Abnormal WM microstructural trajectories of autistic children from 2 to 7 years of age

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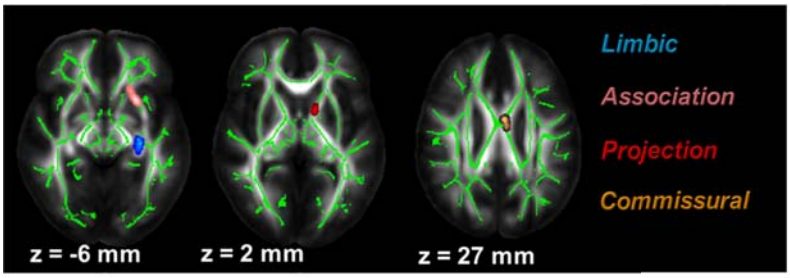
Target audience: Clinicians, MR physicists, psychiatrists and psychologists interested in studying autism with MRI.

Introduction: Autism is a neurodevelopment disorder characterized by three core features: impairments in social interaction, abnormal development of language and repetitive and ritualized behaviors [1]. The majority of the studies using diffusion tensor imaging (DTI) method to investigate the white matter (WM) integrity in the autistic brains have been focusing on the age range from mid-childhood to adolescence [2]. WM disruption in corpus callosum, a commissural tract connecting the left and right hemispheres, has been reported extensively. DTI studies including autistic children from 2 to 7 years of age are relatively rare and the results in the literature [e.g. 3-6] are inconsistent. Age between 2 and 4 is a critical period for early intervention and also the important period for the formation of the neural wiring patterns in human life [7]. In this study, we hypothesized that the growth trajectories of the microstructural metrics of WM tracts from 2 to 7 years of age is different between autistic children and children with typical brain development, and these differences are widespread to all four functionally distinguished WM tract groups, namely limbic, commissural, association and projection tract groups [8]. To test these hypotheses, high-quality DTI of a total of 51 children was acquired and trajectories of DTI metrics of all WM voxels were examined.

Methods: *Participants:* 31 children diagnosed with autism (2.33 ~7 years, 4.1±1.4) and 20 typically developing children (1.99 ~6.83, 4±1.4) participated in this study. The diagnosis of autism was confirmed by ADOS/ADI structured diagnostic procedures [7] using DSM-IV criteria and the Childhood Autism Rating Scale (CARS). The exclusion criteria for typically developing children include nervous system diseases, psychiatric disorders and systemic disorders by experienced clinicians. *DTI acquisition:* All MR scans were performed on a 3T Philips Achieva MR system. DTI data were acquired using a single-shot, echo-planner imaging sequence with SENSE parallel imaging scheme. The imaging matrix size = 128×128, field of view = 256×256 mm^2, TR/TE = 7958.4/82.8ms. Axial slices of 2 mm thickness were acquired parallel to the anterior-posterior commissure line. A total of 70 slices covered the entire brain without a gap. The diffusion weighting was encoded along 30 independent directions and the b-value was 1000 s/mm^2. To increase the signal-to-noise ratio, two repetitions were performed. *Data analysis:* Tensor fitting was conducted with DTIstudio [8] after affine registration of diffusion weighted images to b0 to obtain DTI-derived metric, namely fractional anisotropy (FA). All FA maps were aligned to the JHU ICBM-DTI-81 WM atlas and skeletonized FA was obtained using the tract-based spatial statistics (TBSS/FSL) [9]. Analysis of covariance (ANCOVA) was applied to the skeletonized FA data to explore the age and group interaction using MATLAB. The clusters with significant age and group interaction (FDR corrected $p<0.05$) and size greater than 10 voxels were identified. Linear regression analysis was performed between the age and the mean FA value in those clusters.

Results: Fig.1 shows the location of four representative clusters covering all four tract groups. Each cluster belongs to one of the following four tract groups, limbic, association, projection and commissural tract groups. These clusters show significant ($p<0.005$) differences of age and group interaction with ANCOVA analysis. Clusters in limbic, association, projection and commissural tract with significant group by age interaction are shown in blue, pink, red and brown, respectively. Fig.2 shows the linear regression analysis between age and mean FA value in these four representative clusters. In each panel of the figure, FA value in the control group sharply increased with age when compared with the relative absence of FA increase with age in the autism group. There is a crossing point around 4 years between the regression lines of control and autism groups in each cluster. Before 4 years of age, FA values in autism group appear to be larger than those in control group. After 4 years, FA values of autistic group appear to be smaller than those of control group. More than 50 significant clusters covering all four tract groups were identified with ANCOVA. Table 1 shows the coordinate information of several representative clusters with abnormal growth trajectories in each of the four tract groups.



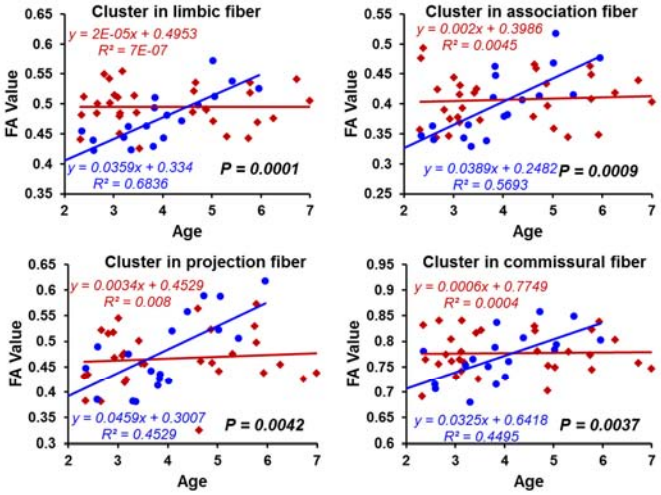


Fig. 1 ***(left) Clusters with significant age and group interaction located in four different tract groups. The mean FA skeleton mask is shown in green.***

Fig. 2 ***(right) WM growth trajectories with mean FA value in the four representative clusters of autistic patients (red) and control subjects (blue). The four clusters belong to four tract groups, respectively.***

Table 1: (see below) The list of representative clusters with abnormal growth trajectories in the four tract groups.

Discussion and conclusion:

We have revealed the abnormal WM growth trajectories in all four functionally distinguished tract groups for autistic children from 2 to 7 years of age. These findings indicated early overgrowth from 2 to 4 years of age and later slower growth of WM from 4 to 7 years of age. The atypical microstructural development in corpus callosum (CC), a commissural tract, has been reported previously [2]. Our study suggests that abnormality of WM growth trajectories in young autistic children occurs extensively in the brain WM, affecting not only commissural tract, but also limbic, projection and association tracts. These findings provide the structural basis of altered brain circuits and connectivity of autistic children [e.g.12] and new insight into the regional distribution and maturational pattern of WM microstructures in autism.

Tract group	White matter tract	MNI coordinate x	y	z	Voxel size
Limbic	Fornix	-28	-25	-5	97
Association	IFO-L	-26	13	-6	70
	SLF-L	-45	-37	37	97
	IFO-R	26	-70	1	72
Projection	ATR-L	-12	7	1	17
	CST-R	21	-29	45	65
Commissural	Corpus callosum	-6	-2	27	20
	Fminor	-7	25	26	12
	Fminor	0	5	25	10

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