

## Atypical Gray and White Matter Microstructure in Autism Spectrum Disorders

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### Introduction

Autism Spectrum Disorders (ASD) are complex disorders characterized by a wide range of behavioral and cognitive deficits that have an effect on many areas of day to day functioning of the affected children and adults. Abnormal brain development, reflected by abnormal growth curves of white (WM) and gray matter (GM) volumes has emerged as one of the significant features of the disorder (1). However, there is still little understanding of the microstructural deficits and their age dependence in ASD. In this study we investigate the gray (GM) and white matter (WM) microstructural integrity in the temporal and prefrontal lobes and in the cerebellum, three regions that have been shown to be characterized by both functional and anatomical deficits in ASD (1).

### Methods

Diffusion, field map, and anatomical data was collected in 14 subjects with a diagnosis of high functioning autism disorder (ASD) and 14 typically developing (TD) individuals aged 18 to 25 year old using a 3T Siemens scanner. Diagnosis was confirmed using ADOS for all ASD participants and ADI-R for 10 subjects for who a caregiver was available to participate. IQ measures were obtained for all participants using WAIS-III. There were no significant differences between the two groups on age (TD: 21.6±2.4, ASD: 21.2±2.28,  $p=0.622$ ) and full scale IQ (TD: 112±10, ASD: 110±17,  $p=0.700$ ). Diffusion data was acquired for two b values (1000 and 2000 s/mm<sup>2</sup>) and for  $b_0=0$  s/mm<sup>2</sup>. Twelve uniformly distributed encoding directions were sampled for  $b=1000$ s/mm<sup>2</sup> and 42 for  $b=2000$ s/mm<sup>2</sup>. Two averages were collected for the diffusion weighted images and 10 for the  $b_0$  image. Images were corrected for distortions due to B0 field inhomogeneities using the acquired field map. Image registration was used to correct for motion. A kurtosis approximation of the diffusion signal was used to calculate the diffusion and kurtosis tensor at each image voxel (2). Mean diffusivity (MD), mean kurtosis (MK), and fractional anisotropy (FA) maps were calculated for each subject. Radial (RD and RK) and axial (AD and AK) components of the diffusivity and kurtosis indices were also obtained. Segmentation of WM and GM regions were performed for each subject using the MPRAGE image and the FreeSurfer software package. The segmented maps were then registered to the diffusion data. Automatic and manual approaches were subsequently used to define masks of the prefrontal, temporal, and cerebellar WM and GM and the mean values of the parameters of interest were obtained for each region of interest.

### Results

**Prefrontal Brain Regions:** Whereas diffusion measures of prefrontal WM and GM did not differ significantly between groups, MK correlated significantly with age in the control but not in the ASD group for both GM and WM (Figure 1). RK but not AK correlated significantly with age in the TD group only.

**Temporal Brain Regions:** Significantly larger MK and RK were found in temporal WM and GM in the TD versus the ASD group (Figure 2). Whereas MD did not differ significantly between groups, significantly larger RD in the autism group was detected in GM. RK of GM was significantly correlated with age in the control group ( $r=0.594^*$ ,  $p=0.025$ ), with MK correlation close to significant. No correlation with age was found in the ASD group for any of the diffusion measures in the temporal GM. However, quite interestingly, close to significant correlations with age of RK in WM were found for both groups (TD:  $r=0.442$ ,  $p=0.114$ ; ASD:  $r=0.492$ ,  $p=0.074$ ).

**Cerebellum:** Significantly larger RK was found in cerebellar GM in the control versus the autism group ( $p=0.021$ ), with MK showing the same trend but not quite reaching significance. A significant correlation with age of the RK ( $r=0.561^*$ ,  $p=0.037$ ) was found in the TD but not the ASD group. No significant differences between in any of the examined measures were found in the cerebellar WM.

### Conclusions

These results indicate that the integrity and development of WM and GM microstructure is affected in autism within extended brain regions. In particular, we report for the first time that GM microstructural maturation appears to follow atypical developmental curves in all the regions investigated. Kurtosis is a measure of non-gaussian diffusion and thus gives a measure microstructural complexity (2). Decreased kurtosis in the GM of the ASD group may indicate a delay or failure to develop a proper synaptic network. Abnormal GM microstructure may explain some of the functional deficits reported in ASD. In WM, our results are consistent with previous findings (3, 4) and demonstrate that the abnormal development of WM microstructure previously reported in adolescents with ASD (3) continue into young adulthood. RK appears to be the most sensitive parameter in detecting both between group differences and dependence with age. This is the first study, to our knowledge, to employ the diffusion kurtosis formalism in the ASD population. One limitation of this study is the relatively small number of participants. Future studies will examine GM and WM microstructure in larger groups and over an extended age range.

**References** 1. Verhoeven JS et al., *Neuroradiology*, 2010, 32:3. 2. Jensen JH and Helpert JA. *NMR in Biomed.* 2010, 23:698. 3. Cheng Y et al. *Neuroimage*, 2010;872. 4. Lee et al, *Neuroimage*, 2009, 44:870.

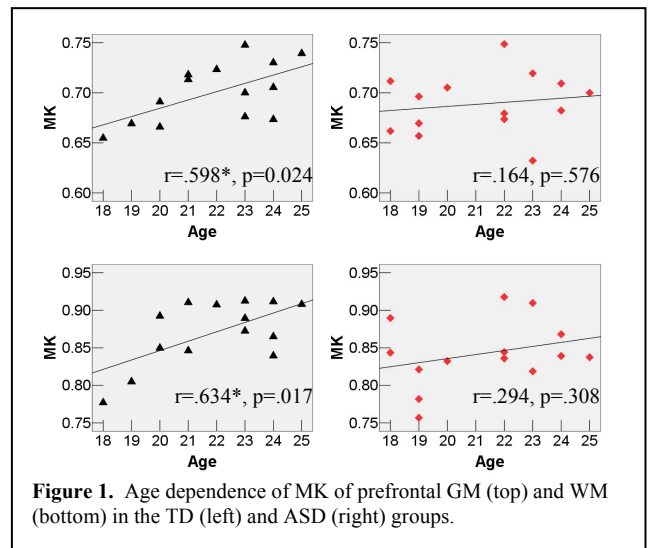


Figure 1. Age dependence of MK of prefrontal GM (top) and WM (bottom) in the TD (left) and ASD (right) groups.

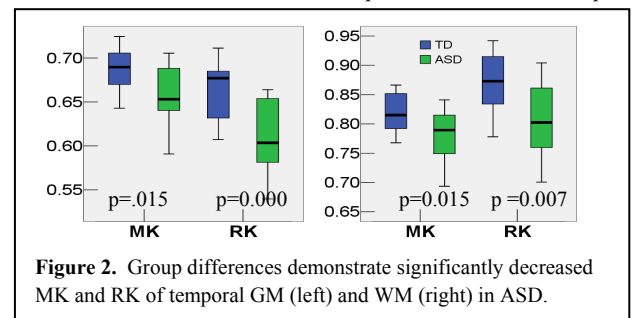


Figure 2. Group differences demonstrate significantly decreased MK and RK of temporal GM (left) and WM (right) in ASD.