

Differences between groups were tested by the Kruskall-Wallis test for nonparametric one-way analysis of variance (ANOVA), followed by Dunn's test or the Student-Newman-Keuls test as a post hoc test. Differences between two groups were tested using the Mann-Whitney-Wilcoxon test for multiple comparisons on the ranks for independent samples. All results are presented as mean±standard deviation (SD) (SigmaStat 3.5, Jandel Scientific, Erkrath, Germany); $p<0.05$ was considered significant. The variability of the different methods was evaluated and visualized by a Bland-Altman plot. The limits of agreement during Bland-Altman analysis were the average difference±1.96 standard deviation of the difference [3].

Results

From May to December 2010, 30 patients with tumors in or adjacent to the precentral gyrus as well as in the subcortical white matter motor tract were examined by NBS.

NBS mapping

NBS was performed successfully in all cases. One patient experienced NBS as unpleasant, but none as painful. All patients underwent DTI studies during preoperative MRI for neuronavigation. Therefore, DTI-FT was possible in all patients.

Differences from standard fiber tracking

When comparing DTI-FT based on NBS with conventional tracking, it was much easier to recognize the precentral

gyrus, and the calculated fiber tracts seemed more compact (Figs. 1 and 2). Therefore, we tried to find parameters that can be quantified to find measureable differences.

When using NBS as the seed region for DTI-FT, we observed a significantly smaller number of fibers within the tracked CST compared to standard tracking (NBS: 916±986 fibers; standard: 1,298±1,279 fibers; p<0.01; Fig. 3).

Furthermore, we were not able to detect any differences in the proximity of the calculated CST to the tumor (NBS: 5.0± 5.7 mm; standard: 6.0±6.9 mm). However, there was a greater variability when using the standard definition of seed regions.

Moreover, the mean volume of the calculated CST was significantly greater for standard tracking (NBS: 18.3±14.0 cm³; standard: 23.0±15.3 cm³; p<0.01), and it had greater variability and spread than DTI-FT based on NBS (Fig. 4).

We also detected significantly fewer aberrant tracts differing from the CST when using NBS data as the seed region (NBS: 0.3±0.5 aberrant tracts/tracked CST; standard: 0.6±0.5 aberrant tracts/tracked CST; p<0.001).

Intraobserver differences

In both modalities, we were not able to show any significant differences between the two measurements of each observer for any examined item (data not shown). This comparison
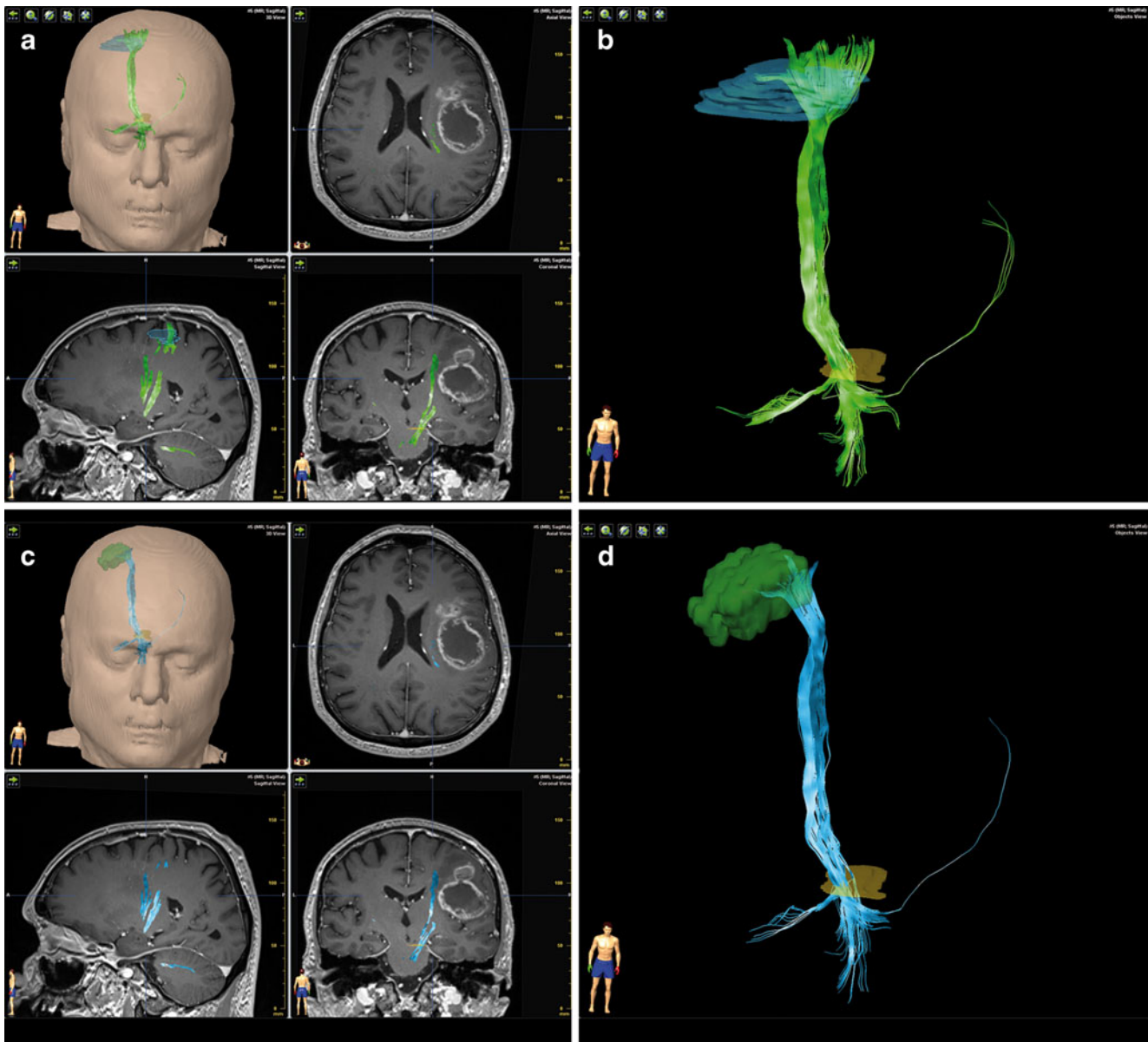

Fig. 1 When comparing conventional (**a**, **b**) diffusion tensor imaging fiber tracking (DTI-FT) with tracking based on navigated brain stimulation (NBS) (**c**, **d**), it is easier to recognize the precentral gyrus, and the calculated fiber tracts seem more compact
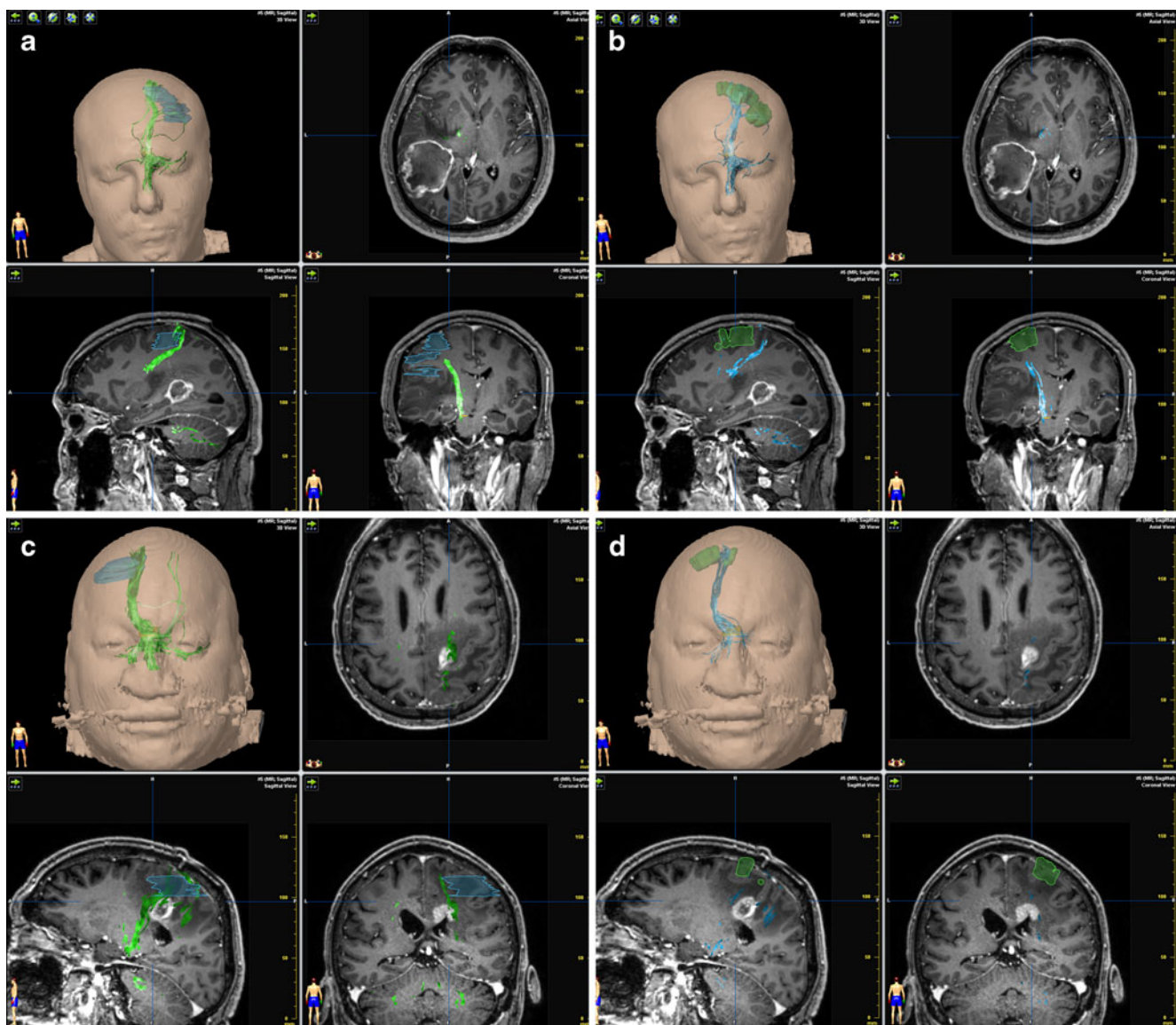
Fig. 2 Case 2 (**a**, **b**) and 3 (**c**, **d**) showing the difference between conventional (**a**, **c**) diffusion tensor imaging fiber tracking (DTI-FT) and DTI-FT based on navigated brain stimulation (NBS) (**b**, **d**)

between the different observers proves the good validity of the method in repeated testing.

Interobserver differences

Figure 5 shows the interobserver variability of both methods by presenting the difference of each measurement in the mean value against the measured values themselves using a Bland-Altman plot [3]. When comparing NBS and the conventional definition of the ROI, we observed less interobserver variability in the number of tracked fibers (Fig. 5 a+b), distance to the tumor (Fig. 5 c+d), and CST volume (Fig. 5 e+f) when DTI-FT was based on NBS data.

Moreover, the standard definition of cortical seed regions led to a greater variability of aberrant tracts between observers that reached statistical significance (*$p < 0.01$), while NBS-based DTI-FT not only produced fewer aberrant tracts but also failed to show statistical significance between observers (Fig. 6).

Discussion

This study assessed the influence of NBS data on the DTI-FT of the CST for motor-eloquent tumors of the brain. The improvement of DTI-FT offers the chance to verify the course of subcortical structures of the CST in relation to brain lesions [10, 18].

In earlier evaluations, the localization of DTI fiber tracks was related to the results of subcortical mapping with a comparatively good concordance to detect CST fibers [1, 2].
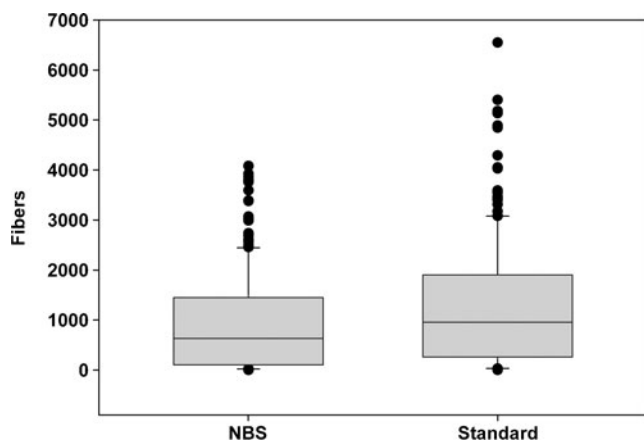
Fig. 3 By using navigated brain stimulation (NBS) as the seed region for diffusion tensor imaging fiber tracking (DTI-FT), we observe a significantly smaller number of fibers within the tracked corticospinal tract (CST) compared to standard tracking (NBS: 916.0 ± 986.0 fibers; standard: $1,297.9\pm1,278.7$ fibers; $p<0.01$)

From a technical point of view, the use of NBS motor mapping data for the determination of functionally crucial seed areas was easy to apply, and compatibility between the Nexstim eXimia 3.2 and iPlan® Cranial 3.0.1 using iPlan® Net was given by the DICOM standard and remained trouble-free when changing to iPlan® Cranial Unlimited (BrainLAB AG, Feldkirchen, Germany).

More fibers, larger tracts, and more aberrant fibers were calculated when using traditional definition of the cortical seed region. When tumors affect the rolandic region, traditional outlining of the primary motor cortex can be quite challenging because of mass effects and edema. This leads to a broader and, therefore, more unspecific definition of the cortical seed region when it is outlined conventionally. Thus, even tracts from outlined non-eloquent regions are
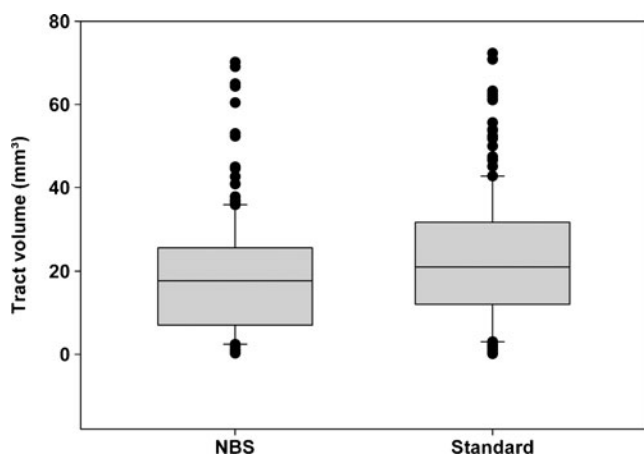

Fig. 4 Mean volume of the calculated corticospinal tract (CST) is significantly greater for standard tracking (NBS: 18.3 ± 14.0 cm³; standard: 23.0 ± 15.3 cm³; $p<0.01$), and has a greater variability and range than DTI-FT based on NBS

included and cause a wider defined and, therefore, less specific definition of the CST.

Furthermore, tumors within the CST or the precentral gyrus can facilitate cerebral plasticity so that functionally important motor areas do not have to coincide with standard anatomical landmarks, which are also frequently hard to identify [8, 15, 17, 24]. Due to this fact, we should be aware that only NBS data and not anatomical landmarks can reliably detect the location of functionally crucial motor regions prior to the operation. As our described technique is based on functional anatomy, it is supposed to provide more precise white matter fiber reconstruction as well.

The course of fiber tracking from cortex to midbrain or vice versa has an influence on the detection of fibers [2]. Thus, this study used the same protocol for every mapping.

Concerning confounding factors such as the problem of crossing fibers [2], fibers of the superior longitudinal fasciculus cross the CST fibers and, therefore, hamper the identification of a primary eigenvector of a voxel and thus the tracking of fibers. Fibers adjacent to tumor margins or tumor edema are also vulnerable to false-negative results due to low anisotropy [2]. This can make DTI-FT inadequate and thus unreliable.

Therefore, the selectivity and specificity of DTI fiber tracking are weakened, and the significance of the tracked fibers in the vicinity of the future resection borders remains unclear. DTI-FT can, therefore, only provide additional information about intraoperative neuromonitoring, such as by defining the initial position for subcortical mapping, and thus might reduce the time required for surgery, as reported previously [26].

Image-guided resection was not able to show a positive influence on the extent of resection or outcome in the past [16, 26], but it was shown to be helpful for the surgeon from a personal point of view in 74% of the cases and is regarded as an essential modality in selected cases [4]. Similarly, DTI-FT might increase the safety of operations in eloquent areas, which is not quantifiable as the extent of resection or neurological outcome. Therefore, it should be used in combination with intraoperative neuromonitoring as part of a multimodal approach that also includes preoperative NBS.

However, we have to be aware that in case of large volume lesions or in largely infiltrating tumors, NBS might not be able to stimulate all the fibers that form the CST because of infiltration or distortion of these fibers by tumor or edema. Therefore, the tract might appear more compact than observed with the usual tractography. These are the fibers, which are located around the tumors in standard tractography in the upper part of the tract, which seem to be missing in the NBS designed tracts.

As DTI-FT for visualization of the CST has several vulnerable points and, therefore, offers a wide range for potentially improving measures, such as increased standardization. This study demonstrates that precise and reliable
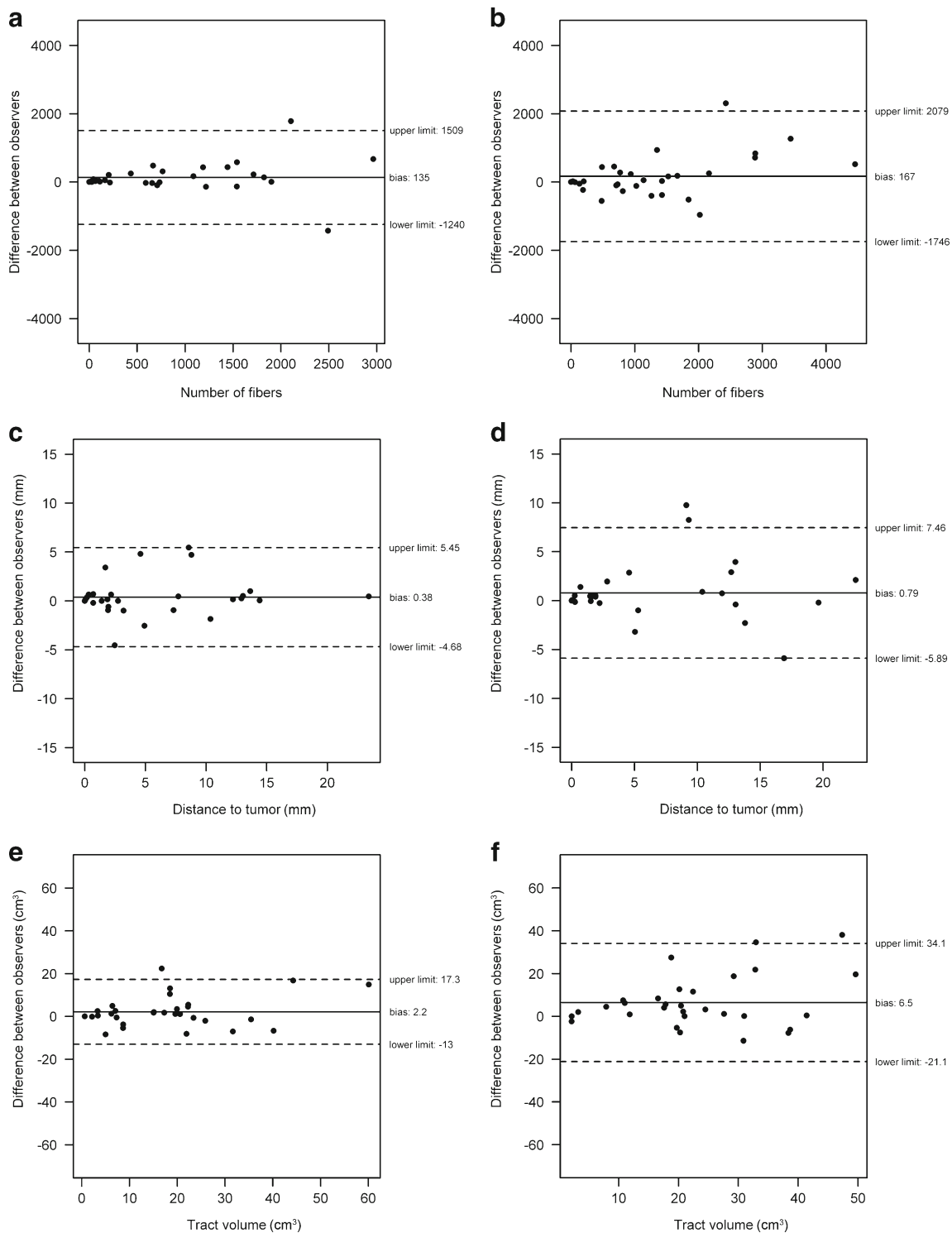
Fig. 5 Variability of both methods evaluated and visualized by a Bland-Altman plot. The graph shows the difference between standard diffusion tensor imaging fiber tracking (DTI-FT) and NBS-based DTI-FT between observers in correlation to the number of fibers (**a**: NBS; **b**: standard), distance to tumor (**c**: NBS; **d**: standard), and tract volume (**e**: NBS; **f**: standard)

NBS data can facilitate a more standardized tractography of the CST. The combination of these two techniques is promising for the preoperative evaluation of functionally essential white matter networks, and there is a high potential to broaden its application to further functional systems within the brain, such as the sensory system and speech, as well as for research on brain plasticity or development far beyond neurosurgical purposes. Nevertheless, NBS data have to be
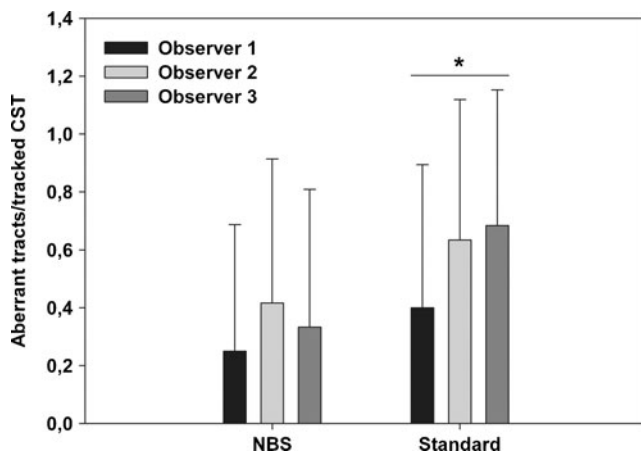
Fig. 6 Significant differences in the number of aberrant tracts between the observers are only seen in the standard definition of the seed, thus showing an advantage of NBS-based DTI-FT with more consistent results independent of the observer (*$p<0.01$)

available, and we have to question whether the exclusive use of DTI-FT justifies the costs and amount of time required for NBS mapping within a clinical setup in neurosurgery. However, in combination with preoperative assessment of the rolandic region, it will be a promising expansion for the application of NBS in neurosurgery.

Conclusion

The use of NBS data for tractography of the CST makes DTI-FT almost independent of the experience of the investigator and of distortion of the central region. As already investigated for traditional CST tractography, we have to evaluate the precision of NBS-aided DTI-FT versus subcortical mapping during tumor resection. However, this study is only capable of showing the feasibility of this new method.

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