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Comparison of Seeding Methods for Visualization of the Corticospinal Tracts Using Single Tensor Tractography

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Abstract

Objectives—To compare five different seeding methods to delineate hand, foot, and lip components of the corticospinal tract (CST) using single tensor tractography

Methods—We studied five healthy subjects and 10 brain tumor patients. For each subject, we used five different seeding methods, from (1) cerebral peduncle (CP), (2) posterior limb of the internal capsule (PLIC), (3) white matter subjacent to functional MRI activations (fMRI), (4) whole brain and then selecting the fibers that pass through both fMRI and CP (WBF-CP), and (5) whole brain and then selecting the fibers that pass through both fMRI and PLIC (WBF-PLIC). Two blinded neuroradiologists rated delineations as anatomically successful or unsuccessful tractography. The proportions of successful trials from different methods were compared by Fisher's exact test.

Results—To delineate hand motor tract, seeding through fMRI activation areas was more effective than through CP ($p < 0.01$), but not significantly different from PLIC ($p > 0.1$). WBF-CP delineated hand motor tracts in a larger proportion of trials than CP alone ($p < 0.05$). Similarly, WBF-PLIC depicted hand motor tracts in a larger proportion of trials than PLIC alone ($p < 0.01$). Foot motor tracts were delineated in all trials by either PLIC or whole brain seeding (WBF-CP and WBF-PLIC). Seeding from CP or fMRI activation resulted in foot motor tract visualization in 87% of the trials (95% confidence interval: 60-98%). The lip motor tracts were delineated only by WBF-PLIC and in 36% of trials (95% confidence interval: 11-69%).

Conclusions—Whole brain seeding and then selecting the tracts that pass through two anatomically relevant ROIs can delineate more plausible hand and lip motor tracts than seeding

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from a single ROI. Foot motor tracts can be successfully delineated regardless of the seeding method used.

Keywords

Diffusion tensor imaging; functional imaging; Image-guided procedures; brain tumors; corticospinal tract

Introduction

Diffusion-tensor imaging (DTI), despite its limitations and criticisms [1], has proven useful for preoperative planning and intra-operative guidance in neurosurgery [2, 3], especially in combination with neurophysiological subcortical mapping [4, 5]. Diffusion tensor remains the most commonly used model in streamline tractography in commercially available neuronavigational platforms.

Delineation of the corticospinal tracts (CSTs) by Diffusion tensor tractography is a useful tool in preoperative planning for surgical lesions that are located close to the pyramidal tract to avoid or predict postoperative motor deficits [6, 7]. Such delineation is of utmost importance considering the pivotal functional role of the motor tracts. However, hand and face components of the CST are known to be technically challenging to delineate using conventional tractography methods [8, 9].

A wide range of methods, including the “gold standard” intraoperative neurophysiologic techniques, have been used for functional motor mapping of the human cortex and depicting a “motor homunculus” [10] [11]. Based on the anatomic motor homunculus, foot, hand, and face components of the CST are expected to originate from different areas of the precentral gyrus. These cortical areas can be determined noninvasively by functional magnetic resonance imaging (fMRI). In order to seed the CST, the cerebral peduncle (CP) has been commonly used as the anatomic region of interest (ROI) [12, 13]. However, seeding from the CP and using the conventional single-tensor tractography often results in depicting only a subset of CST that propagates vertically to the parasagittal cortex, and according to the motor homunculus, mainly serves lower extremity motor function. This can be visually confirmed by aligning the fMRI activation areas (obtained during hand clenching, foot tapping, or lip pursing) with the anatomical image that contains tracked fibers (figure 1). Depicted CSTs by other authors using streamline deterministic approach show the same issue [2, 3, 9].

Probabilistic tracking algorithm and q-ball diffusion models have been shown to offer better sensitivity in delineating CST compared to the deterministic DTI fiber tracking approach [14]. While significant advantage of such methods in clinical applications require further validation using larger case studies, most commercially available neuronavigational platforms still use the deterministic DTI approach. Therefore, optimizing modifications of this method remain desirable for patient care at least for the years to come.

Researchers have used two different approaches to optimize deterministic DTI method. One is to use alternative tractography methods such as two-tensor model instead of conventional

single-tensor tractography [15, 16]. Despite suggested advantages of such models, they are difficult to implement and are computationally intensive. The second approach involves optimization of the seeding method for the single-tensor tractography, as we investigate here. Ideally these two approaches could be combined.

To seed the CST, some authors have used the PLIC as an ROI [3]. Others have used fMRI activation and its subjacent white matter as an ROI for tractography and reported promising preliminary results [17- 21]. Another possible approach involves seeding in the whole brain and then selecting the fibers that pass through relevant ROIs [22-24]. Although two-ROI approach, also known as Brute-Force, has been shown to increase the validity of tractography in animal model [25], to the best of our knowledge, within subject comparison between multiple different seeding methods for delineation of the CST has not previously been published. In this study we tested five different seeding approaches for delineating the hand, foot, and lip (perioral) motor fibers, and empirically determined which method provided more comprehensive delineation of the motor tracts.

Materials and Methods

Fifteen subjects were studied, including five healthy volunteers and ten brain tumor patients. This study was approved by the Institutional Review Board of the Partners Healthcare System. Written informed consent was obtained from all participants.

Gender/age (in years) for the healthy subjects 1 to 5 were M/38, F/29, M/28, F/26, and F/25, respectively. Gender, age, tumor type, and tumor location for the patients are listed in table 1. The patients were scanned prior to undergoing surgical resection of solitary intracranial lesions. These lesions included nine intra-axial tumors and one left frontoparietal meningioma. In the case of meningioma, fMRI and tractography were considered relevant given the location of the tumor and mass effect on the cortical/subcortical portions of the motor pathway.

Data Acquisition and Analysis

MR imaging was performed with a 3T scanner (Signa system with Excite 14.0; General Electric, Milwaukee, WI).

a) Anatomical imaging—Whole brain T1-weighted axial spoiled gradient-recalled (SPGR) images were acquired with an eight-channel head coil (TR/TE 7500/30 ms; matrix 256×256; field of view (FOV) 25.6 cm; flip angle 20°; 124 contiguous sections).

b) Functional imaging—Blood oxygen-level-dependent (BOLD) functional imaging was performed using a quadrature head coil with a T2*-weighted echo-planar imaging (EPI) sequence (in-plane spatial resolution 2×2 mm²; TR/TE 2000/40 ms; matrix 128×128; FOV 25.6; flip angle 90°; slice thickness 4 mm; 27 interleaved slices). For mapping motor areas, the tasks were self-paced at each subject's comfort level. However, when we explained the tasks to the subjects prior to scanning, we described them as about 1 hand clench, toe wiggle, or lip purse per second for all healthy subjects and patients. The fMRI paradigm consisted of a blocked design of alternating task blocks (hand clenching, foot tapping, and

lip pursing) and rest blocks. In each motor task, four task blocks (30-second duration) were interleaved with three rest blocks (10-second duration). For healthy subjects, the tasks were performed for both left and right hand and foot. For patients, depending on the tumor location and clinical suspicion of motor involvement, the tasks were selectively performed for body parts and lateralization corresponding to the lesion location. After image reconstruction, Statistical Parametric Mapping software (SPM2) (Wellcome Centre, London, UK) was used for motion correction to preprocess the data and single subject level fMRI analysis. Individually determined threshold was used for each subject, such that BOLD activation was observed within the primary motor cortex. We used an extent threshold of 10 voxels, and smoothing was 6 mm. Both the mean functional image and the anatomical high resolution 3D-SPGR were subsequently registered to the baseline diffusion-weighted imaging (DWI) scan using mutual information rigid registration [26] implemented in 3D-Slicer version 3.6 (www.slicer.org). For all subjects a visual inspection of the registration was performed on three orthogonal views, with particular attention to the quality of registration of cortical sulci/gyri, and lateral ventricles. A visually identifiable misregistration was considered an exclusion criterion. In all our subjects, the registration was satisfactory. We also generated a three-dimensional model for each cortical fMRI activation to facilitate differentiating fibers that intersect the activation area from those that merely over- or underlie the activation area in a two-dimensional view.

c) Diffusion-Tensor imaging—This sequence was a single-shot diffusion-weighted spin-echo EPI (TR/TE 14000/30/450 ms; matrix 128×128; FOV 25.6 cm; voxel size 2 x 2 x 2.6 mm; slice thickness 2.6 mm; b value 1000 s/mm²; gradient directions 55). We used open-source publicly available software 3D-slicer version 3.6 in all cases to calculate the tensor and to seed and delineate the 3D fiber tracts with a 1-mm seedpoint grid. Fiber assignment by continuous tracking (FACT) algorithm [27] was used with a seed density of 100 seeds/voxel, an FA threshold of 0.15, fiber length of 20-800 mm, and curvature angle threshold of 60°/mm.

Seeding methods

We performed five different seeding methods in order to delineate motor tracts. In each subject, the seeding methods were applied for each hemisphere separately and independently.

1) CP—The cerebral peduncle was manually outlined using 3D-slicer software. Color-coded directional maps and an anatomical atlas were used to guide the tracings [28]. The blue area on the axial directional color map at the level of the midbrain was used as a guide to outline the CP on 3 consecutive slices. Seeding was performed from the CP labelmap.

2) PLIC—The posterior limb of the internal capsule was manually outlined with a similar method as used for CP on 3 consecutive slices. Seeding was performed from the resulting PLIC labelmap.

3) fMRI—The fMRI activation areas were obtained as described in the *functional imaging* section, and were outlined using 3D slicer software. Each fMRI activation area was dilated

three times using the integrated “dilate” module in 3D-slicer software to include the subjacent white matter that is necessary for tractography. Each operation of the dilation would add one layer of extra pixels to the label map in each slice. Seeding was performed from the resulting dilated labelmaps.

4) WBF-CP—(Whole brain-fMRI-CP) Seeding was performed in all voxels throughout the brain with a 1-mm seedpoint grid. Out of the resulting fibers, those that passed through both CP and fMRI activation areas of interest were selected.

5) WBF-PLIC—(Whole brain-fMRI-PLIC) Seeding was performed in all voxels throughout the brain with a 1-mm seedpoint grid. Out of the resulting fibers, those that passed through both PLIC and fMRI activation areas of interest were selected.

Based on the selective tasks performed during functional imaging of patient subjects, we performed a total of 20 hand, 15 foot, and 11 lip motor tractography trials across healthy and patient groups. We used the above-described seeding methods for each hemisphere separately and independently.

Evaluating the results

The results of each trial were recorded and visually assessed by a CAQ certified neuroradiologist with about 30 years of experience, and a neuroradiology fellow with about 5 years of experience on fMRI and DTI who were both blinded to which method had been used for seeding. The results were scored on a two-point arbitrary scale: 0 (unsuccessful tractography) reflecting “no tracts” or “tracts that approach but do not reach the fMRI ROI”, and 1 (successful tractography) reflecting “correct tracts”. A correct tract was identified as a tract that followed the expected anatomical trajectory of the CST, and reached the related fMRI ROI. The 3-D models of fMRI ROIs were used to better evaluate the spatial relationship of the tracts and these ROIs.

For statistical analysis, we used binomial exact confidence intervals that were more appropriate than large sample approximations for small sample sizes and extreme probabilities such as those observed in our data. The hypotheses were tested using Fisher's exact test, and the P values for 2-sided tests were reported. We used STATA version 12.1 (StataCorp, College Station, TX) for the statistical analysis.

Results

There was %100 concordance between the two readers in defining successful versus unsuccessful tractography. The scores for different cases and seeding methods are shown in table 2.

The proportions of the trials that successfully delineated hand motor tracts along with the 95% confidence interval for each value are shown in table 3. For foot motor tracts, seeding from the PLIC or whole-brain seeding (WBF-CP and WBF-PLIC) delineated the tracts in all the trials. Seeding from the CP or foot fMRI ROI delineated the tracts in 87% (95% confidence interval: 60-98%) of trials. In one subject, WBF-PLIC resulted in a considerably

larger number of tracts than seeding from the PLIC. Only the WBF-PLIC method was able to delineate the lip motor tract, with success rate of 36% of trials (95% confidence interval: 11-69%).

Seeding from fMRI ROI for all three motor compartments resulted in visualization of a group of short fibers originating from motor cortex, passing a short descending course in the white matter and then making a sharp curve back toward the cortex in the vicinity of the originating point (figure 2). In other words, a considerable portion of the generated fibers did not reach the PLIC. Out of 15 trials in which foot motor tract was seeded from fMRI activation area, 7 cases demonstrated a few corpus callosum fibers in addition to the descending motor tracts (figure 2). Since the only way to identify an incorrect fiber is by human interpretation and in the case of tumor with potential displacement, this interpretation is difficult, we did not analyze the incorrect fibers in this study.

The comparison results for tractography of each component of the CST were: **Hand:** Based on the percentages of successful trials using each seeding method (table 3), seeding from the fMRI ROI was more successful than seeding from the CP ($p=0.008$), but not significantly different from seeding in the PLIC ($p>0.1$). WBF-CP was a more successful method than seeding from the CP ($p<0.05$). Similarly, WBF-PLIC worked significantly better than the seeding from the PLIC ($p<0.01$). WBF-PLIC showed a trend to being better than seeding from the fMRI ROI but the difference was not statistically significant ($p = 0.065$). **Foot:** all seeding methods seemed to be quite successful and there was no significant difference among them ($p>0.48$). **Lip:** We were able to delineate the lip motor tract using WBF-PLIC method in four out of 11 subjects. No other method was successful in depicting this tract.

Discussion

We showed that in all subjects, whole-brain seeding and selecting the fibers that pass through two anatomically relevant ROIs is similar to or better than the single ROI-based seeding for visualizing the CST. In delineating hand motor tracts, whole-brain seeding showed a statistically significant advantage over the ROI-based seeding. Selection based on the fMRI and PLIC demonstrated the most anatomically plausible results. In delineating the foot motor tracts, all methods worked quite well and there were no statistically significant differences among them. Lip motor tract was the most difficult component to delineate. Whole-brain seeding and selection based on the fMRI activation and PLIC successfully depicted this tract in 36% of the trials, and no other seeding method was able to delineate it.

The CP and PLIC are commonly used anatomic ROIs to seed the CST. Based on our experience, as shown in Figure 3a-b, seeding from PLIC results in “denser” and thicker tracts compared to seeding from CP using similar seeding resolutions. This could be explained by the fact that the PLIC is bigger than the CP and real fibers are more densely packed in the CP. However, with a 1mm grid, we can generate a limited number of streamlines. Therefore, we can expect that increasing the seeding resolution in CP could be more beneficial than in PLIC. This hypothesis was not tested in our study and can be the subject of future investigations.

Our experience showed that some of the fibers seeded from the CP or PLIC project toward areas other than the motor cortex. This has been previously reported by other authors as well [17]. In addition, the hand and face motor fibers are usually not delineated by this method [15, 16]. To solve this problem, some authors have proposed combining the information obtained from the fMRI with the diffusion tensor tractography of the corticospinal tract [20]. These authors performed seeding from the subjacent white matter of the fMRI activation area and showed advantages over seeding from the other anatomic landmarks, especially in tumor patients where the trajectory of the CST may be affected by the tumor [21]. In our study, seeding from dilated fMRI activation areas resulted in many curved fibers due to low anisotropy of the gray matter and presence of the U fibers (figure 3c). Based on our results, seeding from the fMRI activation area is better than that from the CP in visualizing the hand motor tract, but is not significantly different from seeding from the PLIC.

Due to the limited number of patients in our study, it is difficult to elaborate on how motor tracts are impacted by a tumor of specific pathologic type. Other authors showed that different brain tumors might displace or infiltrate adjacent white matter tracts [29, 30].

To evaluate a tractography method, both sensitivity and specificity should be considered. An ideal method is able to detect a streamline that represents the tract of interest (sensitivity) and excludes other undesired tracts (specificity). In the initial years of tractography, a single ROI was defined to trace the diffusion vectors, and the tracts allowed to propagate to a minimum fractional anisotropy (FA) threshold [27]. To increase the sensitivity of tractography, one can decrease the FA threshold. However, this will lead to reduced specificity and inclusion of extra fibers that are not part of the CST [17]. To deal with this trade-off between sensitivity and specificity, Holodny et al., introduced a technique in 2001 to better define the CST by selecting two ROIs, including the PLIC and the fMRI activation area [17]. They seeded a large number of fibers that emanated from each of these ROIs. To eliminate the tracts that were depicted in each tracing but were not part of the CST, they selected only those that were present on both maps by mathematically overlapping the two tracings, and concluded that this method could remove the extra fibers such as U fibers or fibers connecting to the non-motor cortex. In other words, they could increase the specificity of fiber tracking using this selection step, which also enabled them to decrease the minimum FA to achieve a higher sensitivity. Kim et al. used a similar approach in their report, with fMRI activation area and the blue (representing superior-inferior principle diffusion direction) portion of the anterior pons on the color-coded directional map, as the two relevant ROIs [31]. In our study for the seeding methods WBF-CP and WBF-PLIC, we performed the seeding in the “whole brain” rather than in the two ROIs. As such, seeding was performed in every voxel of the white matter in the brain. We then selected only those fibers that intersected two ROIs. These two ROIs included the fMRI activation area corresponding to the tract of interest, plus either the CP or PLIC. Using two ROIs could serve to differentiate the components of the CST and to manage the large number of generated tracts following the whole-brain seeding. We expected the whole brain seeding methods to increase the sensitivity of the tractography by reducing the effect of seeding resolution as a limiting factor in the brain regions where fibers are naturally denser. Our results were consistent with this assumption as the WBF-PLIC was a more efficient method than seeding from the PLIC alone. Similarly, WBF-CP was more efficient than seeding from

the CP alone. Using the fMRI activation as a second ROI would increase the specificity of tract delineation.

In 10 out of 12 cases in which seeding from the fMRI could delineate hand motor tracts, these tracts included parts that are more lateral in the corona radiata. This lateral part could not be demonstrated in the trials where seeding was performed from the CP or PLIC (figure 3). This is consistent with the finding that visualization of complete CST, particularly the lateral portions, is hindered by the crossing fibers of superior longitudinal fasciculus (SLF). The SLF is a large white matter tract that intersects with the face and occasionally hand motor tracts caudad to the precentral gyrus and cephalad to the PLIC. This intersection precludes tracing of these tracts, since the computer-generated tract either terminates at the intersection or follows the course of the longitudinal fasciculus [9]. Some researchers have introduced alternative tractography methods such as multitensor [15] [16] or probabilistic methods [32] to address the fiber crossing issue. Probabilistic q-ball fiber tractography has been shown to have better sensitivity and accuracy in delineating the corticospinal tract [14]. However, given the ease of use and availability, deterministic tractography is still commonly used for clinical applications and optimization of this method is still of interest for the patient care.

One can argue that whole-brain seeding methods are time-intensive choices. Depending on the available computational device, this can be true; however, the whole-brain seeding can be performed off-line and before the actual data analysis. Once performed, the seeded tracts can be used for visualizing only the relevant tract within the brain by choosing the appropriate ROIs for selection. This can be a considerable advantage for intra-operative guidance applications. In addition, the same idea can be applied by seeding through a part of the brain instead of the whole brain. Furthermore, for a patient with an intracranial lesion, it suffices to seed throughout the voxels in the diseased hemisphere, or in a large mask surrounding the tumor instead of the whole brain.

Our results were obtained using 3D-Slicer version 3.6. Results using other versions of the 3D-Slicer or other software platforms may be variable. 3D-Slicer is a research platform not approved by the U.S. Food and Drug Administration (FDA) for clinical use.

In future studies, different seeding methods can be combined with multitensor tractography approaches to achieve potentially better results. In the absence of intraoperative electrical stimulation data, assessment and comparison of the sensitivity and accuracy of fiber tracking using different seeding methods is not possible. This can also be the subject of future studies.

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Highlights

- We compared five different seeding methods for single-tensor corticospinal tractography.
- Whole brain seeding and selection based on 2 ROIs was more successful than single ROI seeding.
- Lip motor tracts were the hardest and foot motor tracts were the easiest to delineate.

Figure 1.

Tractography of the corticospinal tract in a healthy subject determined from seeding in the cerebral peduncle. FMRI was used to define primary motor cortex for the foot (blue), hand (purple), and lip (magenta). This seeding region resulted in delineation of the portions of the CST linking to the motor cortex subserving the lower extremity. However, the hand and lip portions of the CST were not delineated.

Figure 2. Seeding from fMRI activation areas to delineate hand (yellow), foot (blue), and lip (green) motor tracts. Most fibers do not extend beyond the PLIC. Short subcortical curved fibers and a few fibers from corpus callosum are also demonstrated.

Figure 3.

Tractography of the corticospinal tract in a 33-year-old patient is illustrated. A metastatic brain tumor in the left parietal region is demonstrated in green. Three-dimensional models representing the fMRI activation regions for foot (blue) and hand (purple) are projected onto a T1 coronal image. The applied seeding methods were CP (a), PLIC (b), fMRI activation area (fMRI) (c), whole-brain seeding with cerebral peduncle and fMRI activation as selection ROIs (d), and whole-brain seeding with PLIC and fMRI activation area as selection ROIs (e).

Table 1

Gender/age (in years), tumor type, and tumor location in participating patients.

	Gender/Age	Tumor type	Tumor location
1	M/35	Oligoastrocytoma (II)	Right frontal
2	M/38	Metastasis	Right frontal
3	M/38	Metastasis	Right frontal
4	F/64	Meningioma	Left frontoparietal
5	M/33	Metastasis	Left parietal
6	M/25	GBM	Right Parietal
7	F/67	Glioma (low grade)	Right frontal
8	M/22	Oligodendroglioma (II)	Left frontal
9	F/37	Astrocytoma (II)	Left parietal
10	F/54	GBM	Left frontal

Table 2

Scores for each tractography result based on a binary scale consisting of 0 (unsuccessful tractography) or 1 (successful tractography), determined by two neuroradiologists blinded to the method applied in each trial. There was complete concordance between the two readers.

	subject	Seeding method				
		CP	PLIC	fMRI	WBF-CP	WBF-PLIC
HAND	C1R	1	1	1	1	1
	C1L	1	1	1	1	1
	C2R	0	0	1	0	1
	C2L	0	0	1	0	0
	C3R	0	0	0	0	1
	C3L	0	0	0	1	1
	C4R	0	0	0	0	
	C4L	0	0	0	1	1
	C5R	0	0	1	1	1
	C5L	0	0	0	0	1
	P1	0	0	0	0	1
	P2	0	1	1	1	1
	P3	0	1	1	0	1
	P4	0	0	1	0	1
	P5	0	1	1	1	1
	P6	1	1	1	1	1
	P7	0	1	0	1	1
	P8	0	1	1	1	1
	P9	0	0	0	0	1
	P10	0	0	1	0	1

Table 3

The percentage of trials that successfully delineated hand motor tracts along with the 95% confidence interval for each value.

Seeding method	Successful trials/total trials (%)	Binomial exact 95% Confidence Interval (%)
CP	15	3-38
PLIC	40	19-64
fMRI	60	36-81
WBF-CP	50	27-73
WBF-PLIC	90	68-99