TBSS may be sub-optimal for detection of DTI parameter changes in crossing fiber regions

Vincent Schmithorst[1], Jessica Wisnowski[1], and Ashok Panigrahy[1]
[1]*Radiology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, United States*

Target Audience

Researchers interested in performing voxelwise analyses of DTI parameters.

Introduction

In order to perform voxelwise analyses of DTI parameter maps, the maps must first be transformed into a standard space. A popular technique is Tract-Based Spatial Statistics (TBSS)[1]. In TBSS, FA maps are warped to a "skeleton" containing only the tract centers (the same transformation may then be used for other DTI parameter maps). This scheme is likely optimal for finding differences in major fiber pathways such as the corticospinal tract, corpus callosum, and arcuate fasciculus. However, in regions of crossing fibers, attempting to coregister images to a single tract, when there are in fact multiple tracts crossing through the region, may be sub-optimal. We investigated the performance of TBSS as compared to an alternative technique[2], which involves spatial normalization to a white matter template instead of an FA skeleton. The comparison involved the relation of DTI parameters to functional network topology, where differences are expected to predominantly occur in crossing fiber regions adjacent to network hubs.

Methods

The participants were recruited from a developing region in northeast Brazil (Montes Claros, pop. ca. 410,000). Participants consisted of pre-adolescent twin pairs (ages 9-13 years) born late preterm (>32 weeks) and at full term. For this analysis, one participant was selected at random from each family, resulting in a total of N = 18 participants.

DTI scans were acquired on a Philips Achieva 1.5 T scanner. The following parameters were used: Spin-Echo EPI, TR = 6000 ms, TE = 90 ms, slice thickness = 2 mm, matrix = 112 X 112, FOV = 22.4 X 22.4 cm, SENSE factor = 2, b value = 1000 s/mm^2, one scan acquired without diffusion weighting and 32 scans acquired with gradient direction according to the Philips Achieva 32-direction sequence. Motion and eddy current correction and slice dropout removal were performed according to routines written in FSL. FA maps were computed for all participants.

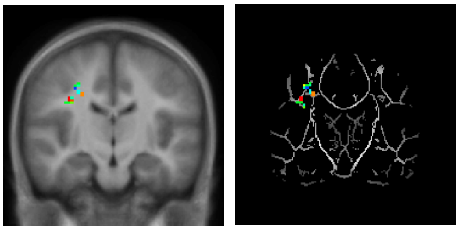

Figure 1. Region with significant correlation of global network cost-efficiency with FA, found via normalization to a white matter template, overlaid on T1-weighted anatomical **(left)** and FA skeleton from TBSS analysis **(right)**. Coronal slice with Y = -18 mm (MNI coordinate space). Images in radiologic orientation.

Intrinsic-connectivity ("resting-state") fMRI data was also acquired during the same scanning session, and used to calculate global cost-efficiency, a metric describing functional network topology[3]. The following parameters were used: TR = 3000 ms, TE = 50 ms, FOV = 211.2 X 211.2 mm, imaging matrix = 80 X 80, slice thickness = 4 mm, 30 slices acquired covering the whole brain, SENSE factor = 2, 100 volumes acquired for a total scan time of 5 minutes per run. Two scan runs were acquired: one with eyes open, and one with eyes fixed. After motion correction, datasets were transformed into Montreal Neurologic Institute (MNI) space using SPM8. Time-courses were extracted for each participant for each region using the 90-region AAL template; time-courses from the two runs were concatenated together. Using the correlations between the time courses from each set of two regions, global cost-efficiency (a measure of network integration) was calculated according to previously published methods[3].

Spatial normalization was carried out according to the TBSS routines in FSL. These steps involve: aligning all FA images to 1X1X1 mm standard space (we used the recommended FMRIB58_FA template as the target); creating a skeleton from the mean FA image (we used the recommended threshold of FA > 0.2 and verified this choice via visual inspection); and finally, projection of each participant's FA map onto the skeleton. An alternative method for spatial normalization was carried out following a previously published procedure[2], using routines in SPM8. The T1-weighted anatomical images were segmented into gray matter, white matter, and CSF, in native space. FA maps were co-registered to the white matter probability maps. Each white matter probability map was then normalized to the white matter template, and the same transformation was then applied to the FA maps. To minimize the risk of spurious results due to imperfect spatial normalization, subsequent analysis was restricted only to voxels with FA > 0.25 and white matter probability > 0.9 in all participants.

For the second-level analysis, global cost-efficiency was the variable of interest and age, sex, and preterm status were covariates of no interest. The suggested voxelwise analysis procedure in FSL was used, consisting of the *randomise* routine (which generates statistical parameter maps using permutation techniques) with the threshold-free cluster enhancement (TCFE) option (which generates family-wise error (FWE) corrected statistics without the need to specify a specific spatial filter or cluster extent/weight threshold). Regions with FWE corrected $p < 0.05$ were deemed significant.

Results

When the SPM8 normalization procedure was used, we found a region in deep white matter (Figure 1, left) with a significant correlation with global network efficiency in a crossing-fiber region in the right hemisphere involving the corona radiata, superior longitudinal fasciculus, and callosal fibers. Via visual inspection, post-hoc analysis also verified that the significant region was in the identical area of white matter for all participants, indicating sufficient robustness in the spatial normalization algorithm. However, no regions with significant correlation were found using the TBSS normalization; in fact no regions even reached a significance level of FWE-corrected $p < 0.5$. Most of the significant voxels found using the SPM8 normalization were located close to, though just outside, the TBSS FA skeleton in the region of intersection of the three fiber bundles (Figure 1, right).

Discussion

While not a rigorous comparison of the two techniques, our results suggest the TBSS algorithm of alignment to a skeleton consisting of tract centers may be a sub-optimal approach for detection of DTI parameter changes in regions consisting mainly of crossing fibers. These regions are not at the center of any particular tract, and will have lower FA values than are typically found in tract centers. Since the TBSS algorithm for projection onto the skeleton searches in a perpendicular direction to the tract for the maximum FA value, voxels with crossing fibers will likely not be projected onto the skeleton and hence will not enter into the subsequent voxelwise analysis. TBSS may be more optimal for detection of changes in tract centers, as it will correct for small residual misalignment which would decrease the available power. However, we are not able to confirm this hypothesis on this dataset, as TBSS found no significant correlations of FA with cost-efficiency in the major fiber bundles either. We note that implementation of a DTI voxelwise analysis technique also involves additional decisions such as how to perform voxelwise statistics, how (or whether) to spatially filter, and how to correct for multiple voxel comparisons; these issues are not considered here as previously published methods in FSL were used.

Conclusion

For DTI voxelwise studies in which changes are hypothesized in regions with crossing fibers, normalization to a white matter template should be considered as a complementary analysis strategy to TBSS.

References

1. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *Neuroimage.* 2006;31(4):1487-1505.

2. Schmithorst VJ, Holland SK, Dardzinski BJ. Developmental differences in white matter architecture between boys and girls. *Hum Brain Mapp.* Jun 2008;29(6):696-710.

3. Fornito A, Zalesky A, Bassett DS, et al. Genetic influences on cost-efficient organization of human cortical functional networks. *J Neurosci.* Mar 2 2011;31(9):3261-3270.