

Increased Coherence of White Matter Fiber Tract Organization in Adults with Asperger Syndrome: A Diffusion Tensor Imaging Study

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To investigate whether there are global white matter (WM) differences between autistic and healthy adults, we performed diffusion tensor imaging (DTI) in 14 male adults with Asperger syndrome (AS) and 19 gender-, age-, and intelligence quotient-matched controls. We focused on individuals with high-functioning autism spectrum disorder (ASD), AS, to decrease heterogeneity caused by large variation in the cognitive profile. Previous DTI studies of ASD have mainly focused on finding local changes in fractional anisotropy (FA) and mean diffusivity (MD), two indexes used to characterize microstructural properties of WM. Although the local or voxel-based approaches may be able to provide detailed information in terms of location of the observed differences, such results are known to be highly sensitive to partial volume effects, registration errors, or placement of the regions of interest. Therefore, we performed global histogram analyses of (a) whole-brain tractography results and (b) skeletonized WM masks. In addition to the FA and MD, the planar diffusion coefficient (CP) was computed as it can provide more specific information of the complexity of the neural structure. Our main finding indicated that adults with AS had higher mean FA values than controls. A less complex neural structure in adults with AS could have explained the results, but no significant difference in CP was found. Our results suggest that there are global abnormalities in the WM tissue of adults with AS. *Autism Res* 2013, 6: 642–650. © 2013 International Society for Autism Research, Wiley Periodicals, Inc.

Keywords: diffusion tensor imaging (DTI); clinical psychiatry; neuroimaging; autism spectrum disorder

Introduction

Autism spectrum disorder (ASD) includes syndromes characterized by severe impairment in social interaction and restricted, repetitive patterns of behavior, interests, and activities. According to current diagnostic criteria, Asperger syndrome (AS) differs from infantile autism so that individuals with AS do not show a clinically significant delay in speech or cognitive development.

Deficits of social cognition may manifest in a variety of ways. Often, individuals with AS do not have peer relationships appropriate to their developmental level. They may lack understanding of the social conventions and social and emotional reciprocity. The restricted and repetitive behavior often manifests as encompassing preoccupation about a circumscribed topic. Typically, individuals with AS depend on routines to handle challenges of daily living. Thus, an individual with AS might have a high intelligence quotient (IQ) and excellent grammati-

cal skills, but because of the difficulties in encountering and understanding other people, the everyday life may be challenging.

It has been suggested that there are widely distributed abnormalities in the brain connectivity of individuals with ASD [Belmonte et al., 2004; Schipul, Keller, & Just, 2011; Wass, 2011]. The hypothesis of abnormal connectivity was first based on functional imaging studies, but recently, a noninvasive technique called diffusion tensor imaging (DTI) has made it possible to also study the anatomical connections in the brain [Basser, Mattiello, & LeBihan, 1994; Jones, Knösche, & Turner, 2013; Jones & Leemans, 2011; Tournier, Mori, & Leemans, 2011]. With DTI, the diffusion of water molecules is probed in several directions. In white matter (WM) tracts, the diffusion is hindered more by the cell walls of the axons than along the main orientation of the axons, and thus, diffusion is anisotropic. Fractional anisotropy (FA) is the most commonly used index to tell how anisotropic the diffusion is

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and can be used to quantify the coherence or organization of the WM fiber microstructure [Beaulieu, 2002].

DTI studies of ASD support the theory of abnormal connectivity [Pina-Camacho et al., 2012; Travers et al., 2012]. However, the results from previous studies are inconsistent, as both decreased and increased FA values have been reported in many WM tracts in ASD compared with typically developing control subjects [Pina-Camacho et al., 2012; Travers et al., 2012]. This could be partly due to the use of different analysis approaches [Cercignani, 2010; Deprez, Billiet, Sunaert, & Leemans, 2013; Jones & Cercignani, 2010]. Some studies have focused on predefined regions of interest (ROIs) [Beacher et al., 2012; Fletcher et al., 2010]. Others have performed tractography for selected neural tracts of interest [Langen et al., 2012; Verhoeven et al., 2012; Wolff et al., 2012]. Most of the whole-brain analyses have been performed by using voxel-based analyses [Barnea-Goraly, Lotspeich, & Reiss, 2010; Billeci, Calderoni, Tosetti, Catani, & Muratori, 2012; Bloemen et al., 2010; Bode et al., 2011; Jou et al., 2011; Shukla, Keehn, Smylie, & Müller, 2011], typically with the tract-based spatial statistics (TBSS) approach [Smith et al., 2006]. Groen and coworkers also investigated the global FA differences in adolescents with ASD, but did not find significant differences in mean FA, only in average mean diffusivity (MD) [Groen, Buitelaar, van der Gaag, & Zwiers, 2011]. The majority of the studies have focused on children and adolescents with ASD, reporting both increased and decreased FA values [Pina-Camacho et al., 2012; Travers et al., 2012]. Decreases in FA [Shukla, Keehn, & Müller, 2011] and in the variability of FA [Cascio et al., 2012] in global WM were reported in children with ASD. In adults, mostly decreases in FA have been found [Bloemen et al., 2010; Catani et al., 2008; Langen et al., 2012; Thakkar et al., 2008]. Furthermore, ASD represents a very heterogeneous group regarding both the genetic background and the spectrum and degree of severity of symptoms present in an individual. Only one whole-brain study included exclusively subjects with AS [Bloemen et al., 2010]. The authors used a voxel-wise method to analyze the FA values of the WM in 13 male individuals with AS, and 13 age and IQ-matched male controls and mainly found regions with decreased FA in adults with AS.

To date, the main focus in investigating individuals with ASD has been in detecting local changes of FA and MD. Although the local or voxel-based approaches may be able to provide detailed information in terms of location of the observed differences, such results are known to be highly sensitive to partial volume effects, registration errors, or placement of the ROIs [Cercignani, 2010; Jones & Cercignani, 2010]. Therefore, the aim in our study was to investigate the global differences in FA and MD in individuals with AS, a clinically well-characterized and homogeneous patient group without a clinically sig-

nificant delay in speech and cognitive development (International Classification of Disease; World Health Organization; 1993). To this end, we used two common approaches for analysis of DTI data: fiber tractography and the tract skeleton of TBSS. Histograms of FA and MD were calculated for both approaches and compared between individuals with AS and gender-, age-, and IQ-matched controls. To further investigate the underlying reasons for differences in FA, a measure for fiber complexity, planar diffusion coefficient (CP), was calculated as a post hoc analysis [Reijmer et al., 2012; Westin et al., 2002]. In addition, to investigate the relationship of the differences in DTI measures and various symptoms, the measures were correlated with questionnaire scores. Based on the previous studies, reporting mostly decreases in local FA in adults with AS [Pina-Camacho et al., 2012; Travers et al., 2012], we expected that the FA would be decreased also in our sample of adults with AS.

Methods

Participants

We studied 14 male individuals with AS and 19 gender-, age-, and IQ-matched control subjects without any neuropsychiatric disorders. The mean age of individuals with AS was 28.6 ± 5.7 years and that of controls 26.4 ± 4.7 years. To minimize the effect of age-related changes on the neural structure, only individuals aged 40 years or less were eligible for the study. The mean IQs for the AS and control groups were 125.1 ± 14.5 and 127.9 ± 10.0 , respectively, as obtained with the Wechsler's Adult Intelligence Scale—Third Edition (The Psychological Corporation, 2005). The individuals with AS were recruited from a private neuropsychiatric clinic in Helsinki (NeuroMental) and from the neuropsychiatric clinic in Helsinki University Central Hospital. Only individuals fulfilling ICD-10 (International Classification of Disease; World Health Organization; 1993) criteria, diagnosed by experienced clinicians specialized in AS, were included in the study. Both individuals with AS and controls were screened for other neuropsychiatric disorders by psychiatrists. Benton Facial Recognition Test (FRT) [Benton, Sivan, Hamsher, Varenly, & Spreen, 1983] and Reading the Mind in the Eyes Test (Eyes Test) [Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001] were carried out for all subjects. In addition, all subjects completed autism spectrum quotient (AQ) [Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001], empathy quotient (EQ) [Baron-Cohen & Wheelwright, 2004], and systemizing quotient (SQ) [Baron-Cohen, Richler, Bisarya, Gurunathan, & Wheelwright, 2003] questionnaires as self-reports. The questionnaires were translated into Finnish, and the translation was confirmed by a back-translation. Control subjects were paid for their attendance in the study, and for individuals with AS the

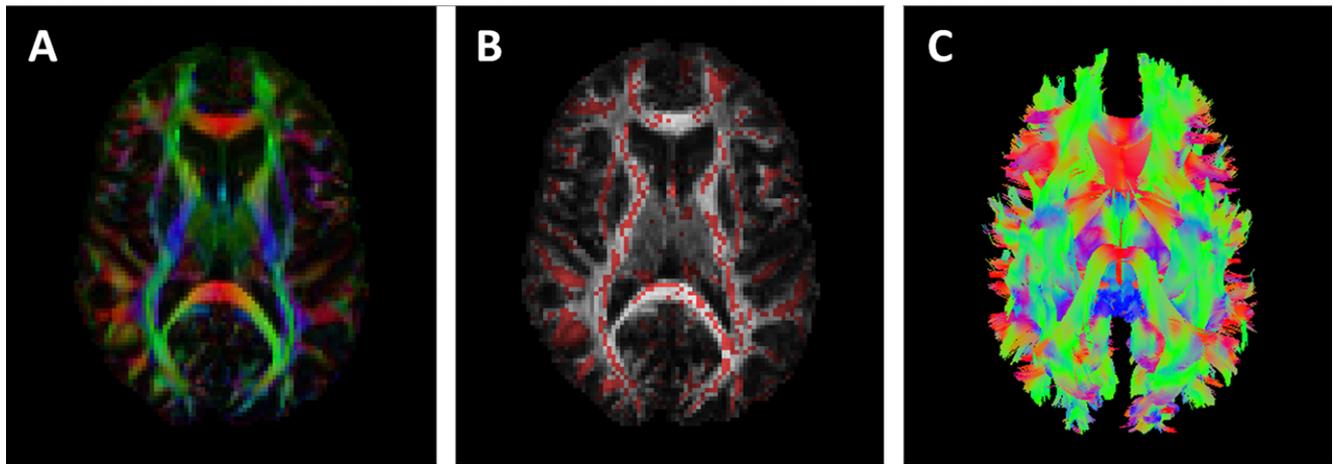


Figure 1. (A) A color-coded fractional anisotropy (FA) map; (B) FA skeleton (in red) overlaid on a grayscale FA map; (C) a whole-brain tractography from an individual with Asperger syndrome (AS). The colors indicate the orientation of the tracts: red = left-right, green = anterior-posterior, blue = cranio-caudal. Higher FA corresponds to a brighter color in A and B.

expenses and the loss of income were compensated. The ethics committee of Hospital district of Helsinki and Uusimaa approved of the research protocol, and all participants signed a written informed consent form before participating in the study.

Data Acquisition

The magnetic resonance (MR) images were acquired with a Signa VH/i 3.0T scanner with HDxt upgrade (General Electric, Milwaukee, WI, USA). A quadrature receiving eight-channel high-resolution brain array coil was used (MRI Devices Corporation, Gainesville, FL, USA). The maximum field gradient amplitude of the magnetic resonance imaging system was 40 mT/m, with a slew rate of 150 T/m/sec. A high-order shimming with 24 cm field of view was applied prior to diffusion weighted (DW) imaging. A spin echo pulsed sequence of 60 unique gradient orientations arranged on the unit sphere was used. Eight non-DW B0-images were acquired, and all of the 60 orientations were repeated twice resulting in 120 DW images in total. The b-value, which controls the diffusion weighting, was 1000 sec/mm². Echo time was set to the minimum (approximately 98 msec). Repetition time was 10 sec, and the number of excitations was one. The imaging area covered the whole brain with 53 contiguous axial slices. The acquired in-plane resolution of the slices was 1875 mm × 1.875 mm, and the thickness of the slices was 3.0 mm. The matrix size was 128 × 128.

Data Analysis

MR images were analyzed with ExploreDTI [Leemans, Jeurissen, Sijbers, & Jones, 2009]. The DW images were corrected for subject motion and eddy current-induced

distortions, after which the diffusion tensors were fitted. The skeletonization of the FA and MD images was done as introduced in TBSS [Smith et al., 2006]. A threshold of FA > 0.2 was used to create the final mask as recommended in Smith et al., 2006. MD was calculated for the same voxels in this mask. The whole-brain tractography was performed with deterministic tractography with the same FA threshold of 0.2, a maximum angle deviation of 30 degrees, and step size of 1 mm. The minimum length of the fiber was set to 50 mm. In Figure 1, a color-coded FA map, a skeletonized FA map, and a whole-brain tractography image are shown from a typical individual with AS.

Histograms for FA and MD were calculated for each subject from both skeleton and tractography data, and normalized by the number of the voxels in each subject's data to be able to calculate mean histograms for each group. Univariate analysis of variance was used to test for group differences in global mean, median, mode, and mode value of FA and MD across all individuals, and partial correlation was used to calculate the correlations between the mean FA and MD and AQ, EQ, and SQ scores. Equality of variances between the groups was tested by using Levene's test. All statistical tests were performed in SPSS (IBM Corporation, Armonk, NY, USA) and controlled for age and IQ.

As a post hoc analysis, the degree of fiber complexity was quantified by calculating CP both for the skeleton and tractography data [Westin et al., 2002]. A higher CP describes a more disc-shaped diffusion tensor, typically caused by crossing fibers [Ennis & Kindlmann, 2006; Vos, Jones, Jeurissen, Viergever, & Leemans, 2012; Wiegell, Larsson, & Wedeen, 2000]. CP is important in interpreting any changes in FA between controls and subjects with AS because a lower FA value could be caused by higher fiber

Table 1. Mean and Standard Deviation of the Two Groups and Results from the Two-Tailed *t*-Test Between the Two Groups Are Provided for the Following: Age (in Years), Handedness (1 = Right, 2 = Left), Total, Verbal and Performance Intelligence Quotient (IQ), Benton Facial Recognition Test (FRT), Reading the Mind in the Eyes Test (Eyes Test), Autism Spectrum Quotient (AQ), Empathy Quotient (EQ), and Systemizing Quotient (SQ)

Variable	Patients	Controls	<i>t</i> -value (F-value)	<i>P</i> -value
Age	28.6 ± 5.7	26.4 ± 4.7	-1.16	0.26
Handedness	1.0 ± 0.0	1.1 ± 0.3	-1.00	0.34
Total IQ	125.1 ± 14.5	127.9 ± 10.0	0.63	0.54
Verbal IQ	125.1 ± 15.3	128.4 ± 10.4	0.70	0.49
Performance IQ	121.9 ± 12.9	124.9 ± 9.8	0.74	0.47
FRT	46.4 ± 3.7	46.5 ± 6.2	0.10	0.92
Eyes Test	24.7 ± 4.8	25.8 ± 2.7	0.76	0.46
AQ	30 ± 7.5	11.1 ± 6.7	-7.60 (49.13)	1.5e-8 (1.0e-7)
EQ	24.6 ± 15.6	42.2 ± 11.5	3.74 (11.91)	7.6e-4 (1.7e-3)
SQ	39.0 ± 17.4	31.4 ± 7.3	-1.72 (3.61)	0.095 (0.068)

AQ, EQ, and SQ were tested also with univariate analysis of variance by using age and IQ as covariates, and the respective *P*- and F-values are marked in brackets.

Table 2. A Comparison of Fractional Anisotropy (FA) and Mean Diffusivity (MD) Values in Individuals with AS and Controls

Method	Property	Quantity	AS	Controls	Equality of means		Equality of variances	
					F-value	<i>P</i> -value	F-value	<i>P</i> -value
Whole brain tractography	FA	Mean	0.4804 ± 0.007418	0.4701 ± 0.01295	8.179	0.007774	2.309	0.1387
		Median	0.4727 ± 0.009205	0.4610 ± 0.01488	7.190	0.01197	1.028	0.3186
		Mode	0.4607 ± 0.01284	0.4526 ± 0.01844	2.825	0.1035	1.101	0.3022
	MD	Mode value value	0.06258 ± 0.001874	0.06474 ± 0.002646	7.471	0.01057	0.9481	0.3377
		Mean	7.978E-4 ± 0.1182E-4	8.026E-4 ± 0.1650E-4	0.8188	0.3730	0.3944	0.5346
		Median	7.519E-4 ± 0.1255E-4	7.573E-4 ± 0.1468E-4	1.253	0.2722	0.002142	0.9634
		Mode	7.214E-4 ± 0.2568E-4	7.421E-4 ± 0.1873E-4	7.073	0.01261	7.159	0.01181
FA skeleton	FA	Mode value value	0.2806 ± 0.02613	0.3042 ± 0.01993	6.530	0.01611	0.05105	0.8227
		Mean	0.4458 ± 0.007501	0.4368 ± 0.01133	6.102	0.01963	0.6216	0.4365
		Median	0.4254 ± 0.01158	0.4164 ± 0.01495	2.883	0.1002	0.03545	0.8519
	MD	Mode	0.2268 ± 0.006682	0.2250 ± 0.0000	2.146	0.1537	3.374	0.07584
		Mode value	0.07399 ± 0.005030	0.07535 ± 0.005311	0.3287	0.5709	0.1923	0.6640
		Mean	7.576E-4 ± 0.3735E-4	7.660E-4 ± 0.3493E-4	0.4923	0.4885	0.5071	0.8233
		Median	7.230E-4 ± 0.09139E-4	7.316E-4 ± 0.1360E-4	3.212	0.08356	1.459	0.2362
Mode	Mode	7.143E-4 ± 0.2344E-4	7.342E-4 ± 0.2388E-4	5.933	0.02124	0.4949	0.4870	
	Mode value	0.2133 ± 0.02010	0.2296 ± 0.01778	4.625	0.03999	0.4698	0.4982	

Age and IQ were used as covariates.

AS, Asperger syndrome.

complexity. Univariate analysis of variance was used to test for group differences in global mean, median, mode, and mode value of CP across all individuals. Equality of variances between the groups was tested by using Levene's test. The results were controlled for age and IQ.

Results

As expected, AQ scores were significantly higher ($F = 49.13$, $P = 0.0000001$) and EQ scores significantly lower ($F = 11.91$, $P = 0.0017$) in individuals with AS compared with the control group. The difference in SQ scores did not reach significance ($F = 3.61$, $P = 0.068$). The

results were controlled for age and IQ. No significant differences were found in IQ, age, FRT, or Eyes Test. The group means and the significance of the differences are presented in Table 1.

In the tractography data, the mean FA was significantly higher ($F = 8.18$, $P = 0.0008$) in individuals with AS (0.4804 ± 0.0074) than in controls (0.4701 ± 0.0130), as shown in Table 2 and Fig. 2. The skeleton data supported this finding, although the differences were somewhat weaker (Table 2): the mean FA was significantly higher ($F = 6.10$, $P = 0.020$) in individuals with AS (0.4458 ± 0.0075) than in controls (0.4367 ± 0.0113). No significant differences were found in group variances of FA values.

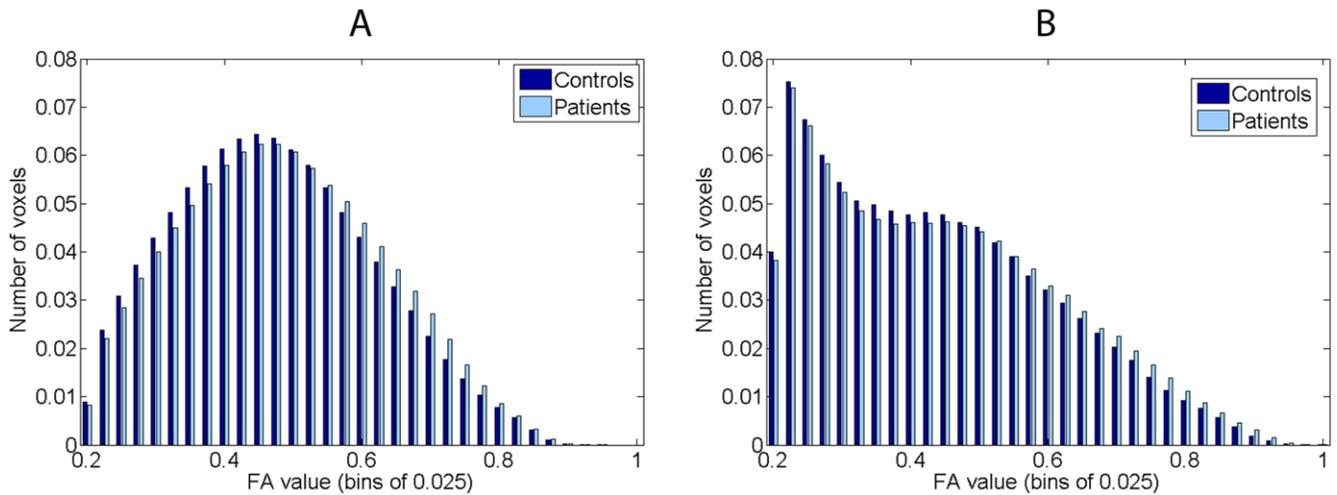


Figure 2. A mean histogram of individuals with Asperger syndrome (AS) and controls for (A) fractional anisotropy (FA) derived from the whole-brain tractography and (B) FA derived from the FA skeleton.

Table 3. Correlation of FA and MD with Autism Spectrum Quotient (AQ), Empathy Quotient (EQ), and Systemizing Quotient (SQ)

Questionnaire	Group difference		Fractional anisotropy				Mean diffusivity			
			Tractography		Skeleton		Tractography		Skeleton	
	F-value	P-value	Correlation	P-value	Correlation	P-value	Correlation	P-value	Correlation	P-value
Autism quotient	49.13	1.0E-7	0.426	0.017	0.250	0.174	-0.072	0.701	0.046	0.808
Empathy quotient	11.91	1.7E-3	-0.311	0.088	-0.141	0.449	0.269	0.144	0.008	0.966
Systemizing quotient	3.61	6.8E-2	-0.041	0.826	0.171	0.357	-0.006	0.974	0.211	0.256

FA, fractional anisotropy; MD, mean diffusivity.

No significant changes were observed in mean CP (Table S1 and Fig. S1) or in mean MD (Fig. S2) in the tractography or the skeleton data, but there were differences in the position and height of the mode peak in both MD histograms ($F = 4.63-7.07$, $P = 0.01-0.04$, see Table 2), and in the height of the tractography-based FA ($F = 7.47$, $P = 0.01$) and CP histograms ($F = 4.70$, $P = 0.04$) (Table 2 and Table S1). The variance of the whole-brain tractography MD peak position was significantly different between groups ($F = 7.16$, $P = 0.01$).

There was a positive correlation between mean FA and AQ scores in the tractography data ($P = 0.02$) (Table 3), calculated using the data of both controls and individuals with AS. The strongest correlation of mean FA and AQ subscores in the tractography data was with poor attention switching/strong focus of attention ($P = 0.002$), while the most significant difference between the two groups in the AQ subscores was in social skills ($F = 53.14$, $P = 0.00000005$), as shown in Table 4. No correlations were found in the skeleton data, and in the tractography data, only the correlation with poor attention switching/strong focus of attention would endure a Bonferroni cor-

rection for multiple comparisons. Because there was a significant difference in AQ and EQ between individuals with AS and controls in the tractography data, we also tested their correlation separately in the two groups. No significant correlations were found.

Discussion

We compared global values of FA and MD in the brain WM between male adults with AS and age-, sex-, and IQ-matched healthy controls. Two histogram approaches were used, one based on the FA skeleton [Smith et al., 2006] and one based on whole brain tractography. The mean FA was significantly higher in individuals with AS. There were differences in the position and height of the mode peak in both MD histograms, and in the height of the tractography-based FA and CP histograms. No differences were seen in the mean CP or MD in either the tractography or the skeleton data, but the variance of the whole-brain tractography MD peak position was significantly different between the two groups.

Table 4. Correlation of FA and Autism Spectrum Quotient (AQ) Subscores

AQ subscores	Group difference		FA tractography		FA skeleton	
	F-value	P-value	Correlation	P-value	Correlation	P-value
Social skill	53.14	5.0E-8	0.388	0.031	0.277	0.131
Imagination	12.10	1.6E-3	0.302	0.098	0.204	0.271
Communication	34.00	2.5E-6	0.432	0.015	0.209	0.259
Attention to details	10.21	3.4E-3	0.082	0.660	0.043	0.820
Attention switching	23.10	4.3E-5	0.528	0.002	0.0289	0.114

FA, fractional anisotropy; MD, mean diffusivity.

AQ correlated positively with FA in the tractography data, with the most significant correlation being in the poor attention switching/strong focus of attention subarea.

Intact cell membranes are the primary source of anisotropic diffusion in neural fibers [Beaulieu, 2002]. In addition, myelination and many other tissue properties can modulate the degree of anisotropy [Vos et al., 2012; Vos, Jones, Viergever, & Leemans, 2011]. Perhaps the most dominant factor that can affect the FA, however, is the geometric configuration of the underlying fiber network [Jeurissen, Leemans, Tournier, Jones, & Sijbers, 2012; Wedeen et al., 2012]. For instance, in regions with crossing fibers, voxels typically show low FA and/or high CP values. Therefore, a less prominent configuration of crossing fibers could be the cause of the observed higher FA values in AS subjects. To explore this possibility, we also compared the CP between the subject groups. We found no significant differences in CP, indicating that complexity of fiber configurations is not the underlying reason for the differences in FA.

Physical connectivity is not equivalent to functional connectivity. It has been speculated that the synaptic pruning in ASD could be abnormal [Frith, 2003] and that because of difficulties in differentiating signal from noise, strong physical connectivity and low computational connectivity could actually reinforce each other [Belmonte et al., 2004]. Finally, one could argue that more intensive training of the social and communication (or other lacking) skills may lead to increased FA values in adults with AS, as it has been shown that training can induce an increase in FA [Scholz, Klein, Behrens, & Johansen-Berg, 2009; Schlegel & Rudelson, 2012].

A positive correlation between AQ and FA was found in the tractography data, but the correlation was not found for each of the groups separately. Strongest correlation between AQ subscores and FA was with poor attention switching/strong focus of attention, and other correlations would not endure the Bonferroni correction for multiple comparisons. One of the main symptoms in AS is, indeed, the abnormally intense interest or focus on a specific topic. Iidaka and coworkers found a positive cor-

relation in the superior temporal sulcus and amygdala between AQ scores and the volume of the tracts [Iidaka, Miyakoshi, Harada, & Nakai, 2012], which supports our results as higher tract volume could be one of the reasons for an observed higher FA [Vos et al., 2011].

Our finding of increased mean FA in individuals with AS is in contrast with previous studies, where in adults with ASD, mostly decreased FA values or no FA related findings have been reported. Thakkar and coworkers investigated the WM underlying the anterior cingulate cortex in individuals with ASD (eight individuals with autism, two with AS, and two with pervasive developmental disorder not otherwise specified) [Thakkar et al., 2008]. Catani and coworkers performed tractography for cerebellar peduncles and intracerebellar fibers in adults with AS [Catani et al., 2008], and Langen and coworkers performed tractography for frontostriatal tracts for adults with autism [Langen et al., 2012]. They all found decreased FA values in individuals with ASD. However, none of the aforementioned authors performed the analyses for the whole brain. Beacher and coworkers investigated sex differences in predefined ROIs and found significant interactions between sex and age in FA in body of corpus callosum, cingulum, and corona radiata [Beacher et al., 2012]. They found a trend of lower FA in AS males compared with control males in the same regions. In some studies in adults with ASD, no group differences in FA related measures were reported [Thomas, Humphreys, Jung, Minschew, & Behrmann, 2011; Conturo et al., 2008].

Bloemen and coworkers performed a whole brain analysis of WM FA values in AS [Bloemen et al., 2010]. They found mostly decreased FA values in several areas but also four small regions with increased FA in adults with AS. The differences with our results could be at least partly explained by the differences in methodology. We investigated the global effects, whereas Bloemen and coworkers investigated local voxel-wise effects. Our approach did not require smoothing, and the analyses were done in native space, circumventing potential confounds known to exist in voxelwise analyses [Van Hecke et al., 2007, 2008, 2010, 2011; Jones, Symms, Cercignani,

& Howard, 2005]. There were a few differences in sample characteristics. For instance, the subjects with AS in our study had a mean IQ of 125, whereas in Bloemen's study, their mean IQ was 110. In addition, our subjects are younger, as in our study the mean age of AS subjects is 28.6 ± 5.7 and of controls 26.4 ± 4.7 , whereas in Bloemen's study the ages are 39 ± 9.8 and 37 ± 9.6 , respectively. The higher age makes it possible that age-related effects are starting to appear making the groups more heterogeneous [Hsu et al., 2008, 2010].

We used two approaches, skeletonization of FA and tractography. Histograms of both the tractography and skeleton data showed significant increases in FA of individuals with AS compared with controls. There are some possible reasons for the results being more significant in the tractography data. In the skeleton data, only voxels where the FA is locally maximal are inspected, but the differences in FA values might be larger in other voxels of the tracts. In the tractography data, the thicker tract bundles are weighted more than in the skeleton data.

Limitations of the study include the absence of the Autism Diagnostic Interview—Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS), which are standard instruments in the diagnostics of ASD in many countries. In Finland, they were not in standard use at the time of diagnosis, and therefore we do not have ADI-R or ADOS information for our AS subjects. However, AQ, EQ, and SQ have been especially designed for high-functioning individuals with ASD. Our sample is also relatively small. Nevertheless, both individuals with AS and controls were thoroughly screened to exclude other psychiatric disorders. In doing so, our groups of individuals with AS and controls reflect a representative sample.

In conclusion, our findings suggest that individuals with AS have higher mean FA values in their WM tracts than controls. For the tractography data, the mean FA correlated with AQ, and from the AQ subscores, the most significant correlation was found with poor attention switching/strong focus of attention. The observed higher FA found in individuals with AS in this work, however, is in strong contrast to previous studies calling for more in-depth investigations.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. A mean histogram of patients and controls for Westin planarity coefficients (CP) from (A) tractography data and (B) skeleton data.

Figure S2. A mean histogram of patients and controls for mean diffusivity (MD) derived from (A) whole-brain tractography and (B) FA skeleton.

Table S1. A comparison of planarity coefficient (CP) values in patients with Asperger syndrome (AS) and controls. Age and intelligence quotient (IQ) were used as covariates.