In Vivo Detection of Reduced Purkinje Cell Fibers with Diffusion MRI Tractography in Children with Autism Spectrum Disorders

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Targeted audience: Clinical trainees and researchers in pediatric neuroradiology. Purpose: Postmortem neuropathology studies report reduced number and size of Purkinje cells (PC) in a majority of cerebellum specimens from persons with autism spectrum disorders (ASD). This study investigated whether structural changes related to decreased PC could be detected in vivo by measuring streamlines connecting the posterior-lateral region of the cerebellar cortex to the dentate nucleus using an independent component analysis with a ball and stick model (ICA+BSM)2. We hypothesized that the reported decrease in number and size of the PC may result in differences in the detection of PC efferent streamlines due to decreased directional coherence of streamlines near the voxels of PC efferent pathways. Decreased PC cell number and size might also cause significant changes in other conventional DW-MRI metrics such as fractional anisotropy (FA), streamline volume (SV), and streamline count (SC).

Methods: This study included fifteen children with ASD (age: 6.2 ± 3.1 years, range: 3.6-13.3 years, 11 boys) and fourteen typically developing children (TD, age: 6.8 ± 3.1, range=4.0-14.0 years, 11 boys). A 3T Sigma EXCITE scanner was utilized to acquire the whole brain DW-MRI data at b=1000 s/mm² and 55 diffusion gradient directions. To compensate for physiological artifacts and motion confound, we utilized a software package called the Tolerably Obsessive Registration and Tensor Optimization Indolent Software Ensemble (TORTOISE, https://science.nichd.nih.gov/confluence/display/mhp/TORTOISE) for 1) preprocessing the DW-MRI data for the correction of motion and eddy current distorsion using DIFF_PREP, 2) estimating diffusion tensor data using informed Robust Estimation of Tensors by Outlier Rejection (iRESTORE) using DIFF_CALC, and 3) calculating the maps of FA, AD, and RD from the tensors of iRESTORE. The ICA+BSM tractography to isolate the orientation of multiple crossing streamlines (up to 3) was performed using a cerebellar cortex seed region (crus I and II) and two sorting regions, the dorsal dentate nucleus (DDN) and the ventral dentate nucleus (VDN) obtained from “Spatially Unbiased Infratentorial Template (SUIT)”3. For each of the pathways projecting to the DDN and VDN, a streamline visitation map was created by the number of streamlines passing each voxel. Voxels having more than 5 visits were assumed to belong to each pathway, and the values of FA for the voxels in each pathway was averaged for comparison.

SV was measured by summing the volume of all voxels belonging to the pathway. SC was calculated by counting the total number streamlines per pathway. Results: Figure 1 shows representative examples of streamlines connecting the cerebellar cortex and the dentate nuclei in age-matched boys with TD and ASD. It is visually apparent in this figure that the streamline volume connecting the posterior-lateral cerebellar cortex with dentate nucleus is reduced in the child with ASD, compared with the TD child. Representative examples of directional compartments of streamlines identified by the ICA+BSM tractography (i.e., primary eigenvectors of the stick compartments) are shown in Figure 2a. The directional stick compartments are significantly reduced near the voxels of the cerebellar cortex in the child with ASD (marked by red in Figure 2b), which results in fewer streamlines in the child with ASD, compared with the TD child. Interestingly, the total volume of voxels having no stick compartments was significantly higher in the children with ASD, especially in the youngest children (Fig. 2c). Age-related reduction of no stick voxels was notable in the TD group (R²=0.30, p=0.043) but not in the ASD group (R²=0.07, p=0.341). The multi-variate analyses revealed that FA was significantly lower in three pathways in the ASD group, compared to the TD group: pathways projecting to the right DDN (p=0.008) and pathways projecting to the VDN bilaterally (left: p=0.020, right: p=0.010). In the left VDN and the right DDN, the reduced FA was apparent at all ages in children with ASD (Fig. 3b). Both SC and SV were significantly lower only in the pathway projecting to the right VDN (p=0.015 and 0.048 for SC and SV, respectively) in ASD group, compared to the TD group. Discussion and Conclusion: The present study found that 73.3% of children with ASD (11 of 15 studied ASD cases) showed reduced FA in fibers connecting cerebellar cortex to right VDN using a threshold 3 standard errors below the mean of the TD group. Similarly, Palmen et al. reported that 72.4% of subjects with ASD (21 of 29 studied cases) had a decreased number of PC. Thus, the diffusion methods in the current study may detect white matter pathology in pathways connecting the lateral cerebellar cortex to the dentate nuclei in a similar portion of cases as in postmortem pathology showing decreased PC in lateral posterior-lateral cerebellar cortex, which may be a marker cerebellar pathology in children with ASD.