Abnormal diffusivity changes in white matter regions of the children with autism spectrum disorder: comparison of TBSS, TSPOON, and SPM analysis

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Introduction: Autism spectrum disorders (ASD) are well known pediatric developmental disorders that are typically characterized by impaired language, reciprocal social interaction, repetitive and stereotypical behaviors. Many diffusion tensor imaging (DTI) studies point to both microscopic and macroscopic white matter (WM) abnormalities in children with ASD [1-2]. Although these studies have showed significant changes in diffusivity of WM pathways in ASD, the localization of affected WM region seems to highly depend on several factors such as how diffusivity maps are spatially registered and how resulting maps are analyzed across subjects (voxel-based vs. skeleton-based). To abbreviate this problem in investigating the changes of WM integrity that are manifest in children with ASD, this study combined three complimentary analyses including tract-based spatial statistical analysis (TBSS [3], skeleton based), tissue specific smoothing compensation analysis (TSPOON [4], voxel based), and conventional statistical parametric mapping analysis (SPM, voxel based) . We presume that WM regions overlapping the results of three analyses may provide the most reliable localization of the WM regions affected by ASD.

Meterials and Methods: Thirty-one children with ASD (mean age: 5±1.7 years; 28 males), 11 children with DD (mean age: 4.4±1.7 years; 9 males), and 14 typically developing children (TD, mean age: 5.5±1.9 years; 12 males) underwent DTI and behavioral assessments. Whole brain DTI acquisition was performed using a 3T Signa EXCITE scanner (GE Healthcare, Waukesha, WI) equipped with an eight channel phased–array head coil at a diffusion weighting of b=1000 s/mm^2 and 55 diffusion gradient directions, TR/TE = 1250/88.7 ms, voxel size = 1.88×1.88×3mm. An additional acquisition without diffusion weighting at b=0 s/mm^2 was also obtained. The fractional anisotropy (FA) map was evaluated from each subject using multivariate least square fitting algorithm and then spatially normalized into pediatric MNI FA template space. Spatial normalization and subsequent statistical test for assessing the group difference were separately performed by three different analyses, 1) FSL TBSS modules(www.fmrib.ox.ac.uk/fsl/tbss) , 2) in-house implementation of TSPOON algorithm, and 3) SPM using two sample t-test module in SPM 8 (www.fil.ion.ucl.ac.uk/spm). For TBSS analysis, all FA images were normalized using nonlinear registration. The normalized FA images of all participants were combined to create a group specific mean FA image. This mean FA image was then thinned to create a mean skeleton image of the white matter tracts. Following the search for the maximum FA value along the width of the white matter tract, perpendicular to the skeleton voxel, the maximum FA values were projected onto the skeleton voxel to be used as an input for further statistical test. In our implementation of TSPOON, the b0 image were first segmented into the WM probability map using conventional SPM segmentation algorithm in SPM 8. The thresholding was applied to generate the binary WM mask. Nonlinear deformation field to normalize the WM map of individual subject to the WM template was parameterized by single flow field model in SPM DARTEL and applied to normalize both binary WM mask map and WM masked FA. These normalized images were separately smoothed by 8 mm FWHM Gaussian. Then, the smoothed WM masked FA image was voxel-wisely divided by the smoothed WM mask image in order to compensate the blurring artifact caused by smoothing and partial volume. The divided-smoothed-masked FA image was finally used as an input for the statistical test. Meanwhile, SPM analysis, we used the smoothed-masked FA image as an input for the statistical test. The group differences were evaluated in framework of voxel-based ANCOVA using two sample t-test under following contrasts, H_1: TD > ASD, H_2: TD < ASD. Nonparametric permutation tests (5000 permutations/design) with a cluster size threshold of >3 and a p value of <0.05 for significance were applied after correcting for multiple comparisons. Age was used as a covariate. The results of the statistical tests obtained from three different approaches were restricted in the voxels whose WM probability is greater than 0.9 as defined by WMPM Type III atlas [5]. Clustered voxels, which were obtained from two testes (H_1 and H_2), were isolated and labeled by the WMPM Type III atlas. Since there is no direct way to measure the reliablity of detection that each method made in clinical data, the overlapping of three methods seems to provide the most reliable regions that show significant FA change in ASD group.

Results and Discussion: Figure 1 shows white regions showing reduced FA in ASD group compared to TD group, which wre obtained form three different methods at significance level of 0.05. It is clear that TBSS detected localized more focal clusters than other two methods. Meanwhile SPM localized more noisy clusters. TSPOON compromised these two methods. This finding was clearly shown in Table 1. Surprisingly, only six regions were commonly overlapped in 54 clusters of TBSS, 28 clusters of TSPOON, and 37 clusters of SPM, implying that the detection power of each method clearly depends on the features of each method. This discrepancy is based on different types of spatial normalization, smoothing, and statistical power of adapted statistical analysis. Table 2 shows WM regions obtained by overlapping all clusters that each method localized at an identical significant level (corrected P < 0.05). The ASD shows signicant FA reduction in several WM regions associated with bilateralarcuater faciculus (left superior longitudinal fasciculus, left and right lateral frontal WM, left inferior frontal WM), bilateral uninate fasciculus (right inferior frontal WM, left infrerior frontal WM), bilateral inferior frontal occipito fasciculus (right inferior frontal WM, right inferior occipital WM, Left inferior frontal WM), and right inferior longitudinal fasciculus (right inferior occipital WM). This study suggests that there may be different developmental dysregulation in the formation of neuronal networks in ASD. **Reference:** [1]Sundaram et al.,Cereb Cortex, 2009. [2] Kumar et al. Cerel Cortex, 2010. [3] Smith et al., Neuroimage,2004. [4] Lee et al., Neuroimage, 2007. [5] Oishi et al. Neuroimage, 2009.

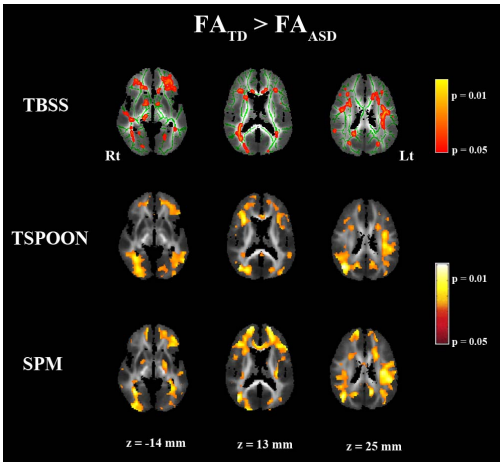

Figure 1. White matter regions with reduced FA in ASD obtained from separate approaches. Colorbar indicates p value for each approach. Gray colored background image shows mean FA image of TD group.olored background.

Table 1. Number of overlapped white matter regions.

condition	TBSS & TSPOON &SPM	TBSS & TSPOON	TSPOON &SPM	TBSS &SPM	TBSS only	TSPOON only	SPM only
$FA_{TD}>FA_{ASD}$	6	8	10	10	30	4	11

Table 2. White matter regions showing $FA_{TD} > FA_{ASD}$ in all three methods.

region	MNI (mm)			t_{max}	Size (mm^3)	FA mean (SD)		Cohen's d
	x	y	z			TD	ASD	
Lt. Superior longitudinal fasciculus	-34	-22	28	3.68	1384	0.38(0.05)	0.35(0.03)	0.94
Rt. inferior frontal WM	32	20	18	5.02	936	0.31(0.03)	0.29(0.03)	1
Rt. inferior occipital WM	36	-52	0	4.04	568	0.38(0.04)	0.35(0.03)	1.09
Lt. lateral frontal WM	-34	-2	22	3.69	424	0.32(0.04)	0.30(0.02)	0.91
Lt. inferior frontal WM	-32	24	14	3.51	352	0.28(0.02)	0.26(0.02)	1.02
Rt. lateral frontal WM	26	14	20	3.73	256	0.38(0.06)	0.34(0.03)	0.91