Age-related abnormalities of white matter tracts in autism spectrum disorder: A diffusion spectrum imaging study using whole brain tract-specific analysis

Chien-Hung Lu[1], Yu-Jen Chen[2], Yu-Chun Lo[2], Yung-Chin Hsu[2], Susan Shur-Fen Gau[3,4], and Wen-Yih Isaac Tseng[2,4]

[1]*School of Medicine, National Taiwan University, Taipei, Taipei, Taiwan,* [2]*Center for Optoelectronic Medicine, National Taiwan University College of Medicine, Taipei, Taipei, Taiwan,* [3]*Department of Psychiatry, National Taiwan University College of Medicine, Taipei, Taipei, Taiwan,* [4]*Graduate Institute of Brain and Mind Sciences, National Taiwan University, Taipei, Taipei, Taiwan*

Purpose Atypical brain structure and function across a wide range of age in autism spectrum disorder (ASD) have been investigated by many brain imaging studies. Significant enlargement of brain volume particularly in the frontal lobe, temporal lobe, and amygdala has been reported in young children with ASD [1], but it seems to resolve in adolescence [2]. Widespread reductions in white matter integrity in adolescents and adults with ASD have documented in diffusion tensor imaging studies [3]. However, fractional anisotropy values show increasing in early childhood of ASD [4]. To date, the development of white matter tracts over the whole brain is not clearly defined in ASD. This study aimed to investigate abnormalities of white matter tracts across a wide range of age using diffusion spectrum imaging (DSI). We hypothesized that the development of white matter tracts was altered in ASD.

Methods Sixty-three males with ASD and 63 matched typically developing (TD) participants (ASD: 14.4 ± 4.6, range: 7-29 years old; TD: 14.3 ± 5.0, range: 7-29 years old), were recruited in this study. Images were acquired on a 3T MRI system with a 32-channel head coil (Tim Trio, Siemens, Erlangen, Germany). DSI was performed using a twice-refocused balanced echo diffusion echo planar imaging sequence, TR/TE = 9600/130 ms, image matrix size = 80 x 80, spatial resolution = 2.5 x 2.5 mm^2, and slice thickness = 2.5 mm. 102 diffusion encoding gradients with the maximum diffusion sensitivity b_{max} = 4000 s/mm^2 were sampled on the grid points in a half sphere of the 3D q-space with $|q| \leq 3.6$ units [4]. For DSI tractography analysis, a tract-based automatic analysis (TBAA) method was applied via a high quality DSI template and predetermined white matter tracts in the whole brain. The DSI template was constructed by coregistering 122 healthy participants' DSI datasets using a registration method under the Large Deformation Diffeomorphic Metric Mapping (LDDMM) framework [5]. A total of 117 white matter tracts were reconstructed on the template by an expert using multiple regions of interest defined in the Automatic Anatomical Labeling system. Each reconstructed tract was subdivided into 100 steps with even spacing and the step coordinates along tracts were saved as sampling coordinates. The procedures of TBAA method were as follow. 1) A study specific template (SST) was created via coregistering all participants' DSI datasets using LDDMM. 2) The SST was coregistered to the DSI template. 3) Sampling coordinates of the tracts were transformed from the DSI template to individual DSI datasets via the transformation matrix between DSI template and SST as well as the matrix between SST and individual DSI. 4) Generalized fractional anisotropy (GFA) values were sampled in the native DSI space using the transformed sampling coordinates, resulting in a 2D array (117 tracts x 100 steps) of GFA profiles for each subject. In this study, mean GFA for each tract was calculated for further analysis and comparison. Fisher's exact z test was applied to test the difference in correlation coefficients between the two groups.

Results We found a significant difference in age effect in 11 white matter tracts between ASD and TD (Figure 1). In the association fibers, the significant tracts were bilateral inferior frontal-occipital fasciculus (IFOF), left cingulum, and left inferior longitudinal fasciculus (ILF). In the callosal fibers, two portions of corpus callosum were identified, including fibers connecting bilateral cuneus and bilateral supplementary motor areas. Moreover, bilateral frontal-striatal (FS) tracts, bilateral thalamo-frontal tracts, and right thalamo-occipital tracts also showed significant differences. All of the 11 tracts showed higher GFA growth with age in TD than in ASD (Table 1).

Discussion According to Travers and colleagues' review of 48 DTI studies, atypical developmental trajectory of white matter in ASD was indicated. Individuals with ASD tended to show decreased FA in white matter tracts of many brain regions, but most consistently in the corpus callosum, cingulum, and aspects of the temporal lobe [6]. In Shukla's study, they indicated altered maturation of short-distance tracts in frontal, temporal, and parietal lobes in ASD across the ages [7]. In our study, with a large sample size and a broad range of age, GFA presented an atypical growth pattern in ASD compared to TD. The present data suggested that the time trajectory may differentiate brain maturation in ASD.

References [1] Courchesne et al. (2001) Neurology. [2] Aylward et al. (2002) Neurology. [3] Barnea-Goraly et al. (2011) Arch Gen Psychiatry. [4] Wedeen et al. (2005) Magn Reson Med. [5] Hsu et al. (2012) Neuroimage. [6] Travers et al. (2012) Autism Research. [7] Shukla et al. (2011) Neuropsychologia.

Table 1. The correlation coefficient and Fisher's exact z test results of each tracts.

	Left cingulum	Left IFOF	Right IFOF	Left ILF	Left FS	Right FS
r of TD	0.3260	0.6443	0.5833	0.3652	0.5679	0.6255
r of ASD	-0.1081	-0.0677	0.0180	-0.0847	-0.0784	-0.1322
p value	0.0215	0.0002	0.0027	0.0164	0.0007	0.0001
	Left Thalamo-Frontal	Right Thalamo-Frontal	Right Thalamo-Occipital	Callosal-supplementary motor	Callosal-cuneus	
r of TD	0.4627	0.5102	0.3088	0.4032	0.3832	
r of ASD	-0.0727	-0.0245	-0.1831	-0.0506	-0.0280	
p value	0.0051	0.0051	0.0093	0.0164	0.0278	

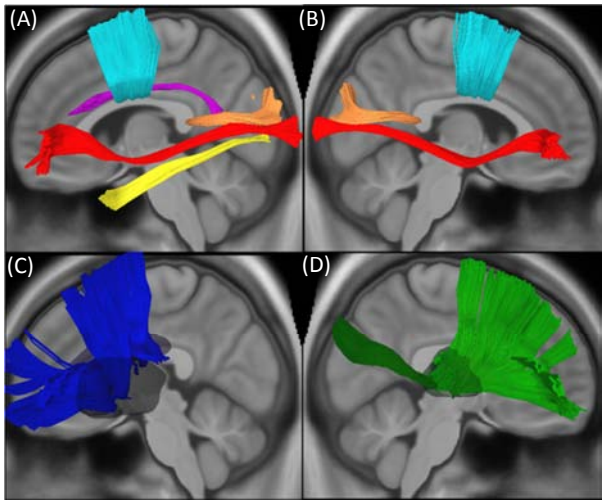

Figure 1. (A)Left cingulum(purple), left inferior fronto-occipital fasciculus(red), left inferior longitidunal fasciculus(yellow), callosal-supplementary motor tract(light blue), callosal-cuneus tract(orange)(B)right inferior fronto-occipital fasciculus(red), callosal-supplementary motor tract(light blue), callosal-cuneus tract(orange) (C)Left fronto-striatal tract(dark blue) (D)Right thalamo-frontal tract(light green) and right thalamo-occipital tract(dark green)