Atypical Development of White Matter Microstructure in Adolescents with Autism Spectrum Disorders

K-H. Chou[1], I-Y. Chen[2], Y-W. Cheng[2], J. Decety[3], Y-T. Fan[2], and C-P. Lin[2,4]

[1]Institute of Biomedical Engineering, National Yang-Ming University, Taipei, Taiwan, [2]Institute of Neuroscience, National Yang-Ming University, Taipei, Taiwan, [3]Departments of Psychology and Psychiatry, The University of Chicago, Chicago, United States, [4]Institute of Biomedical imaging and Radiological Sciences, National Yang-Ming University, Taipei, Taiwan

Introduction

Autism spectrum disorders (ASD) is a relative common brain developmental disorder that occurs in one in 150 children. It is characterized by early onset of impaired social reciprocity and communication difficulties, along with restricted interest and stereotyped behavior. Several lines of evidence suggested that cascade failure of neurodevelopment is most likely the core deficit of ASD [1-2]. Current evidence suggested that the brain of ASD individuals, as indexed by head circumference and brain volume, underwent a period of precocious growth during early postnatal life followed by a deceleration in age-related growth, as compared to typically developing [3-4]. Disproportional increased in white matter (WM) were postulated to account for this abnormal brain enlargement, as indicated by studies of young children [2,4]. In addition, abnormal structures of gray matter may be related to malformations of WM, which is especially intriguing in ASD considering the fact that the cognitive deficit was most likely to arise from impaired integrative processing through intrahemispheric and interhemispheric transfer of information [5]. Thus, whether aberrant WM development persisted into later childhood and adolescence was a crucial issue to probe. The aim of the present study was to examine WM microstructure between ASD and healthy groups using diffusion tensor imaging (DTI) and to investigate its relations to age in adolescents with ASD.

Methods

25 non-medicated male ASD participants (mean age: 13.71±2.54 y/o) and 25 typically developing adolescents participants (mean age:13.51±2.20 y/o) were enrolled in the study. All participants were right-handed ethnic Chinese males with IQ > 80 as estimated by Wechsler Intelligence Scale for Children (Mean IQ for ASD group: 101.60±18.91; Mean IQ for healthy group: 109.04±9.45). These two groups were matched in age, gender, IQ and handedness. The diagnosis of ASD was confirmed using the DSM-IV diagnostic criteria as well as the Autism Diagnostic Interview-Revised (ADI-R). All MR scans were performed on a 1.5T MR system (Excite II; GE Medical Systems, Milwaukee, Wis., USA) at the Veterans General Hospital Taipei. Whole brain diffusion-weighted images were acquired using single shot diffusion spin-echo EPI sequence with TR/TE = 17000/68.9 ms, voxel size = 2 x 2 x 2.2 mm^3, b = 900 s/mm^2, 13 directions, and NEX = 6. Whole brain voxel-wise statistic analysis of the FA map was carried out using TBSS [6], which is implemented in FSL (Oxford, UK). Voxel-wise statistical analysis of individual skeleton images of both groups for both contrasts (Normal > ASD) and (Normal < ASD), with age and IQ use as covariates, was performed using a nonparametric permutation test with a cluster size threshold of T>3 and SVC-FDR corrected P<0.05 for significance. To further elucidate different developmental pattern between the two groups, we performed a voxel-by-voxel interaction analysis to test for areas showing linear interactions between group and age. The statistic criteria of this interaction analysis were the same as described above.

Results

Regional FA Value Difference Between Two Groups:

The group-wise comparison of two groups showed that individuals with ASD exhibited greater FA in several clusters including the right superior longitudinal fasciculus of middle frontal gyrus, right cingulate gyrus, right superior corona radiata of frontal lobe, right postcentral gyrus, bilateral insula, right anterior thalamus, right putamen, right superior temporal gyrus, right inferior occipital gyrus, and bilateral middle cerebellar peduncle (Fig 1 A-C). Conversely, there were some regions with lower FA in subjects with ASD vs. controls. The regions included clusters of right angular gyrus, left globus pallidus, and right inferior cerebellar peduncle.(Fig 1 D-F)

Interaction of Age by Groups

The result showed interaction effect mainly occured in the frontal lobe, including bilateral superior frontal gyrus, right paracentral lobule, right cingulate gyrus, corpus callosum, and right inferior occipitofrontal fasciculus, as indicated by age-related gains in WM integrity in the controls and losses in the ASD group. Specifically, the FA value of paracentral lobule (the mean of all voxels in the clusters) had a significantly positive correlation with age in the controls (r= 0.630, P<0.001) but a trend-leveled negative correlation in the ASD (r= -0.464, P = 0.020). Similarly, in the right and left superior frontal gyrus, the controls showed an age-related gain of regional WM integrity (r= 0.661, P < 0.001; r= 0.677, P < 0.001) but the ASD group did not change with age significantly (r= -0.343, P < 0.093; r= -0.044, P < 0.835). (Fig 2)

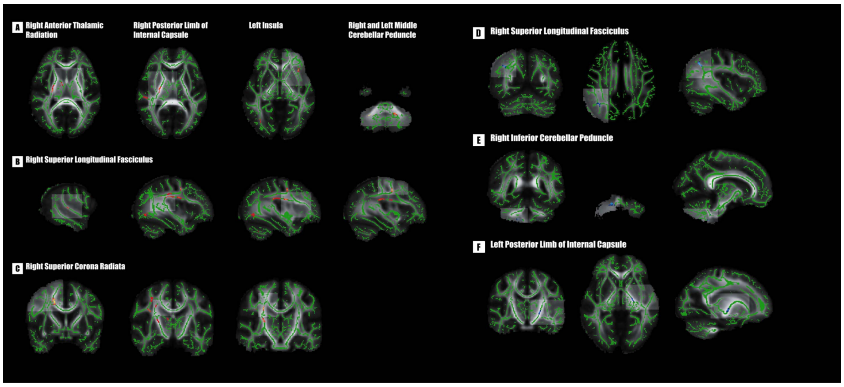

Figure 1.

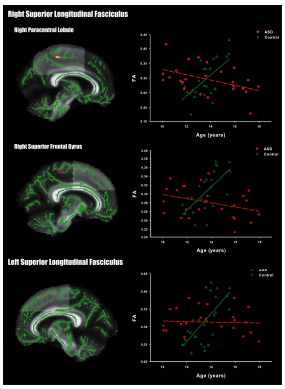

Figure 2.

Figure 1 : Group differences in regional FA value

WM regions showing significant FA difference between two groups were rendered onto the averaged axial FA and it's skeleton images. (Red: ASD > Normal ; Blue: Normal > ASD)

Figure 2 : Interaction of FA and age between groups

WM regions showing significant FA and age interaction between two groups. Top: paracentral lobule. Middle: superior frontal gyrus. Down: superior longitudinal fasciculus

Conclusions

The present study demonstrated that imbalance FA existed between control and ASD adolescent groups. Notably, the frontal lobe area FA, including clusters of the bilateral superior frontal gyrus, right paracentral lobule, right cingulate gyrus, corpus callosum, and right inferior occipitofrontal fasciculus displayed a significant interaction of age by group as shown by age-related gains in the control compared to no significant age-related change or trend-leveled losses in the ASD group. Our findings indicated that the frontal lobe exhibited abnormal WM microstructures as well as an aberrant neurodevelopment during adolescence in ASD, and significantly contributed to the growing literatures to highlight a key role of frontal cortex disconnectivity in the pathogenesis of ASD.

Reference

[1]Geschwind, D.H., et al., Curr Opin Neurobiol. 2007. [2]Courchesne, E. et al., Neuron. 2007. [3]Courchesne, E. et al., JAMA. 2003. [4]Dementieva Y.A., et al. Pediatr Neurol. 2005 [5]Just, M.A., et al. Brain 2004. [6]Smith S.M. et al., Neuroimage. 2006.

Acknowledgements

This study was supported in part by National Science Council grant NSC 98-2923-B-010-001–MY3.