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Quantifying diffusion MRI tractography of the corticospinal tract in brain tumors with deterministic and probabilistic methods☆

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ABSTRACT

Introduction: Diffusion MRI tractography has been increasingly used to delineate white matter pathways in vivo for which the leading clinical application is presurgical mapping of eloquent regions. However, there is rare opportunity to quantify the accuracy or sensitivity of these approaches to delineate white matter fiber pathways in vivo due to the lack of a gold standard. Intraoperative electrical stimulation (IES) provides a gold standard for the location and existence of functional motor pathways that can be used to determine the accuracy and sensitivity of fiber tracking algorithms. In this study we used intraoperative stimulation from brain tumor patients as a gold standard to estimate the sensitivity and accuracy of diffusion tensor MRI (DTI) and q-ball models of diffusion with deterministic and probabilistic fiber tracking algorithms for delineation of motor pathways.
Methods: We used preoperative high angular resolution diffusion MRI (HARDI) data (55 directions, $b = 2000$ s/mm^2) acquired in a clinically feasible time frame from 12 patients who underwent a craniotomy for resection of a cerebral glioma. The corticospinal fiber tracts were delineated with DTI and q-ball models using deterministic and probabilistic algorithms. We used cortical and white matter IES sites as a gold standard for the presence and location of functional motor pathways. Sensitivity was defined as the true positive rate of delineating fiber pathways based on cortical IES stimulation sites. For accuracy and precision of the course of the fiber tracts, we measured the distance between the subcortical stimulation sites and the tractography result. Positive predictive rate of the delineated tracts was assessed by comparison of subcortical IES motor function (upper extremity, lower extremity, face) with the connection of the tractography pathway in the motor cortex.
Results: We obtained 21 cortical and 8 subcortical IES sites from intraoperative mapping of motor pathways. Probabilistic q-ball had the best sensitivity (79%) as determined from cortical IES compared to deterministic q-ball (50%), probabilistic DTI (36%), and deterministic DTI (10%). The sensitivity using the q-ball algorithm (65%) was significantly higher than using DTI (23%) ($p < 0.001$) and the probabilistic algorithms (58%) were more sensitive than deterministic approaches (30%) ($p = 0.003$). Probabilistic q-ball fiber tracks had the smallest offset to the subcortical stimulation sites. The offsets between diffusion fiber tracks and subcortical IES sites were increased significantly for those cases where the diffusion fiber tracks were visibly thinner than expected. There was perfect concordance between the subcortical IES function (e.g. hand stimulation) and the cortical connection of the nearest diffusion fiber track (e.g. upper extremity cortex).
Discussion: This study highlights the tremendous utility of intraoperative stimulation sites to provide a gold standard from which to evaluate diffusion MRI fiber tracking methods and has provided an object standard for evaluation of different diffusion models and approaches to fiber tracking. The probabilistic q-ball fiber tractography was significantly better than DTI methods in terms of sensitivity and accuracy of the course through the white matter. The commonly used DTI fiber tracking approach was shown to have very poor sensitivity (as low as 10% for deterministic DTI fiber tracking) for delineation of the lateral aspects of the corticospinal tract in our study. Effects of the tumor/edema resulted in significantly larger offsets between the subcortical IES and the preoperative fiber tracks. The provided data show that probabilistic HARDI tractography is the most objective and reproducible analysis but given the

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small sample and number of stimulation points a generalization about our results should be given with caution. Indeed our results inform the capabilities of preoperative diffusion fiber tracking and indicate that such data should be used carefully when making pre-surgical and intra-operative management decisions.

1. Introduction

There has been a tremendous interest in the use of diffusion magnetic resonance fiber tracking for presurgical mapping of eloquent regions. Intraoperative electrical stimulation (IES) provides a clinical gold standard for the existence of functional motor pathways that can be used to determine the accuracy and sensitivity of fiber tracking algorithms (Berman et al., 2004, 2007; Clark et al., 2003; Krings et al., 2001; Mikuni et al., 2007; Nimsky et al., 2005a, 2006).

Fiber tracking with the diffusion tensor (DTI) model of tissue water displacements assumes that the direction of least restriction as estimated by principal eigenvector of the fitted tensor, corresponds to the direction of white matter tracts. However, the diffusion tensor model is ideal only for describing a single fiber population within a given voxel. Both deterministic and probabilistic streamline diffusion tensor fiber tracking techniques have well known limitations in delineating the full dispersion of these fiber pathways, parts of which pass through regions of complex white matter, as in the centrum semiovale, where major white matter tracts such as the pyramidal tract, the superior longitudinal fasciculus and the corpus callosum are known to intersect. This has been shown to hinder clinical applications such as preoperative mapping of the pyramidal tract in brain tumor patients. Thus, DTI will not accurately describe the microstructure in complex white matter voxels that contain more than one fiber population, due to intersecting tracts or to partial volume averaging of adjacent pathways with different fiber orientations.

To more accurately delineate pathways within complex regions of white matter, it is desirable to use the information derived from high angular resolution diffusion imaging (HARDI) for fiber tracking. The q-ball reconstruction of HARDI data provides an orientation distribution function (ODF) that can be used to determine the orientations of multiple fiber populations contributing to a voxel's diffusion MR signal (Tuch, 2004; Tuch et al., 2003). Tractography based on the q-ball ODF has the potential to traverse regions of crossing fibers, which are found extensively throughout the human brain. The peaks of the ODF are assumed to point in the direction of white matter tracts. The q-ball ODF is used to propagate fiber trajectories through regions of complex tissue architecture. The q-ball ODF is formulated using the spherical harmonic basis, which results in fast computation of the ODF at each voxel from a HARDI acquisition that can be completed in a clinically feasible time frame (Hess et al., 2006).

Deterministic fiber tracking methods use a linear propagation approach, proceeding according to the principal eigenvector direction (Mori et al., 2002). Probabilistic streamline fiber tracking methods incorporate the uncertainty of diffusion MR measurements to propagate according to a probability distribution function (Jones and Pierpaoli, 2005; Lazar and Alexander, 2003; Parker et al., 2003).

In this study we used the residual bootstrap, a non-parametric statistical technique based on data re-sampling that has been shown to accurately estimate the uncertainty in diffusion data (Berman et al., 2008; Chung et al., 2006). We used IES data as gold standard to evaluate the accuracy and sensitivity of both deterministic and probabilistic propagation with diffusion tensor (DTI) and q-ball fiber tracking methods.

2. Methods

2.1. Magnetic resonance imaging

MR images were acquired using a 3 T Signa scanner (General Electric Medical Systems, Milwaukee, WI) using an 8-channel head coil from 12 patients who underwent a craniotomy for resection of a cerebral glioma (10 M/2 F, mean age 42 years). Preoperative HARDI was acquired using a single-shot spin-echo echo-planar imaging (EPI) in approximately 13 min with the following parameters: in plane resolution = 2.2×2.2 mm^2, slice thickness = 2.2 mm, repetition time/echo time (TR/TE) = 11,350/74 μs, flip angle = 90°, matrix = 100×100; 55 diffusion sensitizing gradient directions at b = 2000s/mm^2,1 set without diffusion weighting, b = 0 s/mm^2, and an iPAT acceleration factor of 2.

High-resolution T2-weighted and post-contrast T1-weighted anatomical MR images were also acquired in the same session for use with the stereotactic surgical navigation system. The T2-weighted images were acquired with an axial fast spin-echo (FSE) pulse sequence as follows: TR 3 = seconds, TE = 105 μs, field of view = 260×195 mm, matrix = 256×192, and voxel size = $1.02 \times 1.02 \times 1.5$ mm with no gap between slices. The T1-weighted images were acquired with a spoiled gradient-recalled (SPGR) sequence as follows: TR = 34 ms, TE = 3 ms, field of view = 260×195 mm, matrix = 256×192, and voxel size = $1.02 \times 1.02 \times 1.5$ mm with no gap between slices. The FSE and SPGR acquisition coverage included the entire head and the fiducial markers attached to the head.

2.2. Intraoperative electrical stimulations

The surgeon performed multiple motor intra-operative electrical cortical and subcortical stimulations on the patients, during the surgical procedure with a 5-mm-wide bipolar electrode, eliciting a 60-Hz square wave with amplitude between 8 and 12 mA (Berger and Ojemann, 1994).

Mapping of the motor cortex was performed in these patients according to the location of the tumor. Cortical and subcortical points that elicited a motor response were stereotactically identified on the anatomical images and cortical stimulation was directly applied to the patient's exposed cortex. The positive motor site was defined as an area that induced an involuntary movement when stimulated. During the surgery, white matter stimulation was applied in some of the cases to identify the pyramidal pathway at the border of the resection. The motor responses in muscle groups in both upper and lower the extremities were monitored through electromyography recordings (Yingling et al., 1999).

The coordinates of the stimulation points were defined from the screen shots of the anatomical images with the aid of the Stealth Station surgical navigation workstation (Medtronic, Broomfield, CO) and then reported to the DWI's space for each subject through an affine transformation.

2.3. Diffusion fiber tracking algorithms

Eddy current and head motion corrections were performed by applying an affine transformation of each diffusion-weighted volume to the first no diffusion-weighted volume (b0) using the Diffusion toolbox (FDT) provided in FMRIB Software Library (FSL). Fiber tracking algorithms were developed in house-built software written in Interactive Data Language (IDL, Research System, Inc., Boulder, CO).

q-Ball (Clark et al., 2003) and DTI (Basser et al., 2000) diffusion models were used to determine estimates of fiber orientations. Deterministic and probabilistic tracking algorithms were used with each diffusion model. The DTI models were used with the fiber assignment by continuous tracking (FACT) algorithm (Mori et al., 1999) and with a probabilistic version of this algorithm based on bootstrap resampling of residuals from the weighted least squares fit (Chung et al., 2006). The deterministic and probabilistic q-ball approaches also used the FACT propagation as implemented previously with residual bootstrap for the probabilistic version (Behrens et al., 2003; Berman et al., 2008). For the FACT algorithm we used as FA threshold equal to 0, 15 and angle threshold equal to 60°.

Diffusion MRI fiber tracks of the pyramidal tract were generated post-operatively in our patients using four different algorithms: Diffusion Tensor (DTI) and q-ball fiber tracking methods both deterministic and probabilistic. We used cortical and subcortical IES sites as a gold standard for the presence and location of the functional motor pathways related to the different components of the corticospinal tract. We drew regions ipsilaterally to the brain tumor for the fiber tracking in each DWI's subject space. We identified as ROIs the cerebral peduncle (CP) using anatomical landmarks in the midbrain as references, and the sites of the cortical stimulations in the precentral gyrus for the motor cortex (MC), creating a 3D squared ROI of 5 × 5 voxels. Using the logical AND operation, the fiber tracks passing through both the cerebral peduncle and the motor cortex or IES cortical sites were isolated and identify as fibers of interest. Using the logical AND operation, the fiber tracks passing through both the cerebral peduncle and the motor cortex related to the areas of the subcortical stimulation points were isolated and identify as fibers of interest for the subcortical stimulations. We used alternatively both the cerebral peduncle and precentral gyrus (or the intra-operative electrical stimulation site in the precentral gyrus) as seed regions. The seeding regions of interest (ROI) were seeded densely with 7 × 7 × 7 seeding points per voxel of the seed region. Connectivity was assessed if the number of streamlines found was 10 or more. This is an approximate guard against spurious connections. The number of streamlines typically follows approximately a Poisson distribution and the variance is equal to the mean; hence choosing streamlines greater than 10 approximates a minimum coefficient of variability of about 0.3 on the estimate of the number of streamlines given the seeding strategy used. These data were all acquired and post-processed and sent to the neuro-navigational unit on the same day with scans occurring sometimes in the evening and surgery is usually scheduled early the next morning. Typical run times for delineation of the corticospinal tract is 30 min.

2.4. Sensitivity analyses

The presence of cortical IES site indicates the presence of functional motor pathways. Here we assessed the ability of the four fiber tracking algorithms to delineate the known functional pathways between the cortical IES site and the cerebral peduncle. The sensitivity was the fraction of cases where the fiber tracking algorithm was able to delineate the known pathway (true positive rate). The sensitivity was determined for each of the four algorithms using alternatively the cortical IES site and the cerebral peduncle as seed regions.

2.5. Positive predictive rate/accuracy analyses

The subcortical IES sites allowed us to determine the accuracy of the course of the delineated fiber tracks by noting the offset between the IES and the nearest fiber track. The offset was measured from the subcortical IES site to the edge of the nearest diffusion fiber track in 3-dimensions. The positive predictive rate of this assignment was also evaluated by comparing the functional stimulation of the intra-operative electrical stimulation (IES) to the known anatomically specific cortical destination of the fiber track.

2.6. Statistical analysis

Four pair-wise t-test comparisons were made for sensitivity comparing diffusion models (q-ball versus DTI), algorithms (probabilistic versus deterministic). For the offsets between subcortical stimulation points and diffusion fiber tracks we calculated the means, medians, quartiles, and interquartile range for the offsets. Pairwise t-tests were performed for offsets from q-ball probabilistic, q-ball deterministic, DTI probabilistic, and DTI deterministic. A step-wise regression was performed with the affected diffusion fiber track appearance at the level of the IES subcortical site, model (q-ball or DTI), and algorithm (probabilistic or deterministic) as variables to test the influence on the observed variation in offsets.

3. Results

We identified 21 cortical motor stimulations points – 8 from the head region (face/mouth) and 13 from the upper extremity region (hand, wrist, forearm, shoulder) – and 8 subcortical motor stimulation points — 1 from the face region (face/mouth), 2 from the upper extremity region (hand, arm), and 5 from the lower extremity region (leg, foot).

3.1. Cortical stimulation

In Table 1 we report the sensitivity found when tracking from the cerebral peduncle to the motor cortex stimulation sites and from motor cortex stimulation sites to the cerebral peduncle with the various fiber tracking algorithms. The sensitivity using the q-ball algorithm (65%) was significantly higher than using DTI (23%) (difference of sensitivity: 42%; $p < 0.001$, CI 23%, 60%) and the probabilistic algorithms (58%) were more sensitive than deterministic (30%) (difference of sensitivity: 28%; $p = 0.003$; CI 11%, 45%).

3.2. White matter–subcortical stimulation

We analyzed 8 subcortical stimulation points from 5 patients shown in Table 2.

High positive predictive rate of the delineated tracts was determined since the closest motor tracks to the stimulation points were found to reach the cortex, where the part of the motor homunculus is known to be located. The concordance was 100% between subcortical functional IES site and end point of fiber tracking for all 4 algorithms when a FT was found (Fig. 1).

For example, all leg and foot subcortical stimulations were closest to delineated fiber tracts that connected with the lower extremity portion of the motor cortex, all arm and hand stimulations were closest to delineated tracts connecting the upper extremity portion of the cortex (Fig. 2), and the face subcortical stimulation was closest to a delineated tract that connected with the face motor cortical area, based on the known anatomical location of these areas of the motor homunculus in the human brain.

Significantly larger offsets between subcortical stimulation and fiber tracts were observed for cases with thinned appearance on the dMRI fiber tracks (14.8 mm versus 3.4 mm; $p < 0.001$). The thinned appearance was assessed to originate from incomplete tracking of the CST

Table 1
Cortical stimulation results.

	Probabilistic q-ball-FT CP → MC/ MC → CP	Deterministic q-ball-FT CP → MC/ MC → CP	Probabilistic DT-FT CP → MC/ MC → CP	Deterministic DT-FT CP → MC/ MC → CP
Face	63%/75%	38%/63%	13%/63%	0%/0%
Upper extremities	92%/85%	62%/38%	15%/54%	15%/23%
All motor sites	79%	50%	36%	10%

Sensitivity found when tracking from the cerebral peduncle (CP) to the motor cortex stimulation sites (MC) and from motor cortex stimulation sites (MC) to the cerebral peduncle (CP) with the various fiber tracking algorithms (FT).

Table 2
White matter/subcortical results.

Subject/ case	Subcortical stimulation	dMRI track at motor cortex	CST involved	dMRI-track appearance at IES sites	Distances to IES sites (mm) qp, qd, dp, dd
1	Leg	Lower extremity	Yes	Thinned/ impaired FT	13, 15, 15, 19
2a	Leg	Lower extremity	Yes	Thinned/ impaired FT	21, 25, 23, 26
2b	Leg	Lower extremity	Yes	Thinned/ impaired FT	9, 12, 13, 11
3	Foot	Lower extremity	Yes	Thinned/ compressed CST	7, 8, 10, 10
4	Foot	Lower extremity	Yes	Normal	3, 3, 6, 8
5a	Arm	Upper extremity	Yes	Normal	1, 4, 1, 1
5b	Hand	Upper extremity	Yes	Normal	1, 2, 1, 3
5c	Face	Face motor	Yes	Normal	4, 5, 4, 8

Results from the obtained preoperative diffusion fiber tracks and white matter/subcortical stimulation (IES) sites (dMRI: diffusion Magnetic Resonance Imaging. IES: Intraoperative electrical stimulation. CST: corticospinal tract. qp: probabilistic q-ball; qd: deterministic q-ball; pd: probabilistic dti; dd: deterministic dti).

(cases 1, 2a, 2b) or compressing of the corticospinal tract (case 3). As shown in Table 3, the offsets were significantly shorter for q-ball probabilistic (mean 7.4 mm) compared to q-ball deterministic (9.3 mm), compared to DTI probabilistic (9.2 mm), and compared to DTI deterministic tracks (11 mm). Overall the differences between approaches were influenced by the presence of edema and tumor that led to a thinned appearance of the dMRI fiber tracks where q-ball and probabilistic approaches gave shorter offsets; in a step-wise regression analysis with affected, model, and algorithm only the thinned appearance was found to independently predict the offsets observed ($rsq = 0.67$, $p < 0.001$). The diffusion fiber track widths measured at the level of the white matter/subcortical IES sites are shown in Table 3. In a step-wise regression with model (q-ball vs DTI), algorithm (probabilistic vs deterministic), and affected appearance as regressors, the probabilistic approaches were found to have significantly larger widths and a trend towards larger widths with the q-ball model.

Table 4 describes in detail the characteristics of each case in terms of histology, involvement of corticospinal tract, tumor location, intraoperative stimulation site and presence of edema.

4. Discussion

Preoperative fiber tracking using diffusion MR imaging is routinely used as part of the preoperative planning and the intraoperative mapping of brain tumors, especially for those close to eloquent brain regions or within known fiber tracts (Henry et al., 2004; Holodny et al., 2001; Kamada et al., 2005; Stadlbauer et al., 2007).

Our study highlights the importance of the validation and quantification of preoperative fiber tracking methods, with the aid of intraoperative electrophysiological data as a gold standard. In this study, we have used intraoperative electrical stimulation to quantify the sensitivity of four different fiber tracking algorithms. In particular, using the cortical motor stimulation sites as gold standard for the location of known cortical motor sites, we were able to evaluate the number of true positives for different diffusion fiber tracking methods. In addition, using white matter/subcortical stimulation points we were able to assess the accuracy and a coarse measure of specificity (positive predictive rate) of preoperative diffusion MRI fiber tracking to predict the course of motor fiber tracts.

Novel findings include quantitative evaluation of the sensitivity, positive predictive rate, and accuracy of conventional and newer approaches to diffusion MRI fiber tracking of the corticospinal tract; also novel is the direct impact of the brain tumor environment on the preoperative mapping of these diffusion fiber tracks. For preoperative brain tumor patients the adverse pathological conditions, such as the presence of brain tumor and the surrounding edema, were shown to affect the accuracy of the diffusion fiber tracks as shown in Fig. 3, using q-ball probabilistic algorithm and in Fig. 4, where we compare the results of the four algorithms.

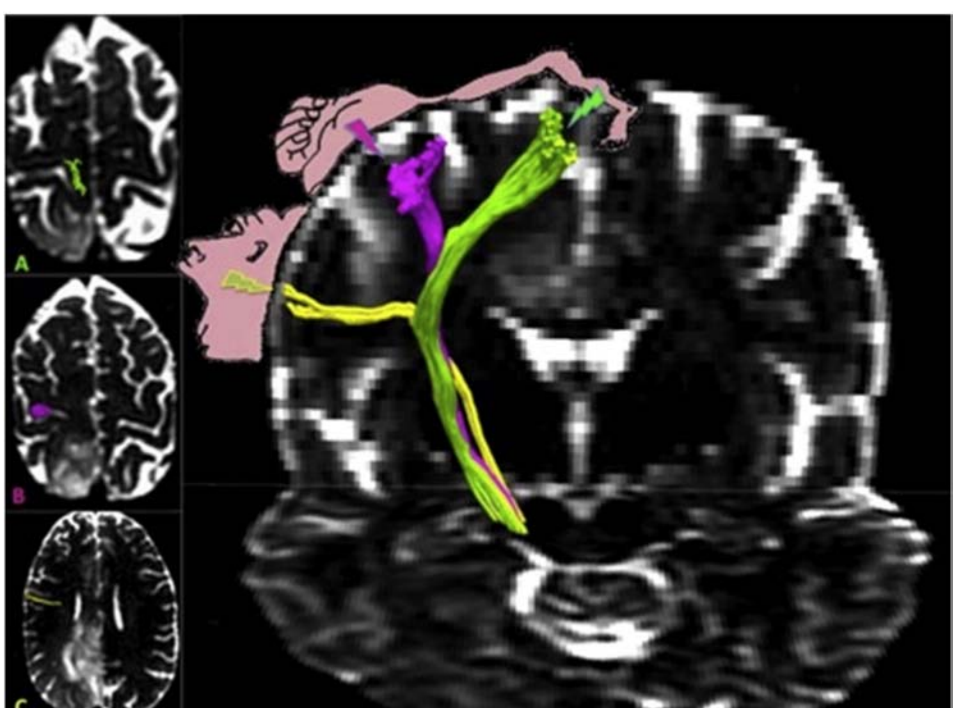

Fig. 1. High positive predictive rate of the delineated fiber tracks: using q-ball probabilistic algorithm, the closest motor tracks to the stimulation points were found to reach the cortex, where the part of the motor homunculus (yellow = FACE, pink = UPPER EXTREMITIES, green = LOWER EXTREMITIES) is known to be located, in perfect (100%) concordance with the intraoperative stimulation (ARROWS). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

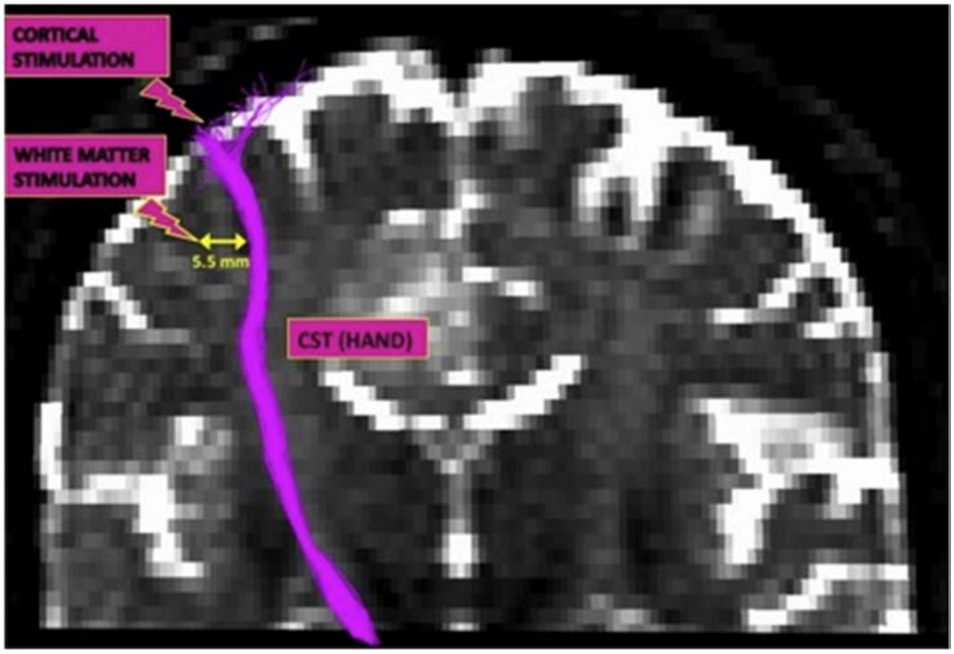

Fig. 2. High positive predictive rate of the delineated fiber tracks: the closest motor tracks to the stimulation points were found to reach the cortex, where the part of the motor homunculus is known to be located. The median offset between the subcortical stimulation site and the edge of the probabilistic q-ball fiber track, found for the upper extremity (CST hand = corticospinal tract for the hand) seeding from the cerebral peduncle to the cortical IES for the hand motor, was as low as 5.5 mm.

Altogether, our results suggest poor performance for DTI fiber tracking with or without probabilistic fiber tracking and substantial improvement with probabilistic q-ball fiber tracking with 79% sensitivity. These results suggest room for improvement and care in interpreting the results of diffusion fiber tracking of the corticospinal tract for clinical management.

4.1. Quantitative validation of fiber tracking methods

The major limitation of DTI fiber tracking is the inability to reconstruct the tracks through regions of crossing fibers, resulting in inaccurate depiction of the motor tract. Our objective comparison of DTI and q-ball models with deterministic and probabilistic algorithms manifested the poor sensitivity of DTI methods to define the lateral pathways for the corticospinal tract. While this has been qualitatively noted previously, our study provides the first quantitative assessment of the comparative performance of these fiber tracking approaches.

Although there are several studies that have emphasized the clinical utility of diffusion MRI fiber tractography to visualize in vivo white matter bundles, such as the corticospinal tract, during neurosurgical planning, only few studies have attempted to validate and optimize these approaches for preoperative neurosurgical mapping. Our data provide a rare chance to validate the performance of diffusion fiber tracking algorithms. Our results suggest that indeed significantly better sensitivity is provided by the use of high order models like q-ball and with probabilistic better than deterministic approaches. Furthermore, the ability to delineate these pathways was quantified and demonstrated poor sensitivity of DTI fiber tracking methods to delineate the lateral pathways of the corticospinal tract.

The analysis of white matter stimulation sites establishes an even more rare opportunity to examine the actual course of the diffusion fiber tracks. Our data suggests that indeed when reconstructed, these tracks may be accurate as reflected in the complete matching of stimulated functional area and putative homunculi areas of the cortex. While this only supports a coarse level of specificity (positive predictive rate), certainly it provides a measure of accuracy of the found pathways. In one case we have able to establish the identity of the delineated fiber track from IES at both the cortical and white matter/subcortical levels, providing a more refined assessment of the positive predictive rate of the fiber tracking in the prediction of the subcortical IES site. More data like these are needed to gain more confidence in the utility of these predictions.

4.2. Implications for preoperative mapping

The poor sensitivity shown in our study, especially of DTI fiber tracking, to the lateral bundles of the corticospinal tract, raises the question about the utility of this method for preoperative planning of resections of tumors near or within these pathways. Previous studies showed the positive impact of the combination of DTI and IES for the identification of eloquent fiber tracts and the enhancement of surgical performance with a high rate of functional preservation (Andreas Stadlbauer et al., 2007; Bello et al., 2008).

Compared to our study, these studies used a different FA threshold, which allowed identifying fiber tracks even in the presence of challenging conditions. In our study, the use of probabilistic q-ball fiber tracking with a FA threshold of 0.15, showed to be the most objective and

Table 3
White matter/subcortical stimulation results.

	Probabilistic q-ball-FT edge	Deterministic edge	Probabilistic DT-FT edge	Deterministic DT-FT edge
Median/mean offset	5.5/7.4 mm**	6.5/9.3 mm	8/9.2 mm*	9/11 mm
Median (range)	2 (1, 4) mm	3.5 (2, 5) mm	2.5 (1, 6) mm	5.5 (1, 8) mm
unaffected-FT affected-FT	11 (7, 21) mm	14 (8, 25) mm	14 (10, 23) mm	15 (10, 26) mm
Track width median (range)	2.3 (1.9, 3.5) mm	2.0 (1.5, 2.6) mm	2.4 (1.2, 2.7) mm	1.7 (1, 2.1) mm

Offsets between white matter/subcortical IES points and preoperative diffusion fiber tracks.
** The offsets using the probabilistic q-ball technique were significantly smaller than all other approaches ($p = 0.003$ compared to q-ball deterministic, $p = 0.008$ compared to DTI probabilistic, $p = 0.001$ compared to DTI deterministic).
* DTI probabilistic was significantly shorter than DTI deterministic ($p = 0.03$).

Table 4
Cortical and subcortical motor stimulation results: Histology, involvement of CST, tumor location, intraoperative stimulation site and presence of edema.

ID	Histology	Tumor location	CST involvement by tumor	Stimulated subcortical sites	Presence of edema
1	Oligoastrocytoma II	Precentral gyrus	Dislocated and infiltrated	1 site: lower extremities	Yes
2	Astrocytoma II	Precentral gyrus	Dislocated	2 sites: lower extremities	Yes
3	Astrocytoma III	Prefrontal gyrus	Dislocated, compressed and infiltrated	1 site: lower extremities	Yes
4	Astrocytoma II	Superior temporal gyrus	Infiltrated at the level of internal capsule	1 site: lower extremities	No
5	Astrocytoma III	Postcentral gyrus	Dislocated but not compressed	3 sites: 2 upper extremities, 1 face	Yes
6	Astrocytoma II	Precentral gyrus	Dislocated but not compressed	Only cortical stimulation	
7	Astrocytoma III	Postcentral gyrus	Dislocated but not compressed	Only cortical stimulation	Yes
8	Astrocytoma III	Postcentral gyrus	Dislocated but not compressed	Only cortical stimulation	Yes
9	Astrocytoma II	Precentral and Postcentral gyri	Mildly dislocated	Only cortical stimulation	No
10	Astrocytoma II	Postcentral gyrus	Mildly dislocated	Only cortical stimulation	No
11	Astrocytoma II	Precentral gyrus	Mildly dislocated	Only cortical stimulation	No
12	Astrocytoma III	Parietal lobe/postcentral gyrus	Dislocated	Only cortical stimulation	Yes

reproducible analysis among the four methods used. However, given the small sample and number of stimulation points a generalization about our results should be given with caution.

Pre-operative mapping of the corticospinal tract can be used to aid in efficient intraoperative stimulation mapping with minimal new risk introduced if the reliability of the data is understood. Indeed, our results inform the capabilities of preoperative diffusion fiber tracking and indicate that such data should be used carefully when making pre-surgical and intra-operative management decisions. In this context, clinical decisions are still based on the intraoperative electrical stimulation mapping.

There are several aspects that we have to take in consideration to explain our results. The use of diffusion MRI and fiber tracking technique presents several limitations. Mistakes in the estimation of the fiber tracts are caused by low signal-to-noise ratios, the selection of the seed regions of interest (ROIs), the choice of the threshold for the anisotropy, the algorithm used in the procedure, or the presence of crossing fibers (Mandelli et al., 2012). Moreover, all these aspects become a challenge in the presence of the tumor and the surrounding edema as they affect the diffusion signal. For current neurosurgical planning, the most widely used approach for the reconstruction of the fibers is the deterministic DTI fiber tracking along the principal direction of the tensor (Nimsky et al., 2005b). The major limitation of this method is its poor sensitivity and the inability to reconstruct the tracks through regions of crossing fibers, resulting in inaccurate depiction of the motor tract (Mandelli et al., 2012). Given the fan-shape configuration of the motor fiber tracks at the level of the centrum semiovale, the deterministic DTI is reliably able to distinguish only the principal direction and to depict the fibers traveling to the vertex of the brain (Mandelli et al., 2012).

The importance of a careful approach when interpreting the results of fiber tracking in the presence of conditions that alter the normal structure of the brain should be stressed. For example, in one case, we showed that in the context of edema, even the use of q-ball probabilistic algorithm cannot ensure the estimation of the fibers of the corticospinal tract.

In our cases (Table 2) we found that the presence of the tumor and/or of the surrounding edema can affect the appearance of fiber tracks. In particular, in two cases where the tumor and the edema were in the precentral region we showed a thinned appearance of the fiber tracks, most likely due to the damage that occurred to the corticospinal tract in its course to the motor cortex, and larger offsets with the white matter stimulation sites.

In another case instead, where the tumor was in the prefrontal region and was compressing but not affecting directly the corticospinal tract, the fiber track appeared thinned because the corticospinal tract was most likely compressed/distorted by the lesion.

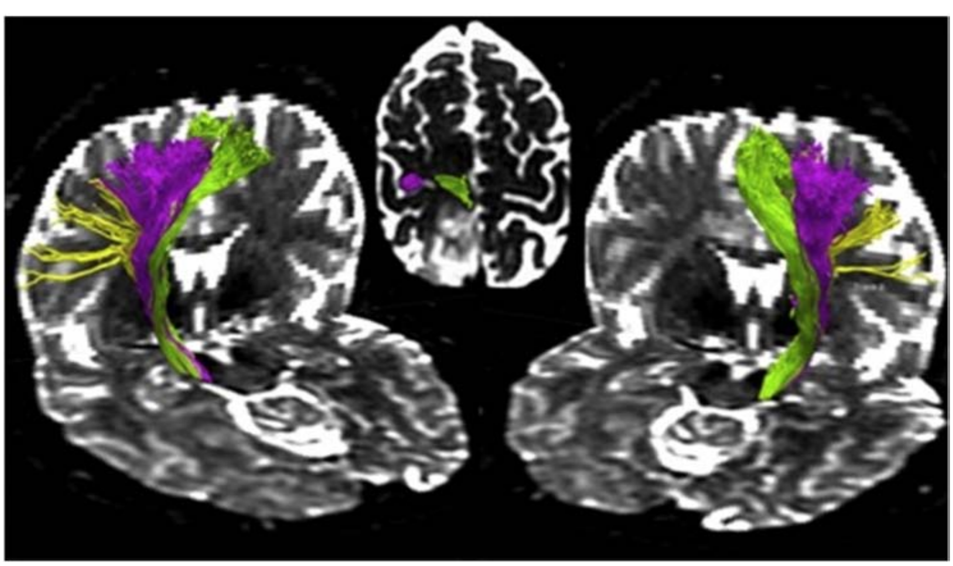

Fig. 3. In brain tumor patients, the adverse pathological conditions, such as the presence of brain tumor and/or the surrounding edema, affect the accuracy and the ability of the diffusion fiber tracking algorithms to fully depict the more lateral aspect of fan-shape configuration the corticospinal tract (yellow fibers), which results thinner and sparse compared to the other, more medial, components of the corticospinal tract (pink and green fibers). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

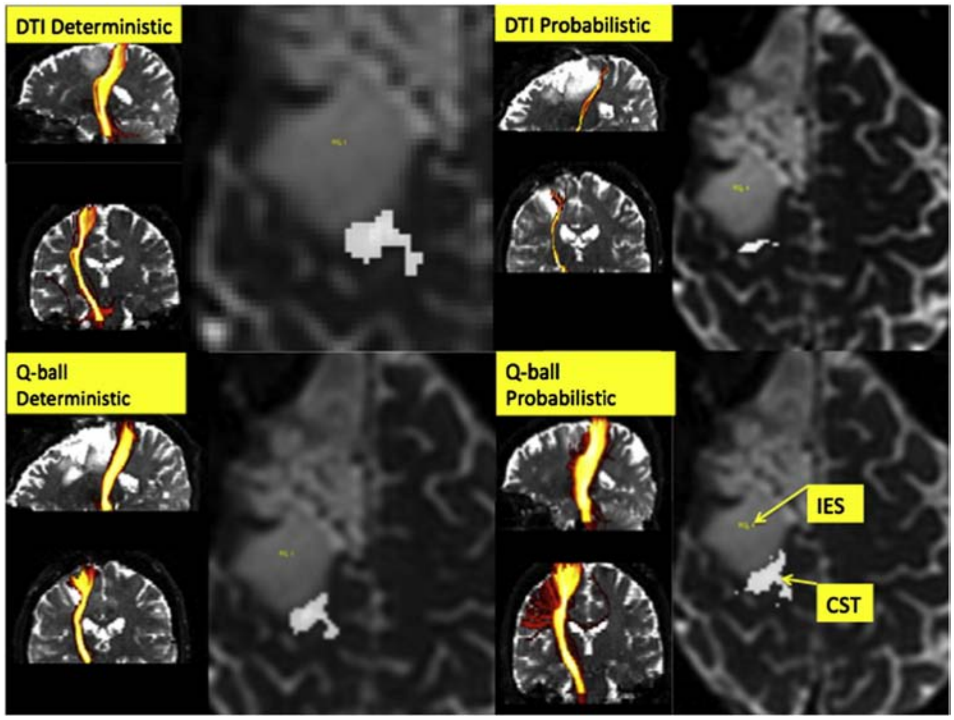

Fig. 4. The presence of the tumor and/or of the surrounding edema can affect the appearance of fiber tracks. When the tumor and the edema are in the precentral region the fiber tracking of the corticospinal tract shows a thinned appearance, most likely due to the damage that occurred in its course to the motor cortex, and a larger offset with the subcortical stimulation sites. The fiber track obtained using q-ball probabilistic algorithm shows a corticospinal tract (CST) with a higher number of streamlines (sagittal image), a fuller depiction of the more lateral aspects of its fan-shape configuration and a smaller offset with the subcortical stimulation site (IES) (axial image).

Finally in the last case we showed how the presence of the tumor in the temporal region affected the fiber tracks in their course to the motor cortex splitting them at the level of the internal capsule for the presence of edema but not affecting their appearance at the level of the white matter/subcortical stimulation site allowing a much shorter offset between the diffusion fiber tracks and the stimulation and a better delineation of the later tracks of the expected corticospinal tract with the probabilistic q-ball approach. The q-ball fiber tracking technique can follow white matter tracts through regions of complex architecture, but the method is still affected by acquisition limitations and assumptions made in the tracking algorithms. The fiber tracking algorithm propagates the streamlines in the most probable orientation of fiber populations by following the maxima of the ODF. If in a voxel more than one population has represented, only one is chosen for propagation, the intersected ones are ignored. In regions where fibers diverge or branch the q-ball ODF could fail in representing the accurate pathway of the white matter tract. Greater spatial resolution, better q-ball angular resolution and further studies including functional mapping techniques will aid in the improvement of diffusion fiber tracking methods.

4.3. Limitations of the study

There are some limitations to the interpretation of the results of our study. The main limitation of this work was its sample size (12 patients and 29 IES sites), with the possibility of some of the observed correlations to be due to chance. For cortical stimulation sites, there is some uncertainty in the association with the pre-operative MRI data due to tissue shifts (largely perpendicular to the surface). For subcortical associations the known effects of current penetration and tissue shifts do not allow us to evaluate the accuracy within a fine spatial scale (Grunert et al., 2003; Keles et al., 2004). Further cases with both cortical and subcortical stimulations of the same pathway would also bolster the notion of accuracy of the diffusion fiber tracking pathways. Therefore, large-scale studies and a higher number of IES are required to confirm our results for a more robust statistical analysis and to assess a higher clinical relevance of the study.

5. Conclusion

Our study showed that probabilistic q-ball fiber tracking approach surpasses prior fiber tracking methods in two main respects. First, it has a higher sensitivity when compared to the other approaches in delineating the connectivity in regions of complex/impaired white matter architecture. Second, using probabilistic q-ball approach, the corticospinal tract can be delineated more extensively than with a standard DTI fiber tracking approach, showing the potential of this new technique to further advance scientific and clinical applications of diffusion fiber tracking methods (Chung et al., 2006; Grunert et al., 2003).

In our study, we attempted a validation for the fiber tractography in estimating the pyramidal fiber tract while comparing four different algorithms for preoperative tractography images with the results of the cortical and subcortical intraoperative electrical stimulation (IES) performed during the surgery. The capacity of the q-ball probabilistic algorithm to reconstruct tracts to the cortical stimulation sites with high sensitivity suggests that this approach should improve the delineation of the fiber for intraoperative mapping (Leclercq et al., 2011).

Due to all the limitations presented, the combined use of the diffusion imaging and the cortical and subcortical stimulations could offer better information and a higher predictive value in preserving the motor functions. For the validation and improvement of fiber tracking algorithms for neurosurgical planning, the use of electrophysiological data and functional image guidance can be very useful, especially under difficult pathological conditions. The clinical relevance of the use of diffusion imaging in neurosurgical planning is increased by use the best diffusion model with better and objective tractography analyses. This reliability can be further improved by the combination with intraoperative mapping, which should be assessed systematically in neurosurgery.

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