Comparison of probabilistic and deterministic fiber tracking of cranial nerves

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OBJECTIVE The depiction of cranial nerves (CNs) using diffusion tensor imaging (DTI) is of great interest in skull base tumor surgery and DTI used with deterministic tracking methods has been reported previously. However, there are still no good methods usable for the elimination of noise from the resulting depictions. The authors have hypothesized that probabilistic tracking could lead to more accurate results, because it more efficiently extracts information from the underlying data. Moreover, the authors have adapted a previously described technique for noise elimination using gradual threshold increases to probabilistic tracking. To evaluate the utility of this new approach, a comparison is provided with this work between the gradual threshold increase method in probabilistic and deterministic tracking of CNs.

METHODS Both tracking methods were used to depict CNs II, III, V, and the VII+VIII bundle. Depiction of 240 CNs was attempted with each of the above methods in 30 healthy subjects, which were obtained from 2 public databases: the Kirby repository (KR) and Human Connectome Project (HCP). Elimination of erroneous fibers was attempted by gradually increasing the respective thresholds (fractional anisotropy [FA] and probabilistic index of connectivity [PiCo]). The results were compared with predefined ground truth images based on corresponding anatomical scans. Two label overlap measures (false-positive error and Dice similarity coefficient) were used to evaluate the success of both methods in depicting the CN. Moreover, the differences between these parameters obtained from the KR and HCP (with higher angular resolution) databases were evaluated. Additionally, visualization of 10 CNs in 5 clinical cases was attempted with both methods and evaluated by comparing the depictions with intraoperative findings.

RESULTS Maximum Dice similarity coefficients were significantly higher with probabilistic tracking ($p < 0.001$; Wilcoxon signed-rank test). The false-positive error of the last obtained depiction was also significantly lower in probabilistic than in deterministic tracking ($p < 0.001$). The HCP data yielded significantly better results in terms of the Dice coefficient in probabilistic tracking ($p < 0.001$, Mann-Whitney U-test) and in deterministic tracking ($p = 0.02$). The false-positive errors were smaller in HCP data in deterministic tracking ($p < 0.001$) and showed a strong trend toward significance in probabilistic tracking ($p = 0.06$). In the clinical cases, the probabilistic method visualized 7 of 10 attempted CNs accurately, compared with 3 correct depictions with deterministic tracking.

CONCLUSIONS High angular resolution DTI scans are preferable for the DTI-based depiction of the cranial nerves. Probabilistic tracking with a gradual PiCo threshold increase is more effective for this task than the previously described deterministic tracking with a gradual FA threshold increase and might represent a method that is useful for depicting cranial nerves with DTI since it eliminates the erroneous fibers without manual intervention.

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KEY WORDS cranial nerves; diffusion tensor imaging; functional neurosurgery; skull base tumors; probabilistic tracking

ABBREVIATIONS CISS = constructive interference in steady state; CN = cranial nerve; DTI = diffusion tensor imaging; FA = fractional anisotropy; FLAIR = fluid attenuated inversion recovery; FMRIB = Oxford Centre for Functional MRI of the Brain; FSL = FMRIB software library; HCP = Human Connectome Project; KR = Kirby repository; MPAGE = magnetization prepared rapid gradient-echo; PiCo = probabilistic index of connectivity; RESOLVE = readout segmentation of long variable echo-trains; ROI = region of interest.

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THERE is great interest in cranial nerve (CN) depiction using diffusion tensor imaging (DTI), as reported in multiple publications on this topic appearing in recent years.^{3,12,13,17,18,23,25} Most studies concern vestibular schwannoma, where the position of the facial and cochlear nerve is commonly obscured by tumor tissue in conventional MRI scans.

However, major discrepancies are apparent in recently published papers. Typically, the exclusion of the so-called “contaminating fibers” or noise is performed manually,^{3,25} sometimes to the extent that only specific, presumably adequate, portions of the original fiber bundle are selected by the operator.¹⁷ Moreover, the resulting depiction depends on many settings of the tracking algorithm, for instance, region of interest (ROI) position, angular threshold, fractional anisotropy (FA) threshold, tracking step size, and type of tracking algorithm. The reported percentage of correctly depicted facial nerves varies between 27% and 93%.^{17,23} In another disagreement, some authors report identifying fiber tracts belonging to both cochlear and facial nerves.^{20,23} However, no correlates to the cochlear nerve could be identified in previous studies.^{3,13,25} According to recent reports, there is no established usable method to separate the fibers corresponding to the nerve from the noise.²⁴ Therefore, manual selection based on operator presumption continues to be extensively used. The claims that the position of the nerve was detected using DTI thus have become questionable, because the decision about which fibers will be displayed was actually made by the investigator.

In a series of recent articles, Yoshino et al.^{22–24} addressed this issue by using a gradual FA tracking threshold increase. They presumed that voxels with higher FA values represent the nerve structure and separate the correct depiction from the surrounding noise. Although the method was rather successful in healthy subjects, it failed to depict the actual position of the facial nerve in the majority of patients with vestibular schwannoma, even when combined with other special imaging techniques.²² One very important finding of this series of studies was that no particular FA threshold applicable in all subjects could be identified. In addition, in other studies varying thresholds had to be used to obtain an acceptable nerve depiction.²⁰

It is important to realize that the goal in these analyses is to infer anatomical information from very noisy data. The diameter of the cisternal portion of the CNs is well below the resolution achievable in DTI scans, meaning that a portion of the voxel containing the nerve is occupied by CSF. This leads to levels of uncertainty in the source data that are supposedly even higher than in the white matter. In deterministic streamline tracking, the uncertainty contained in the diffusion data is overcome by constructing a simple tensor model of diffusion. Moreover, the areas with high uncertainty in the data are usually excluded using the FA thresholding. On the other hand, various techniques of probabilistic tracking explore this uncertainty by using repetitive sampling of the diffusion data and characterizing the data in terms of maps of connectivity probabilities.⁸ Given 2 ROIs and a region between them, where we expect the connection to take place, deterministic tracking will either show a connection or not based on the eigen-

vector direction of the other voxels on the same streamline and on the given threshold and angle settings. This connection represents the maximum likelihood pathway through the data, with no measure of confidence on the location of this pathway.¹ Probabilistic tracking specifically addresses the problem of the uncertainty of direction information and creates multiple streamlines from a selected distribution of possible fiber orientations, resulting in a depiction of a probability value based on the number of observed streamlines passing through the given voxel.⁴ Further, probabilistic fiber tracking has been shown to be superior to deterministic tracking methods in multiple studies comparing both methods in white matter tracking, mainly concerning smaller fiber bundles.^{10,11,15}

To compensate for the supposedly higher levels of uncertainty in the area of CSF-filled basal cisterns, we hypothesized that probabilistic tracking would offer advantages over the deterministic method in the depiction of CNs. Therefore, we examined the utility of the probabilistic tracking method in the depiction of CNs by comparing it to the standard deterministic fiber tracking used in previous publications. To our knowledge, results of probabilistic fiber tracking of CNs have not yet been reported. Moreover, we presumed that a technique of gradual threshold increase similar to that used by Yoshino et al.²³ applied to probabilistic tracking may eliminate the problem with erroneous fibers more successfully. To test this hypothesis, we applied a gradual threshold increase to probabilistic and deterministic tracking methods on the same set of publicly available healthy subject DTI data. Additionally, to verify the utility of the technique, we have included 5 cases of patients with skull base tumors, in whom we attempted to reconstruct the displaced CNs using a gradual threshold increase with deterministic and probabilistic tractography and compared the results with intraoperative findings.

Methods

Data Parameters

The institutional ethics committee approved this study. All patients signed a detailed informed consent prior to inclusion. The committee was consulted regarding the analysis of publicly available data and did not require specific approval. In total, data from 30 healthy subjects were obtained from 2 publicly accessible repositories.

Ten human brain DTI data sets and their corresponding fluid attenuated inversion recovery (FLAIR) and magnetization prepared rapid gradient-echo (MPRAGE) data were downloaded from the Kirby repository (KR), a publicly accessible archive of healthy subjects (<http://www.nitrc.org/projects/multimodal>). The details on the sequences and scanning parameters have been published by Landman et al.⁹ Twenty subjects were added from the Human Connectome Project (HCP) database (<http://www.humanconnectome.org/>).

Additionally, data from 5 patients with skull base tumors were included in this study. The diffusion images were acquired on a Siemens Magnetom Verio 3.0T (Siemens Healthineers). A readout segmentation of long variable echo-trains (RESOLVE) sequence was used, and a

total of 20 diffusion sampling directions were acquired, with a b-value of 800 sec/mm², in-plane resolution of 2 mm, and slice thickness of 2 mm. In these subjects, the deterministic and probabilistic tractography was performed preoperatively, and the results were compared with intraoperative findings. T1 or constructive interference in steady state (CISS) imaging was used for anatomical comparison.

Preprocessing

Anatomical images were coregistered to the DTI data set using the Oxford Centre for Functional MRI of the Brain (FMRIB) software library (FSL) linear registration program. The reconstruction was attempted for cisternal nerve segments that were clearly identifiable in the anatomical data sets. This included the optic, oculomotor, trigeminal, and bundled facial and vestibulocochlear nerves. In this manner, analyses for a total of 8 CNs were performed in each of the 30 subjects, amounting to 240 nerves. ROIs were drawn to simulate a problem, where the course of the nerve is unknown, using anatomical landmarks to place the tracking ROIs. For the optic canal (CN II), the chiasma and the optic nerve in the canal and optic nerve portion adjacent to the eyeball were used as tracking ROIs. In the oculomotor nerve (CN III), tracking ROIs were created at the brainstem and cavernous sinus. For the trigeminal nerve (CN V), tracking ROIs were set at the brainstem and the ganglion, and for the bundle of facial and vestibulocochlear nerves (CNs VII and VIII), the tracking ROIs were created at the brainstem and in the internal acoustic meatus. Additional adaptation of the tracking ROIs to the DTI image was sometimes necessary due to artifacts.

The tracking ROIs were transformed to the DTI space and used for all subsequent analyses. In the clinical cases, nerves clearly displaced by the tumor were selected for the analysis (Table 1). The tracking ROIs were prepared in a manner similar to that used in the healthy subjects.

Fiber Tracking

Two methods of DTI reconstruction were used in this study: DSI-Studio software²¹ for deterministic DTI tracking (<http://dsi-studio.labsolver.org/>) and The Oxford Centre for FMRIB FSL version 5 for probabilistic tracking (<http://fsl.fmrib.ox.ac.uk/>).

In the probabilistic analysis, graphics processing unit-based computation⁵ was used to accelerate the analysis.

TABLE 1. Overview of the clinical cases

Case No.	Type & Location of Tumor	Depicted CNs	Nerves Visible in T1/CISS Image
1	Meningioma, cerebellopontine angle (lt)	5, 7, & 8	CN 5 yes, CN 7+8 no
2	Meningioma, tuberculum sellae	2 (lt & rt)	Yes, partially
3	Meningioma, sphenoid wing (lt)	2 (lt)	Yes, partially
4	Vestibular schwannoma (rt)	7 & 8	No
5	Vestibular schwannoma (rt)	7 & 8	No

CISS = constructive interference in steady state.

The tracking step was subsequently run in a batch for the individual nerves using the predefined ROIs. As a result, probabilistic index of connectivity (PICO) maps were created for each of the nerves. To find the optimal probability threshold for localizing the nerve, the resulting PICO maps were filtered at threshold values of 0.05–0.95 in steps of 0.05, where all voxels below the given threshold were set to zero. These maps of connectivity probability were later compared with the ground truth images created as described above.

The DSI Studio software was used for the DTI deterministic streamline tracking method. The predefined ROIs were loaded into the application, and the tractography was performed for each of the nerves with default seed setting (whole brain mask used as seed for the tractography, ROI-based fiber selection). The analyses were performed with an angular threshold of 80°, step size 0.4 mm, smoothing 0.3, fiber length 0–180 mm, and 8 × 10⁶ seeds. The initial FA threshold was set to 0.01, and after each tracking, the FA threshold was increased in steps of 0.01 until no fibers resulted from the tracking or the preset upper limit (FA 0.50) was reached. All tracking results were generated as binary data for automated comparison with the ground truth nerve images.

Evaluation of the Results in Healthy Subjects

Ground truth images were created by manually segmenting the nerves in the anatomical images (Fig. 1). However, using manual segmentation for automated comparison can lead to artificial and randomly varying spatial mismatch. In both tractographic methods, the fiber tracking usually continues beyond the extent of the nerve without having a detrimental effect on the depiction of

FIG. 1. A: Manual segmentation of the ground truth image of the left optic nerve in the second KR data set. **B:** The overlaid pathways resulting from the deterministic tracking. **C:** The projection of these fibers into the voxel space of the image. **D:** The voxelized image of the fiber tract compared with the ground truth image. Yellow represents the overlap of the red nerve compared with the blue target ground truth image. The equations defining the label overlap measures “false-positive error” and “Dice coefficient” are shown in Klein et al.⁷ Note that the comparison in our analysis actually takes place in diffusion space (demonstrated here in T2 space). Figure is available in color online only.

the nerve itself for a human observer. Moreover, contaminating or turned around fibers that are located far from the expected position can easily be identified by a human observer but cause large changes in the spatial mismatch parameters. Therefore, to make the automated analysis similar to comparison by a human observer, the analyzed tractography images were cropped to the extent defined by the tracking ROIs and at approximately 5 mm from the ground truth image (depending on voxel boundary). Programs from the “fslutils” package of FSL¹⁶ were used for this image manipulation. In this way, contaminating fibers far from the depicted nerve were ignored by the automated evaluation algorithm. Similarly to tracking ROIs, the ground truth images were transformed to the DTI space prior to evaluation.

Two variables were evaluated by comparing the nerve depictions with the ground truth images—Dice coefficient and false-positive error (defined and implemented in the Insight Toolkit¹⁹). For each nerve, the maximum Dice coefficient obtained using the above-mentioned thresholds was determined. This value should represent a similarity measure of the best-obtained depiction with the ground truth image. The false-positive error was obtained for all nerve depictions at the last threshold setting that produced fibers or voxels. In this manner, the parameter represents the accuracy of the detection of the nerve position.

In the data from the KR database, the ground truth images were created twice, by 2 investigators (A.Z. and D.P., both neurosurgeons with 8 and 11 years of work experience, respectively). Interrater reliability of the analysis was assessed using these 2 segmentations by comparing all pooled results using the intraclass correlation coefficient.

Statistically, both parameters were compared between probabilistic and deterministic tracking using the Wilcoxon signed-rank test and between results obtained in KR and HCP data using the Mann-Whitney U-test. We have chosen to use nonparametric tests in our analyses due to the observed non-normality of the false-positive error values. A *p* value < 0.05 was considered significant for all tests performed. The R statistics system (version 3.2.2) together with R commander 2.0.2 was used for the analysis.

Evaluation of the Results in Clinical Cases

In 5 subjects harboring skull base tumors, gradual FA or PICO threshold increase was attempted by using probabilistic and deterministic tracking with the above-mentioned methods. The obtained depictions were evaluated starting with the highest threshold that yielded any results (fibers in deterministic tracking, voxels above the threshold with probabilistic tracking). The depiction that contained structures reconcilable with the shape of a nerve or nerves was presented to the surgeon for comparison with the intraoperative findings and compared with the anatomical images. The depictions were then assessed as accurate or inaccurate by the surgeon. For the assessment of CNs VII and VIII in vestibular schwannoma, we have additionally used the Sampath classification¹⁴ of nerve position to assess the agreement between the actual position of the nerve and the obtained depiction.

Results

Healthy Subjects

According to the Wilcoxon signed-rank test, the false-positive errors of the last thresholding step obtained with probabilistic tracking were significantly lower than those obtained with deterministic tracking (median difference 0.03, *p* < 0.001). The same result was observed when the HCP and KR data were analyzed separately (median differences 0 and 0.12, respectively; *p* < 0.001 in both cases). The Dice coefficients also differed significantly between the probabilistic and deterministic tracking (median difference 0.13, *p* < 0.001). This difference was also significant for the HCP data set (median difference 0.20, *p* < 0.001), but not for the KR data set (median difference 0.01, *p* = 0.6). The mean, standard deviation, and median values for the above-mentioned subgroups and variables are shown in Table 2.

The Mann-Whitney U-test was used to determine the observed difference between false-positive error obtained in data from the HCP and KR data sets. Lower false-positive errors were observed in the results obtained from the HCP data set with deterministic tracking (*p* < 0.001, medians 0 for HCP and 0.21 for the KR data sets, respectively). The differences between the data sets in false-positive errors were insignificant in probabilistic tracking (both medians zero, *p* = 0.06). The Dice coefficients obtained with HCP data were significantly higher than those obtained with KR data in both probabilistic tracking (*p* < 0.001, medians 0.66 for the HCP data set, 0.43 in the KR data set) and deterministic tracking (*p* = 0.02, median 0.46 for HCP and 0.43 for KR data sets, respectively). Illustrative depictions of the results are shown in Fig. 2.

The intraclass correlation coefficient for fixed raters showed good agreement between the 2 investigators (0.75, *p* < 0.001, 95% confidence interval 0.70–0.79).

Clinical Subjects

Visualization of 10 CNs in 5 subjects was attempted using the above-described methods (Table 1). The first depiction resembling a nerve without excess noise was presented to the surgeon and marked as accurate or inaccurate. Using deterministic tracking, accurate depictions could be obtained in 3 (30%) of the 10 nerves. With probabilistic tracking, the depictions were accurate in 7 nerves (70%). The results are summarized in Table 3.

In the first case (patient with meningioma in the left

TABLE 2. False-positive errors and Dice coefficients for each of the methods

Factors	False-Positive Error			Dice Coefficient		
	Mean	SD	Median	Mean	SD	Median
Deterministic	0.22	0.3	0.06	0.44	0.1	0.5
Probabilistic	0.04	0.18	0	0.55	0.19	0.6
HCP–deterministic	0.17	0.32	0	0.45	0.09	0.46
HCP–probabilistic	0.03	0.15	0	0.60	0.19	0.66
KR–deterministic	0.32	0.34	0.22	0.42	0.11	0.43
KR–probabilistic	0.06	0.23	0	0.43	0.16	0.43

Values are also shown separately for the individual data sets.

FIG. 2. Images of one of the healthy subjects obtained from the HCP database. **A:** Deterministic fiber tracking of the left oculomotor nerve with an FA threshold of 0.05. The depiction contains correct fibers; however, it also contains an additional nonexistent pathway connecting the cavernous sinus and the brainstem over the temporal lobe (arrow). **B:** With an FA threshold of 0.08 (highest threshold that produced any fibers), the incorrect pathway has been eliminated. The remaining erroneous fibers are not of concern, because they continue to the brainstem and can be easily recognized as false (arrows). **C and D:** The probabilistic tracking with FSL does not output separate fiber pathways, but a map of PICo. In this depiction, the probability that a given voxel contains a connecting pathway is expressed as voxel intensity from 0 to 1. Here, the probabilistic index is displayed with a “hot iron” color map, with red tones representing lower values and yellow tones higher values of PICo. The PICo map is thresholded at a low probability level and shows many possible, but erroneous, connections (C). Thresholding the PICo map at a higher level leads to correct depiction of the oculomotor nerve with even better elimination of the erroneous fibers than in deterministic tracking (D). **E:** In this case, the attempted depiction of the optic nerve (arrows) failed with deterministic tracking, with only incorrect fibers remaining at higher FA thresholds. **F:** Probabilistic tracking of the same nerve shows the correct position. Figure is available in color online only.

cerebellopontine angle), the position of ventrally displaced CN V was observed in the CISS image, whereas CNs VII and VIII were not visible. Intraoperatively, both CN VII and VIII were located below the meningioma ventrally. The probabilistic tracking displayed the position of all nerves accurately, whereas the deterministic tracking failed for the CN VII+VIII bundle (Fig. 3).

In the second case, the visualization of both optic nerves was attempted. The chiasma and the nerves were severely displaced and flattened by the tumor. Although the intraorbital portion was tracked accurately by both methods, the portion of the nerves distended and displaced by the tumor could not be visualized accurately by either method. The deterministic tracking showed fiber loops running partially through the tumor in this location, whereas the probabilistic tracking showed a displacement of both nerves that

TABLE 3. Overview of tracking results in clinical cases

Case	CN	Deterministic Tracking	Probabilistic Tracking
1	V	Accurate	Accurate
	VII	Inaccurate	Accurate
	VIII	Inaccurate	Accurate
2	II (lt)	Inaccurate	Inaccurate
	II (rt)	Inaccurate	Inaccurate
3	II (lt)	Accurate	Accurate
4	VII	Inaccurate	Accurate
	VIII	Inaccurate	Accurate
5	VII	Accurate	Accurate
	VIII	Not displayed	Not displayed

did not correspond to the anatomical image. Artifacts in the DTI scan caused by the air near to the nerve probably caused this distortion. Nevertheless, the depictions obtained could not be considered accurate (Fig. 4).

In the third case, we attempted to visualize the left CN II in a case of sphenoid wing meningioma. Intraoperatively, the nerve was displaced below the tumor. The depictions obtained using both probabilistic and deterministic tracking were considered accurate by the surgeon (Fig. 4).

In the fourth case, we attempted to visualize CNs VII and VIII in vestibular schwannoma. The probabilistic tracking showed 2 distinct pathways from the brainstem to the internal auditory meatus (Fig. 5). One pathway was in the anterior upper third and the second pathway was in the posterior lower third of the tumor, according to the Sampath classification,³ a rare position present in approximately 1% of cases. Intraoperatively, the facial nerve was identified in the anterior position, the acoustic nerve was found in the posterior position, and the probabilistic depiction was classified as accurate. The deterministic tracking showed a connection in the anterior part of the tumor; however, the depiction was located in the anterior middle third and inside of the tumor. The posterior pathways shown were considered to be artifacts. As such, the depiction of both nerves was classified as inaccurate with deterministic tracking.

In the fifth case, both probabilistic and deterministic fiber tracking showed a connection in the anterior upper third (at brainstem) and middle third (at meatus) of the tumor, corresponding to the intraoperative position of the facial nerve (Fig. 5). The cochlear nerve (observed in the anterior lower third intraoperatively) was not depicted by either method.

Discussion

Our study shows that probabilistic fiber tracking can be used to depict the course of the cranial nerves more successfully than the previously described deterministic tracking. With the use of the gradual threshold increase technique, however, even the deterministic tracking delivered acceptable results corresponding to the known nerve anatomy. Therefore, the gradual threshold technique originally proposed by Yoshino et al. represents a promising method of noise removal in DTI of the cranial nerves.^{22,24} The mean and median false-positive error values as well

FIG. 3. First clinical case, patient with meningioma in the left cerebellopontine angle. The tumor has been rendered as semi-transparent. **A:** Deterministic tracking of the trigeminal nerve with an FA threshold of 0.21 displays correct as well as incorrect fibers. **B:** With probabilistic tracking, the PICo index is displayed as *red* for lower and *yellow* for higher values, showing correct position of the nerve. **C:** At an FA threshold of 0.23, the incorrect fibers were eliminated in deterministic tracking; the PICo voxel cloud is overlaid for comparison. **D:** Results of deterministic tracking at FA 0.23 viewed ventrally. **E:** Deterministic tracking of the facial/vestibulocochlear bundle, at an FA threshold of 0.18, the correct (below the tumor) position is shown alongside 1 incorrect pathway (actually corresponding in part to the trigeminal nerve). **F:** At a threshold of 0.20, the correct pathway was eliminated. Note the sudden changes in the result with minimal changes in the FA threshold, typical for deterministic tracking. **G:** The PICo voxel cloud (*yellow*, marked with an *arrow*) is shown in the frontal view corresponding to the correct pathway. **H:** With PICo at the threshold of 0.3, the probabilistic tracking shows the correct position of the nerve, with all other pathways eliminated. Figure is available in color online only.

as Dice coefficients for both tracking methods show that the majority of trials resulted in acceptable results, where most of the volume of the depiction corresponded to the actual nerve position.

In another important finding of our study, the use of DTI data with higher angular resolution and overall better quality (HCP) led to better depictions of the nerves, confirming the previous finding reported by Roundy et al.¹³ Because cranial nerves only contain fibers in one direction, it is possible that the higher signal-to-noise ratio obtained with repeated scanning plays a more important role than the number of directions itself.

FIG. 4. **A and B:** Second clinical case. Both methods of tracking failed to display the pathway of the optic nerves into the distended chiasm (marked in the T1 image with *arrows* in **A**). The probabilistic tracking shown in **B** could only compute a small number of fiber tracts passing through the ROIs, leading to a result very similar to deterministic tracking. **C–F:** Third clinical case (note that the tumor is shown from below). Deterministic tracking with an FA threshold of 0.18 (**C**). The gradual FA threshold increase leads to selection of a small number of fibers in the correct position, with an FA threshold of 0.20 (**D**). Note the difference from the depiction obtained with an FA threshold of 0.18. The result of the probabilistic tracking (**E**) can be compared with that for the deterministic fiber tracts (**F**). Figure is available in color online only.

The observed improvement in cranial nerve depiction can have important clinical implications. The ability to delineate the course of the cranial nerve preoperatively can facilitate the planning of the approach, a motivation for each of the above-cited studies on DTI depiction of cranial nerves. If manual fiber exclusion can be avoided, the technique will become more robust and reliable.

In previous studies, ad-hoc manipulation of the seed ROI, manual FA manipulation, and manual selection of fibers were used to eliminate the erroneous fibers.^{6,20} Some authors describe modest manual fiber selection (such as excluding fibers not corresponding to the awaited anatomical location^{3,13,18}). Only a minority of authors do not describe any manual fiber selection method.^{2,25} Manual fiber selection and ad-hoc threshold manipulation might be acceptable in a study aimed to prove that diffusion-based methods are overall able to depict fibers corresponding to cranial nerves with a priori knowledge of the anatomical course as described by Hodaie et al.⁶ However, these manipulations are mainly based on investigator expectation of the anatomical position of the nerve, making the claims about possible detection of cranial nerve position weak.

The approach of gradual FA increase proposed by Yoshino et al. in their series of papers appeared very successful (90%) in healthy subjects.²⁴ Of note, they have used a

FIG. 5. Fiber tracking of the facial and vestibulocochlear nerves in patients with vestibular schwannoma. **A:** Fourth clinical case. At an FA threshold of 0.14, many pathways caused by noise are present. With manual fiber selection, depiction of essentially any nerve position would be possible. **B:** With an FA threshold 0.18, the remaining ventral pathways end in the tumor, and dorsal pathways mostly depart from the tumor (arrow). Other dorsal pathways showed a course with improbable curvature from superior to inferior and were considered to be artifacts. **C:** Oblique view from behind. PICo cloud resulting from the probabilistic tracking. This depiction shows a ventral pathway in the anterior upper third according to Sampath classification and another pathway in the posterior lower third of the tumor. This is a rare localization of the nerve (0.9% according to the Sampath et al.¹⁴). Both positions depicted by probabilistic tracking were shown to correspond to the real course of the nerves intraoperatively. **D:** Superior view of the PICo cloud in comparison with the deterministic pathways. **E:** Fifth clinical case, deterministic tracking with an FA threshold of 0.20 shows an incorrect pathway over the superior pole of the tumor. **F:** Ventral view of the depiction. **G and H:** With an FA threshold of 0.22, the incorrect pathway has been eliminated. Probabilistic tracking (also shown in H) produced the same result, corresponding to the intraoperative findings. However, the cochlear nerve was not depicted by either method. Figure is available in color online only.

very restrictive angular threshold in this initial analysis (30°), leading to preferential selection of straight streamlines. However, in our opinion, such restriction in angular threshold cannot be used in situations where we expect the nerve to be displaced by a tumor. Consequently, using the same technique, Yoshino et al. observed DTI depictions corresponding to the facial nerve in only 3 of 11 vestibular

schwannoma patients and depictions corresponding to the cochlear nerve in 6 of these patients.²³ This relatively low success rate is in strong contrast to the above-mentioned studies using manual fiber selection. The authors concluded that good methods for distinguishing a nerve depiction from the noise remain unavailable. Even in their subsequent publication, combining DTI fiber tracking with multifused contrast-enhanced FIESTA (fast imaging employing steady-state acquisition) scans, Yoshino et al. did not reach the rates of nerve depiction reported by other authors.²² However, among the studies published up to now, we consider their approach to be the only useful method for actual detection of cranial nerve position. Although we did not use categorical classification of nerve depictions as correct or incorrect and relied on comparison with a ground truth image with continuous parameters as a result, our results regarding deterministic fiber tracking are comparable to those of Yoshino et al.

The use of automated comparison of the tracking results with manually created ground truth templates in normal subjects represents the main limitation of our study. Fibers that would be easily identified as erroneous by a human observer and excluded might have influenced the results. A visual comparison of the tracking results with the underlying anatomy would perhaps be more useful, because it would be similar to the use of the technique in clinical settings. However, given the number of depictions obtained during the course of the gradual threshold analyses, an accurate and consistent evaluation by human observers became impossible. Moreover, even though the identification of erroneous connections can be considered straightforward in anatomical settings, it might represent a problem in pathological conditions. Therefore, we consider the use of automatic evaluation appropriate. It must be noted that in the PICo map, the thresholding does not necessarily lead to a depiction of structures resembling nerves in shape. As the thresholding eliminates individual voxels, regions containing the connection between the 2 ROIs with high probability remain in the image. Although such depictions do not represent a geometrical correlate to a nerve, given their good correspondence with the actual nerve position, they might be more useful than the artificial nerve fibers customarily used in deterministic fiber tracking. Moreover, higher maximal Dice coefficients show that a geometrically adequate nerve depiction resulted from the thresholding of probabilistic tracking.

As another limitation, we only tested the proposed method using 2 types of DTI sequences, both with fairly high resolution. The validity of our results therefore remains to be confirmed in data acquired clinically. For instance, if the data are acquired with a lower spatial or angular resolution, any tracking algorithm is likely to fail in a higher proportion of cases. Special DTI sequences optimized for cranial nerve imaging should be preferred.

One limitation of the usability of the probabilistic tracking is the time efficiency, which is usually unsuitable for clinical use. For instance, the analyses performed on healthy subjects in this study took 15–28 hours of computation time (Core i5, 16 GB RAM, 1 TB SSD, CUDA-capable nVIDIA graphic card) per subject. This amount of time was needed due to the large volume included in the

analysis (the whole skull base and surrounding brain parenchyma). However, in the clinical cases presented here, the processing time was significantly shortened by adjusting the volume of interest based on our analysis to the region containing the nerves of interest. In the probabilistic tractography, the computing time needed to perform the analysis of a single nerve could be reduced to approximately 30 minutes. The time needed to complete the deterministic fiber tracking in all possible FA thresholds was approximately 15 minutes for each nerve.

Further evaluation of the proposed gradual threshold increase method is warranted. A repetition of this particular analysis, especially in pathological settings, is of great interest and is currently being undertaken at our institution. The 5 clinical cases presented in this report represent the preliminary results of this ongoing study.

Conclusions

Probabilistic tractography combined with the previously proposed method of gradual threshold increase for noise elimination yielded significantly more accurate depictions of cranial nerves than those achieved with conventional deterministic fiber tracking. Therefore, this method might represent a possible solution to the problem with the necessity of manual noise exclusion. Its utility remains to be verified in a larger clinical series.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Zolal, Kitzler. Acquisition of data: Zolal.

Analysis and interpretation of data: Zolal, Sobottka, Podlesek, Rieger, Juratli, Kitzler. Drafting the article: Zolal, Juratli, Kitzler. Critically revising the article: Sobottka, Podlesek, Linn, Rieger, Juratli, Schackert, Kitzler. Approved the final version of the manuscript on behalf of all authors: Zolal. Statistical analysis: Zolal. Study supervision: Sobottka, Linn, Rieger, Schackert, Kitzler.

Supplemental Information

Previous Presentations

The preliminary results of this study (with 5 initial normal subjects) were published at a national congress as an abstract (<http://dx.doi.org/10.3205/15dgnc402>).

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