Tractography-based voxel-wise analysis (TBVA): a new approach for detecting white matter abnormalities in clinical populations

Su-Chun Huang[1,2], Gregory J. Pauley[1], Todd L. Richards[1], Neva M. Corrigan[3], Dennis W. Shaw[3], Alan A. Artru[4], Annette Estes[5], Stephen R. Dager[3], and Natalia M. Kleinhans[1,3]

[1]Integrated Brain Imaging Center, Department of Radiology, University of Washington, Seattle, WA, United States, [2]Institute of Biomedical Engineering, National Taiwan University, Taipei, Taiwan, [3]Department of Radiology, University of Washington, Seattle, WA, United States, [4]Department of Anesthesiology, University of Washington, Seattle, WA, United States, [5]Speech and Hearing Sciences, University of Washington, Seattle, WA, United States

Introduction : Diffusion tensor imaging (DTI) is currently one of the most popular magnetic resonance techniques for evaluating brain white matter integrity *in vivo*. Image analysis approaches based on DTI such as tract-based spatial statistics (TBSS) are able to represent tract specific information at the voxel level. TBSS requires projection of the fractional anisotropy (FA) skeleton onto every subject's FA map to search for the maximum value. This value is assumed to represent the center line along a tract. However, in some cases, this approach may be insensitive to white matter abnormalities that occur in peripheral white matter regions that are excluded from the TBSS skeleton. To get a better understanding of the tract bundle as a whole, tractography in individual spaces are needed. However, a limitation of most tractography studies is that they only report a mean FA value of the whole tract bundle, which may be insensitive to focal alterations in white matter present within the tract bundle. Here we introduce a new analysis pipeline named tractography-based voxel-wise analysis (TBVA), which combines the advantages of TBSS and probabilistic tractography. This approach shows individual tract bundles in MNI standard space and performs voxel-wise comparisons within the tract bundle. We employed TBVA on the cingulum bundle (CB) in a group of participants with autism spectrum disorders (ASD) and age and IQ matched controls, and compared the results from conventional TBSS to the TSVA tractography results.

Materials and Methods Subjects Forty-seven participants with ASD (12 females; age mean: 19.07 ± 5.86 years) and sixty age- and IQ-matched (15 females; age mean: 21.10 ± 8.99 years) controls were recruited in the study. ***Data acquisition*** All images were acquired on a 3T Philips Achieva MR system (version 1.5, Philips Medical system, Best, Netherlands). DTI images were acquired with a single-shot echo-planar sequence (TR/TE/flip angle: 10.5s/63ms/90°, matrix size of 128×128, FoV of 240×240, 2mm slice thickness, 72 slices) with 32 gradient directions and a b-factor of 1000s/mm^2 . ***Data Processing*** All image processing was done with FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl). First, the non-brain tissues were removed from the DTI images, then eddy current and movement correction were applied. Probabilistic tractography maps of the bilateral CB were reconstructed with FDT (FSL Diffusion Toolbox). The tractography was constrained within white matter and a probability threshold of 25 percent was applied. ***Image coregistration*** The individual FA map was nonlinearly transformed to the FMRIB58_FA standard brain, and then linearly-aligned to MNI152 standard brain. Next, the transformation matrixes of the previous steps were applied to individual's CB maps. The coregistration was performed with FSL TBSS toolbox. ***Statistics*** The null distribution was generated by random permutation, then voxel-wise t-tests comparing ASD and control groups were performed. Threshold-free cluster enhancement (TFCE) was performed to correct for multiple comparisons. The corrected significance level was set at $p < 0.05$.

Results Figure 1 shows the spatial relationship of TBVA tractography and TBSS FA skeleton. Figure 2 shows the clusters of FA reduction detected by TBVA and TBSS. TBVA showed a higher sensitivity to detect reduced FA in the posterior and peripheral regions of the CB.

Discussion and Conclusion In summary, we combined TBSS and probabilistic tractography to build a new pipeline to perform voxel-wise analyses in standard space among individual's tract bundles. The results showed that the reduction of white matter integrity in ASD extended beyond the centers of tracts identified using TBSS. Further, TBVA identified additional regions of abnormal white matter that TBSS missed. Overall, TBVA showed better sensitivity for identifying within tract differences and may provide more information regarding macroscopic lesions (such as multiple sclerosis) on a microstructural scale.
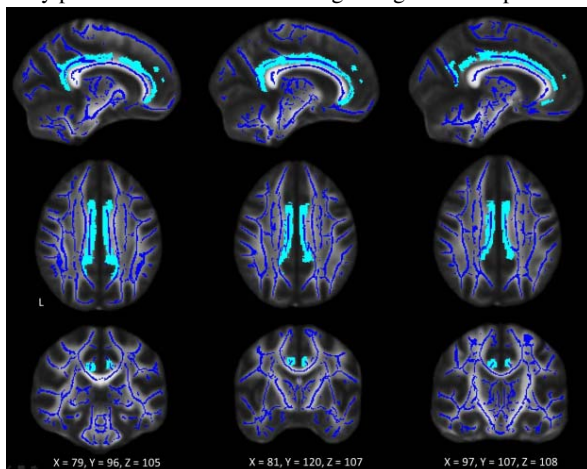

Figure 1. The spatial relationship of TBVA group tractography map and TBSS FA skeleton. The CB is shown in light blue and the FA skeleton is shown in dark blue. The background brain is the FMRIB58_FA standard brain.
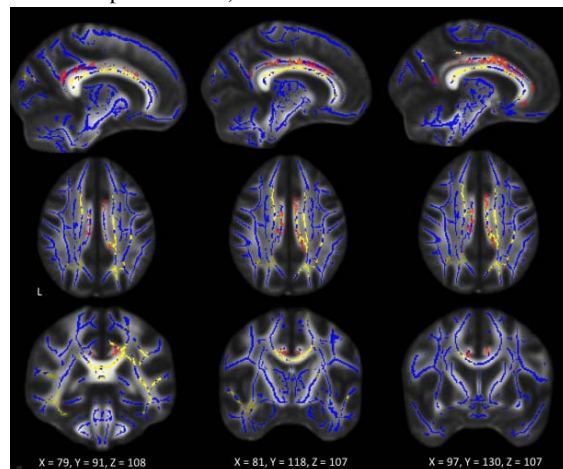

Figure 2. Clusters of FA reduction detected by TBVA and TBSS overlaid on the TBSS FA skeleton (dark blue). The clusters detected by TBVA and TBSS are shown in red and yellow respectively. Areas of overlap are shown in orange. The background brain is the FMRIB58_FA standard brain.