

## Atypical development of dentatothalamic pathway in children with autistic spectrum disorders

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**Introduction:** The dentatothalamic pathway (DTP) is a white matter pathway connecting dentate nucleus of the cerebellum to the contralateral thalamus. Many studies [1-2] suggest disturbance in the intrinsic cerebellar circuitry in autistic spectrum disorders (ASD). The present study utilized Q-ball imaging (QBI) technique to delineate the DTP in children with ASD and quantitatively assess their age-related changes in axonal anisotropy and volume. To address whether conventional QBI technique was adequate to assess this crossing pathway, we tested the feasibility of QBI tractography in clinical DTI data. **MATERIALS AND METHODS:** Sixteen children with a diagnosis of ASD (age:  $6.4 \pm 21.3$ , range: 4.6-9.3 years, all boys) and fourteen typically developing children (TD group, age:  $6.8 \pm 7.1$ , range=4.3-9.2 years months, all boys) were studied. Whole brain HARDI 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<sup>2</sup> and 55 diffusion gradient directions, TR/TE = 1250/88.7 ms, voxel size =  $1.88 \times 1.88 \times 3$  mm. An additional acquisition without diffusion weighting at  $b=0$  s/mm<sup>2</sup> was also obtained. The orientation distribution function (ODF) was reconstructed using regularized and fast analytical algorithm [3] with 0.001 regularization factor and 6-fold tessellated icosahedrons. The directions of three fibers were then selected from local peaks of the ODF for the tractography. The tractography was performed by a modified streamline tracking algorithm implemented on the software package of DSI studio (<http://dsi-studio.labsolver.org>) with 0.2 step size, 60° turn angle threshold, and 50000 seeding/voxel. MNI space ROIs delineating the red nucleus and the dentate nucleus were objectively placed in subject's native space by applying inverse of spatial deformation obtained between the subject's b0 image and MNI b0 template. The fibers for each DPT were sorted to include fibers passing the dentate nucleus and the contralateral red nucleus ROIs. Fractional anisotropy (FA), generalized FA (gFA) [4], and fiber volume were measured separately for the left and right DTP in all subjects. 2 (group)  $\times$  2 (side) repeated measures analysis of variance (ANOVA) were performed to determine how group and side affected each measure. Age related changes in FA, gFA, and volume were also determined in each group using Pearson correlation coefficient,  $r$ .

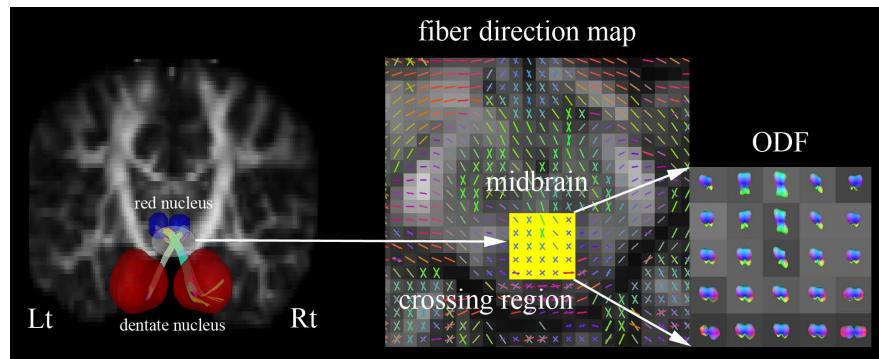


Figure 1: QBI reconstruction for tracking dentatothalamic pathways. Yellow box indicates the voxels that DTPs penetrate near caudal midbrain. The ODFs shows two crossing fiber components at those voxels.

Table 1. Mean and standard error of mean for FA, gFA, and volume in TD and ASD groups.

Left dentatothalamic pathway			Right dentatothalamic pathway			
	TD	ASD		TD	ASD	
FA	0.39(0.01)	0.34(0.01)	0.00017	0.37(0.01)	0.31(0.01)	0.00007
gFA	0.093(0.002)	0.085(0.001)	0.004	0.095(0.003)	0.084(0.002)	0.004
Volume (cm <sup>3</sup> )	0.79(0.12)	0.53(0.11)	0.113	0.83(0.11)	0.40(0.12)	0.010

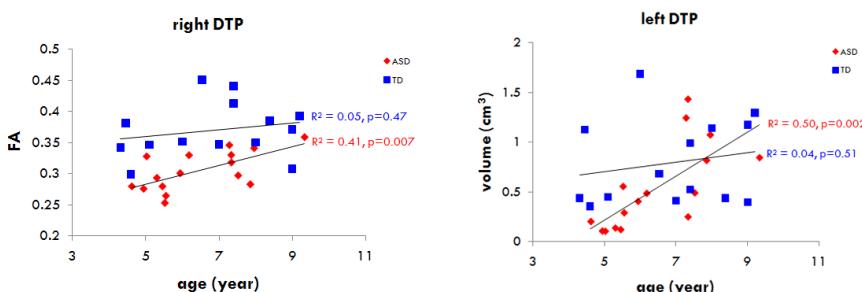


Figure 2: Age-related change in FA of right DTP and volume of left DTP.

**Results and Discussion:** Figure 1 shows representative DTPs along with QBI reconstructed fiber direction map and ODF. The FA, gFA, and volume of DTP were significantly lower in children with ASD compared to TD children, for both left and right DTP (see Table 1). There was no effect of side on any of measured parameters. Within-group analysis revealed that whereas there was no difference in any of the measured parameters between left and right DTP in TD group, the FA and volume of right DTP were significantly lower compared to left DTP in ASD children ( $p$  value=0.007, 0.02 for FA and volume, respectively). While age-related increases in FA and fiber volume were observed for both left and right DTP in both the groups, the age related increase in FA of right DTP and volume of left DTP was significantly higher in ASD group compared to TD group (see Figure 2). Our findings suggest both macrostructural and microstructural abnormalities along with developmental dysregulation of DTPs in ASD children. **Reference:** [1] Chugani D. et al., Ann Neurol., 1997. [2] Yip J. et al., Autism Res. 2009 [3] Descoteaux M. et al., Magn. Reson. Med. 2007. [4] Tuch D.S. Magn. Reson. Med. 2004.