Assessing the implications of complex fiber configurations for DTI metrics in real data sets

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Introduction: Currently, diffusion tensor imaging (DTI) is the most widely used method for assessing white matter (WM) 'integrity' and 'connectivity'. However, in voxels containing multiple fiber orientations, the DTI model has been shown to be inadequate [1-3]. A recent study, using high quality diffusion weighted (DW) data and constrained spherical deconvolution (CSD) [4], has shown that multiple fiber orientations can be detected consistently in approximately 90 % of all WM voxels [5]. This finding has potentially profound implications for fiber tractography and WM 'integrity' metrics derived from DTI. In this work, we assess this impact by performing two analyses: 1) Tractography analyses will obviously be affected by errors in the estimated fiber orientations. Therefore, the angle between the fiber orientations estimated by the primary eigenvector of the diffusion tensor (DT), and the nearest CSD orientation is measured in each voxel. 2) For WM integrity measures, issues will arise if fibers with secondary or tertiary orientations take up a substantial volume fraction of the voxel. Therefore, the ratio of the volume fractions of the non-dominant versus all CSD fiber orientations is estimated in each WM voxel.

Methods: Acquisition: A healthy subject was scanned 12 times on a 3 T scanner using a twice-refocused spin echo EPI sequence with TE = 86 ms and 2.4×2.4×2.4 mm³ voxel size. Diffusion gradients were applied in 60 directions uniformly distributed on a sphere through electrostatic repulsion with b = 1200 s/mm². For each scan, 6 images with b = 0 s/mm² were also acquired. To avoid pulsation artifacts, cardiac gating was applied using a peripheral pulse oximeter with an effective TR = 20 R-R intervals. All scans were concatenated (*not* averaged) into a single data set and corrected for subject motion and residual eddy-current induced geometrical distortions with the required B-matrix adjustments [6], resulting in a total of 720 DW images. With such a large data set, a higher reliability can be achieved for any subsequent analysis than with a traditional scan [7]. WM selection: To restrict the study to WM voxels only, a very strict WM mask was derived from T_1 images of the same subject using the unified segmentation tool from SPM [8], selecting all voxels with WM probability higher than 95%. Orientation extraction: Fiber orientations were extracted from the DW images using CSD using the approach previously described in [5]. First, the fiber orientation distribution function (fODF) was calculated using CSD. Then, a Newton optimization procedure was started from a dense set of equally distributed spherical sample points to find the local maxima of the fODF. Finally, the unique peak orientations with amplitude greater than a fixed threshold were selected. A conservative threshold, avoiding false positives, was selected using simulations as in [5]. For comparison we also calculated the primary eigenvector of the DT, which is commonly used to represent the local fiber orientation with DTI. Assessment of impact: To assess the practical impact of crossing fibers on DTI tractography and anisotropy analyses, two analyses were performed. Tractography analyses will obviously be affected by errors in the estimated fiber orientations. Therefore, the angle between the fiber orientations estimated by the primary eigenvector of the DT, and the nearest peak to this direction in the CSD fODF was measured in each voxel, and displayed both as a spatial map (Fig.1a) and as a histogram over all WM voxels (Fig.1b). For anisotropy analyses, issues will arise if fibers with secondary or tertiary orientations take up a substantial volume fraction of the voxel. Therefore, the ratio of the volume fractions of the non-dominant versus all fiber orientations were estimated in each WM voxel, and displayed both as a spatial map (Fig.2a) and as a histogram over all WM voxels (Fig.2b).

Results: Fig. 1 shows the angular difference between fiber orientation estimated using DTI and the nearest CSD peak. These orientations are consistent between both methods only in single fiber regions (e.g. in the corpus callosum and the corticospinal tracts). The average angular error over all WM voxels is approximately 11°. In half of all WM voxels, the angular error is greater than 8°. It should be emphasized that these errors are provided with respect to the nearest fiber orientation; errors with respect to other fiber orientations that might be present will obviously be considerably greater. Fig. 2 shows the relative volume fraction of the non-dominant fiber orientations with respect to the total volume fraction of all CSD fiber orientations. Most WM voxels contain contributions from non-dominant fiber orientations that would be sufficiently large to affect tensor-derived measures of anisotropy (as well as radial and axial diffusivities). For example, assuming a non-dominant partial volume fraction greater than 25% is sufficient to influence anisotropy measures significantly, approximately 75% of all WM voxels would be affected. Conversely, it can be seen that half of all WM voxels contain more than 40% contamination from crossing fibers.

Fig. 1a

Fig. 1b

Fig. 2a

Fig. 2b
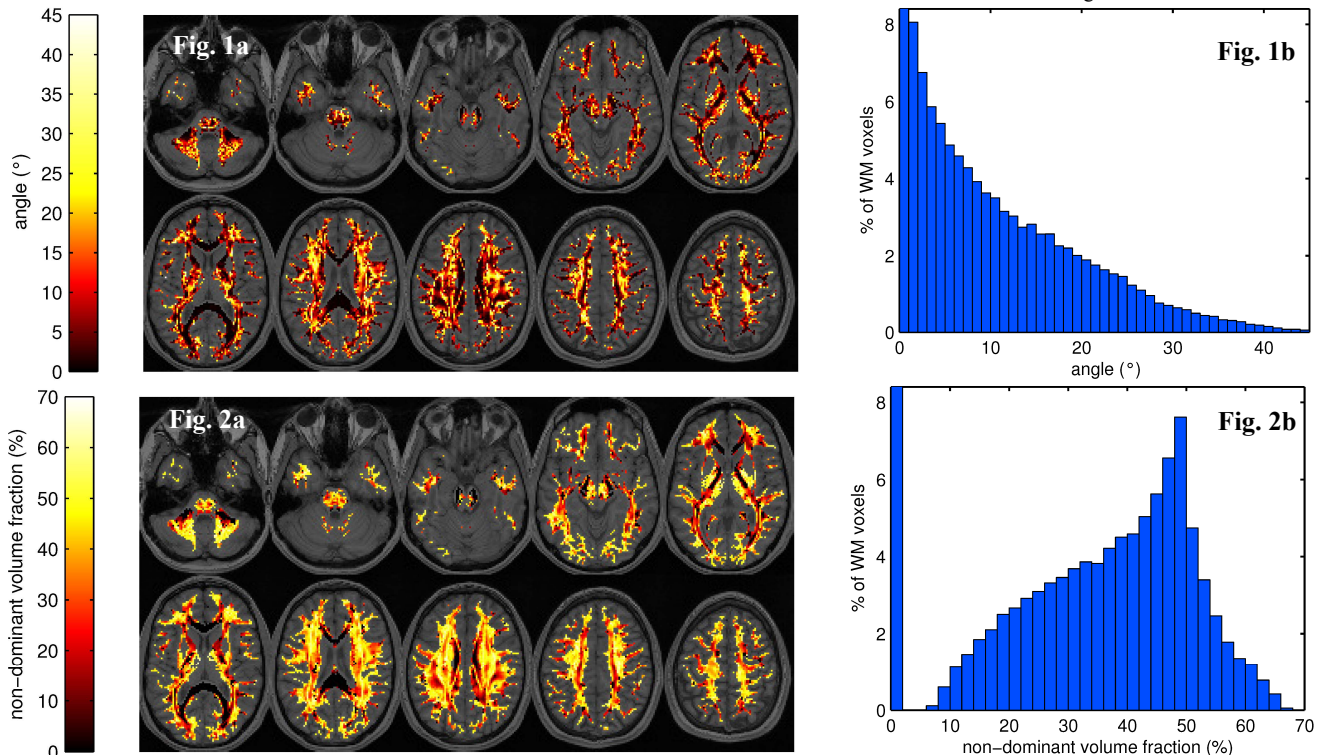
Conclusion: Errors in the estimated DTI fiber orientations are widespread throughout the WM: in over half the WM, these errors are larger than 8°. It follows that these errors will adversely and significantly affect the delineation of WM tracts, and lead to large numbers of both false positive and negative results as the tracking algorithm veers off-course, away from the true end-point of the WM tract (false negatives) [9,10], and/or into adjacent yet unrelated WM tracts (false positives) [10,11]. The proportion of WM voxels where the WM 'integrity' measures are expected to be significantly confounded is of the order of 75%; given that the interpretation commonly ascribed to these measures is only valid in single fiber regions, this implies that there are very few regions of brain WM where these measures (including FA [12] and radial/axial diffusivities [13]) can reliably be interpreted as reflecting WM 'integrity'.

References: [1] Alexander AL et al, MRM 45(5), 2001; [2] Tuch DS et al, MRM 48(4), 2002; [3] Frank LR et al, MRM, 47(6), 2002; [4] Tournier JD et al, NeuroImage 35(4), 2007; [5] Jeurissen B et al, Proc ISMRM 18, 2010; [6] Leemans A et al, MRM 62(6), 2009; [7] Jones DK, MRM 51(4), 2004; [8] Ashburner J et al, NeuroImage 26(3), 2005; [9] Behrens TEJ et al, NeuroImage 34(1), 2007; [10] Jeurissen B et al, HBM 32(3), 2011; [11] Pierpaoli C et al, NeuroImage 13(6), 2001; [12] Jones DK et al, Imaging Med. 2(3), 2010; [13] Wheeler-Kingshott CA et al, MRM 61(5), 2009