Validation of DTI-tractography-based measures of primary motor area cortical connectivity

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INTRODUCTION

DTI tractography provides noninvasive measures of structural cortical-cortical connectivity of the brain. However, the agreement of DTI and histological measures is a concern. In this study, we reconstruct the 3D distribution density maps (DDM) of histological fibers (or cell bodies) and DTI fibers (or fiber ends) projecting to five frontal cortical regions from the primary motor cortex (M1) subarea in the squirrel monkey. We then quantitatively evaluate the agreement of the distribution of fibers (or fiber ends) derived from DTI tractography with the distribution of histological fibers (or cell bodies).

MATERIALS AND METHODS

Data acquisition: The bidirectional neural tracer biotinylated dextran amine (BDA) was injected into 8 sites covering the forelimb movement representation area in the left M1 cortex of the monkey. After two weeks, the brain was extracted, fixed and scanned using a 9.4T Varian scanner (PGSE, TR=4.6s, TE=42ms, gradient directions=32, b=1022s/mm^2, voxel size=0.3mm×0.3mm×0.3mm, data matrix=128×128×192). Then the brain was sectioned in coronal planes at 40μm-50μm thickness on a freezing microtome and the blockface was photographed for every third section. Every sixth section was reacted for BDA and photographed under a light microscope (0.5 X and 4 X objectives).

Data processing: Locations of BDA-stained cell bodies were identified by plotting the centers of the cell bodies and outline of gray matter under 6.3X microscope magnification, assisted by Igro Pro software. Locations of BDA-stained fibers crossing the white-gray matter interface were identified by computer-assisted morphological segmentation on 4X micrographs. Using computer-assisted gridding and counting, the 2D DDMs (256×256) of BDA-stained cell bodies and interface-crossing fibers were produced. The 2D BDA DDMs were transferred from the micrograph space to the DTI space using deformation fields calculated via a thin-plate spline algorithm to register each BDA micrograph to the corresponding blockface image and the adaptive bases algorithm [1] to register the blockface volume to the DTI volume. Finally, the intensities of DDMs were projected onto the 3D white-gray matter interface which was segmented using a variational level set approach [2] on T2w images, after registering the T2w volume to the DTI volume. DTI-studio[3][4] (the FACT algorithm) was used to perform whole brain fiber tracking (stop FA=0.2, stop angle=70°) and also to select the fibers penetrating the injection region which was transferred from the micrograph space. Then the DTI fiber DDM was produced by counting the DTI fibers passing through the gray-white matter interface within every DTI voxel located at the interface. The DTI fiber ends were also mapped to the interface and then counted within every interface voxel to produce a DTI 'fiber ends' DDM. The injection region and different cortical projection regions in micrograph space were manually segmented based on architectonics of BDA-stained and Nissl-stained neurons [5].

Data analysis: We calculated the Pearson's correlation coefficient (CC) to evaluate the agreement of DDMs derived from DTI and histological data for each cortical projection region: $r=\sum_{i=1}^{n}(B_i-\bar{B})(D_i-\bar{D})/\sqrt{\sum_{i=1}^{n}(B_i-\bar{B})^2}/\sqrt{\sum_{i=1}^{n}(D_i-\bar{D})^2}$, where r is the CC of the distribution of BDA fibers (or cell bodies) and DTI fibers (or fiber ends) connecting to a cortical projection region, B_i and D_i are the numbers of BDA fibers and DTI fibers, respectively, distributed in the ith voxel located at the white-gray matter interface directly underneath the projection region, n is the total number of these voxels, and the bar represents the mean. The frontal projection regions of interest include the ipsil/contra lateral supplementary motor areas (iSMA/cSMA), ipsil/contra lateral premotor cortex (iPM/cPM) and contralateral M1(cM1).

RESULTS

Figure 1 displays the DDMs of BDA-stained cell bodies, BDA-stained interface-crossing fibers, DTI fiber ends and DTI interface-crossing fibers rendered on the white-gray matter interface. In the three contralateral regions, the distribution patterns of BDA and DTI fibers (and fiber ends) are significantly different, which indicates that DTI fiber distributions does not fully agree with the local histological distribution. Table 2 lists quantitative evaluation of the agreement: the CC of histological and DTI derived distributions in different projection regions. The agreement in iPM is higher than the other projection regions due to higher sensitivity of DTI along this fiber pathway.

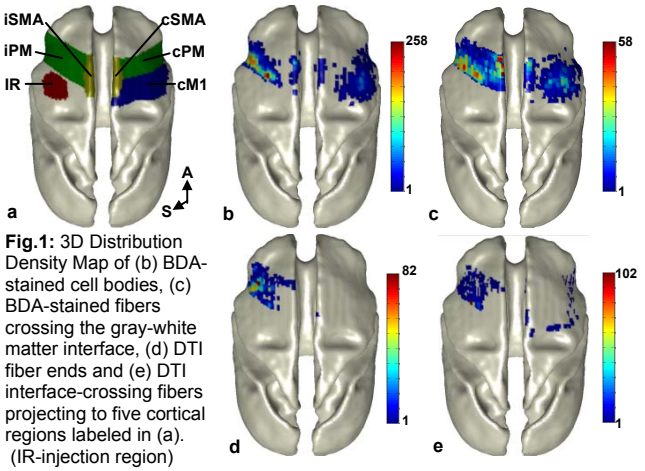

Fig.1: 3D Distribution Density Map of (b) BDA-stained cell bodies, (c) BDA-stained fibers crossing the gray-white matter interface, (d) DTI fiber ends and (e) DTI interface-crossing fibers projecting to five cortical regions labeled in (a). (IR-injection region)

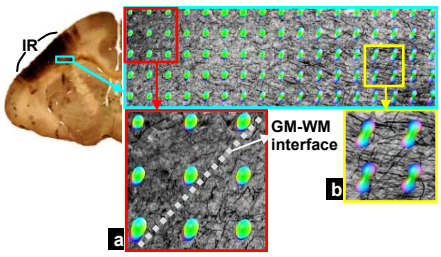

Fig.2: Example of diffusion tensors overlaid on BDA-stained fibers (4X) located at the (a) white -gray matter (WM-GM) interface under the injection region and in (b) deep white matter.

CONCLUSION AND DISCUSSION

The visualization and quantitative comparison of 3D DDMs show that distribution patterns in different cortical projection regions have variable agreement between histological and DTI fibers (and fiber ends). The variation indicates that the FACT algorithm may not uniformly reveal cortical-cortical connectivity within the whole brain due to limitations of the deterministic algorithm and the tensor model–e.g., the difficulty in resolving the directions of crossing fibers. The challenge in tracking commissural fibers is illustrated in Fig. 2. Although BDA-stained fibers connecting the contralateral hemisphere run left/right in this plane, the principal diffusion direction (corresponding to most fibers in these voxels) is oriented anterior/posterior just under the injection region (Fig. 2a). In deeper white matter, most fibers are in the superior/inferior direction (Fig. 2b). The disagreement between the true pathway of fibers bound for the contralateral hemisphere and the dominant fiber orientation prevents DTI fibers from reaching the midline and the other hemisphere. Probabilistic tracking and HARDI methods may provide better sensitivity to crossing fibers, and hence more reliable connectivity measures.

REFERENCES

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Tab.1: Correlation coefficients (with p values) of histological distributions and DTI derived distributions for five projection regions.

		iSMA	iPM	cSMA	cPM	cM1
BDA cell bodies vs. DTI fiber ends	r	0.110	0.425	-0.160	0.000	-0.010
	p	0.067	0.000	0.772	1.000	0.789
BDA fibers vs. DTI fibers	r	0.086	0.126	-0.030	-0.065	-0.047
	p	0.150	0.001	0.590	0.129	0.220