Anatomical Accuracy of Diffusion MRI Tractography: Testing the Fundamental Limits

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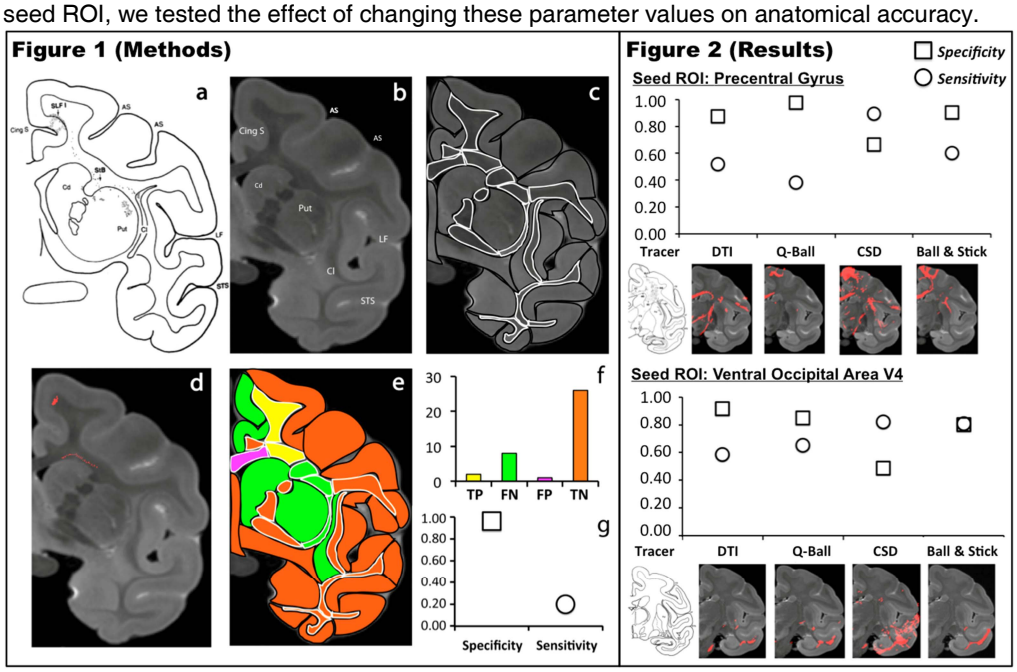
TARGET AUDIENCE: The results of this study will be relevant to those involved in the development of diffusion tractography methods and those who use tractography to explore structure-function relationships in the primate brain.

PURPOSE: Tractography based on diffusion-weighted magnetic resonance imaging (DWI) is the most widely used technique for mapping the structural connections of the human brain in vivo. However, its anatomical accuracy is difficult to assess since it requires a histological gold standard that is not available for in vivo studies. There is a consensus that both reproducibility and accuracy of DWI-tractography are negatively affected by technical factors such as, low quality of clinical DWI data, EPI and eddy current distortions, subject motion, and physiological noise [1]. Moreover, it is generally assumed that these limitations can be overcome by improving DWI data quality and by using sophisticated modeling of the diffusion propagator with high angular resolution (HARDI) algorithms [2]. On the other hand, it can be argued that extracting fiber trajectories from DWI data is fundamentally an ill-posed problem, which cannot be solved even with perfect data. Here, we address this question by evaluating the sensitivity and specificity of various tractography approaches against histological tracer data using high quality ex-vivo diffusion data free from artifacts.

METHODS: We acquired high angular resolution (121 directions), 3D-EPI, DWI data from a healthy adult rhesus macaque brain, ex vivo, at a spatial resolution of 250μm (isotropic), b_{max} = 4800 s/mm^2, (scan time = 72 hours) on a 7T Bruker scanner. We estimate that a scan session of more than 1,000 hours would be needed on a clinical scanner for a comparable quality dataset of the human brain in vivo. As ground truth, we used tracer data from a well-known atlas [3]. We rotated the DWI volume to match the orientation of the tracer atlas brain. Then, we identified for each tracer brain slice a matching DWI slice (Fig.1 a-b). Next, the matched DWI slices were parcellated into a grid (Fig. 1c) composed of discrete gray (black lines) and white matter (white lines) regions. We computed the tracts originating from two candidate seed ROIs (Fig. 2ab), using four diffusion modeling approaches (DTI [4], Q-ball [5], CSD [6] and Ball & Stick Model [7]). We then assessed the agreement between the tracer (Fig. 1 a) and the tractography results (Fig. 1 d) within each cell of the grid (Fig. 1 c). This allowed us to calculate the number of true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN) and compute the sensitivity (TP/(TP + FN) and specificity (TN/(TN + FP)) of tractography (Fig.1 e-g). Finally, given that tractography results change with various user-defined parameters, such as the maximum allowed bending angle and the size of the seed ROI, we tested the effect of changing these parameter values on anatomical accuracy.



RESULTS: In general, a tractography technique with high sensitivity (high rate of true positives) had low specificity (high rate of false positives) (Fig. 2 a-b). Compared to DTI, HARDI methods showed higher sensitivity, but lower specificity. Moreover, the method and choice of parameter values that produced the best combination of sensitivity and specificity for one specific pathway (Fig. 2a) was suboptimal for a different pathway (Fig. 2b). In addition, anatomical accuracy was highly dependent upon several user-defined parameters and the sensitivity was low when the seed ROI was restricted to gray matter (data not shown).

DISCUSSION & CONCLUSION: The anatomical accuracy of a variety of tractography algorithms was found to be suboptimal, showing a clear trade-off between sensitivity and specificity, variable results in different regions, and strong dependency on user-defined parameters. Because these findings are observed across algorithms with DWI data of exceptional quality, this appears to be an intrinsic limitation of diffusion tractography that will not be resolved by advancements in data acquisition alone. More work with animal models that allow independent validation (with histological or neurophysiological methods) of diffusion tractography results is advisable to optimize the anatomical accuracy of tractography algorithms. Ultimately, we probably have to accept that diffusion MRI tractography alone cannot be used as the primary technique to build our understanding of the human brain "connectome".

REFERENCES: **[1]**. Pierpaoli, C., Diffusion MRI, 2011. p. 303-318. **[2]**. Setsompop, K., et al., NeuroImage, 2013. **[3]**. Schmahmann, J.D. and D. Pandya, Fiber pathways of the Brain, 2009. **[4]**. Basser, P.J., et al., Mag. Res. in Medicine, 2000. 44(4): p. 625-632. **[5]**. Tuch, D.S., Mag. Res. in Medicine, 2004. 52(6): p. 1358-1372. **[6]**. Tournier, J., F. Calamante, and A. Connelly. NeuroImage, 2007. 35(4): p. 1459-1472. **[7]**. Behrens, T., et al., NeuroImage, 2007. 34(1): p. 144-155.