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Diffusion-weighted imaging evidence of altered white matter development from late childhood to early adulthood in Autism Spectrum Disorder

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ABSTRACT

Autism Spectrum Disorder (ASD) is thought to reflect disrupted development of brain connectivity characterized by white matter abnormalities and dyscoordination of activity across brain regions that give rise to core features. But there is little consensus about the nature, timing and location of white matter abnormalities as quantified with diffusion-weighted MRI. Inconsistent findings likely reflect small sample sizes, motion confounds and sample heterogeneity, particularly different age ranges across studies. We examined the microstructural integrity of major white matter tracts in relation to age in 38 high functioning ASD and 35 typically developing (TD) participants, aged 8–25, whose diffusion-weighted scans met strict data-quality criteria and survived group matching for motion. While there were no overall group differences in diffusion measures, the groups showed different relations with age. Only the TD group showed the expected positive correlations of fractional anisotropy with age. In parallel, axial diffusivity was unrelated to age in TD, but showed inverse correlations with age in ASD. Younger participants with ASD tended to have higher fractional anisotropy and axial diffusivity than their TD peers, while the opposite was true for older participants. Most of the affected tracts – cingulum bundle, inferior and superior longitudinal fasciculi – are association bundles related to cognitive, social and emotional functions that are abnormal in ASD. The manifestations of abnormal white matter development in ASD as measured by diffusion-weighted MRI depend on age and this may contribute to inconsistent findings across studies. We conclude that ASD is characterized by altered white matter development from childhood to early adulthood that may underlie abnormal brain function and contribute to core features.

1. Introduction

Autism Spectrum Disorder (ASD) manifests as early as infancy and is characterized by impaired communication, social deficits and restricted, repetitive behaviors. Converging lines of evidence support the view that ASD reflects disruptions in the development of brain connectivity in which white matter abnormalities and reduced coordination of activity across brain regions give rise to core features (Agam et al., 2010; Geschwind and Levitt, 2007; Just et al., 2007, 2004; Kenet et al., 2012; Khan et al., 2013; Kitzbichler et al., 2015; Minshew and Williams, 2007). The developmental course and nature of these disruptions are not well-understood and could span from gestation, during which pathogenic events may interfere with the establishment of connectivity, through childhood and adulthood. The present study investigated whether the trajectory of white matter development, from late childhood through early adulthood, is altered in high functioning individuals with ASD compared with typically developing (TD) peers. This age range is characterized by accelerated synaptic proliferation and pruning and the myelination of white matter tracts, which continues into the twenties and beyond, and supports the development of

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highly evolved cognitive and emotional capacities (Benes et al., 1994; Huttenlocher, 1979; Petanjek et al., 2011).

We used diffusion-weighted MRI (DW-MRI) to measure white matter microstructural integrity. DW-MRI measures the amount, rate and direction of water diffusion, which reflects the structural organization of axons. Despite the many DW-MRI studies of ASD, there is little consensus about the presence, location, nature and timing of white matter abnormalities (Rane et al., 2015; Travers et al., 2012). While most DW-MRI studies report decreased fractional anisotropy (orientation specificity of diffusion) (Ikuta et al., 2014; Jou et al., 2011; Keller et al., 2007; Lee et al., 2007; Shukla et al., 2011b; Walker et al., 2012) and increased mean diffusivity (speed of diffusion) either globally or in multiple fiber tracts in ASD compared with TD (Barnea-Goraly et al., 2005; Fletcher et al., 2010; Groen et al., 2011; Shukla et al., 2011b), others report increased fractional anisotropy (Ben Bashat et al., 2007; Billeci et al., 2012; Bode et al., 2011; Roine et al., 2015; Weinstein et al., 2011) or no group differences (Hong et al., 2011; Joseph et al., 2014). Artifacts caused by head motion may contribute to these inconsistencies. During MRI studies, ASD participants tend to move more than their TD peers and head motion can artifactually give rise to findings of reduced fractional anisotropy (Yendiki et al., 2014). For example, Koldewyn et al. (2014) reported reduced fractional anisotropy in multiple white matter tracts in ASD compared with TD, but only one tract difference remained significant after matching groups on motion parameters. This suggests that some prior DW-MRI findings in ASD are confounded by motion artifact and future studies must overcome this problem to be valid. Several studies of ASD have addressed potential motion confounds using techniques that include sedation or rewards for remaining still during scanning, the exclusion of scans corrupted by motion (e.g., “scrubbing”) and statistical controls such as using motion as a regressor (Jou et al., 2011; Koolschijn et al., 2017; Nordahl et al., 2016; Ouyang et al., 2016; Peeva et al., 2013; Shukla et al., 2010; Solso et al., 2016; Walker et al., 2012). In the present study, we minimized the potentially confounding effects of head motion by using a pre-scan training regimen to minimize subject movement and rigorous data quality criteria to both exclude scans corrupted by motion and to match groups on motion parameters.

Another potential culprit in inconsistent findings in DW-MRI studies is the differing age ranges of the samples. During typical development, white matter maturation is most dramatic during the first few years of life, but myelination continues throughout adulthood (Benes et al., 1994). In parallel, fractional anisotropy increases from childhood through adulthood (Barnea-Goraly et al., 2005; Dennis and Thompson, 2013; Hagmann et al., 2010; Kochunov et al., 2012; Lebel et al., 2008) and the rate of increase varies across tracts (Lebel et al., 2008). While higher fractional anisotropy tends to reflect more mature, strongly myelinated tracts and is regarded as a developmental biomarker (Bonekamp et al., 2007; Dennis and Thompson, 2013), its significance in ASD may depend on age. Findings of increased fractional anisotropy in young children with ASD have been hypothesized to reflect excess neurons and axons (Solso et al., 2016) consistent with postmortem studies finding excessive neurons in children with ASD (Courchesne et al., 2011), while reduced fractional anisotropy in older children and adults may reflect decreased myelination, reduced directional coherence of axons and/or fewer or thinner axons (Ikuta et al., 2014; Keller et al., 2007; Shukla et al., 2010, 2011b). Although not tested in longitudinal studies, findings of increased fractional anisotropy in young children with ASD and decreased fractional anisotropy in older children and adults support the hypothesis that ASD is characterized by an early excess of axons, ‘hyperconnectivity’, and a later consequent failure to form and maintain effective long range axonal connections (Courchesne et al., 2007; Courchesne and Pierce, 2005).

In the present cross-sectional study, we examined the correlations of age with diffusion measures in ASD and TD participants from 8 to 25 years. We expected that age would correlate positively with fractional anisotropy in TD participants, that the slope of this relation would be shallower in ASD (Ikuta et al., 2014; Shukla et al., 2011b; Solso et al., 2016) and that reduced fractional anisotropy in ASD would primarily be seen in older participants. While fractional anisotropy was our primary measure of white matter microstructural integrity, we also analyzed mean diffusivity, axial diffusivity (diffusivity in the main diffusion direction) and radial diffusivity (mean of diffusivity perpendicular to the main diffusion direction), which provide complementary information.

Table 1
Participant characteristics.

All participants	TD (n = 36)	ASD (n = 51)	t(85)	p
Age	14.4 ± 4.6	13.9 ± 3.8	0.65	.52
Sex (F/M)	6/30	7/44	$\chi^2 = 0.17$	.76
Education (years)	7.9 ± 4.6	7.7 ± 4.1	0.2	.81
Estimated FSIQ	116 ± 16	114 ± 15	0.8	.42
Handedness[a]	57 ± 55	42 ± 52	1.3	.20
Mean parental education	16.2 ± 2.8	15.9 ± 2.2	0.3	.74
Mean parental SES[b]	1.8 ± 1.1	1.8 ± 0.8	0.2	.86
Translation (mm)	0.58 ± 0.22	0.68 ± 0.31	−1.70	.09
Rotation (degrees)	0.29 ± 0.12	0.34 ± 0.23	−2.16	.03*
Benner score	1.0 ± 0.06	1.0 ± 0.05	−0.01	.92
% Gradients removed	3.5 ± 8.2	7.6 ± 10.9	−1.89	.06

Motion matched sample	TD (n = 35)	ASD (n = 38)	t(71)	p
Age	14.6 ± 4.5	14.3 ± 4.0	0.3	.76
Sex (F/M)	6/29	7/31	$\chi^2 = 0.02$	.89
Education (years)	8.1 ± 4.6	8.2 ± 4.1	0.04	.97
Estimated FSIQ	116 ± 17	116 ± 15	0.2	.87
Handedness[a]	57 ± 55	45 ± 50	1.0	.32
Mean parental education	16.1 ± 2.9	16.2 ± 2.3	−0.2	.86
Mean parental SES[b]	1.8 ± 1.0	1.7 ± 0.8	0.8	.45
Translation (mm)	0.56 ± 0.14	0.58 ± 0.14	−0.72	.48
Rotation (degrees)	0.29 ± 0.12	0.29 ± 0.06	−1.58	.12
Benner score	1.0 ± 0.02	1.0 ± 0	1.04	.30
% Gradients removed	2.5 ± 5.3	3.8 ± 6.1	−0.96	.34

FSIQ: Full Scale Intelligence Quotient based on the Wechsler Abbreviated Scale of Intelligence (49).

* Significant at $p \leq .05$.

[a] Based on the modified Edinburgh Handedness Inventory (76, 77) Laterality scores of −100 and +100 denote exclusive use of left or right hand, respectively.

[b] Socio-Economic Status based on the Hollingshead Index (78). A lower score denotes higher status.

2. Methods

2.1. Participants

51 individuals with ASD without intellectual disability and 36 TD controls, aged 8–25, participated. After data quality exclusions and matching the groups for motion (see description below) 38 ASD and 35 TD participants were retained for analysis. ASD and TD groups were matched for age, sex, education, estimated full scale IQ, handedness, mean parental education and parental socioeconomic status. (Table 1 provides participant characteristics and data quality measures for both the entire sample and the motion-matched sample).

ASD participants were recruited from the Autism Consortium database (http://www.autismconsortium.org). Diagnoses were made by experienced clinicians on the basis of current presentation and developmental history using the Autism Diagnostic Interview-Revised (ADI-R; Rutter et al., 2003) and the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1999). Individuals with known genetic syndromes (e.g., tuberous sclerosis, fragile X, RETT syndrome, neurofibromatosis) were not enrolled. TD participants were recruited from the community

through poster and website advertisements and were screened with the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) to exclude those with histories of ASD or other neuropsychiatric or neurological disorder.

All participants had an estimated full-scale IQ ≥ 70 on the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) and were screened to exclude substance abuse or dependence in the past six months and any contraindications for MRI. The study was approved by the Partners Human Research Committee. After the procedures had been explained, research staff obtained written informed consent from participants ≥18 years., and consent of the parent and assent of participants < 18 years. All participants were paid and children also received small gifts during the study.

2.2. Procedures

2.2.1. Preparation

Prior to their first visit, participants received a link to an online social story that described what to expect and the MRI procedures including samples of MRI sounds (https://prezi.com/afxtce8yu65_/blast-off-manoach-lab-social-story/). Participants completed a mock scanning session of approximately 1 h to acclimate them to the appearance, noise, and confinement of the MRI scanner and to practice lying still for the duration of the scan. Whenever possible the mock scan was conducted on a separate day from the actual scan. During the mock scan participants listened to a soundtrack of the MRI sequences used in the study. As in the actual scan, participants wore earplugs (29 dB rating) to attenuate noise and headphones. They watched a movie of their choice during both mock and actual structural scans.

2.2.2. MRI acquisition

Scanning was performed with a 3T Siemens Trio TIM whole body high speed imaging device equipped with a 32 channel head coil. Head stabilization was achieved with cushioning. At the start of each scan, the Autoalign system (van der Kouwe et al., 2005) automatically detected the head position and aligned the field of view. Anatomical images were acquired using a 3D multiecho magnetization-prepared rf-spoiled rapid gradient-echo MEMPRAGE (T1 weighted) sequence with EPI based volumetric navigators for real time motion correction (Tisdall et al., 2012; van der Kouwe et al., 2008) TR = 2530 ms, Flip Angle = 7°, TEs = 1.74 ms/3.6 ms/5.46 ms/7.32 ms, iPAT = 2; FOV = 56 mm; 176 in-plane sagittal slices; voxel size = 1 mm^3 isotropic; scan duration 6 m 12 s. DW-MRI scans were acquired using standard echo-planar imaging (TR = 8020 ms, TE = 83 ms, b = 700 s/mm^2; 10 non-diffusion weighted T2 images acquired with b = 0; 60 diffusion directions; 128 × 128 matrix; 2 × 2 mm in-plane resolution; 64 axial oblique (AC-PC) slices; 2 mm slice thickness (0 mm gap); scan duration 9 m 47 s. Diffusion images were corrected for b0 inhomogeneities using opposite phase encoding polarities during acquisition (Holland et al., 2010). Resting state functional connectivity MRI scans were also acquired but are not reported here.

2.2.3. Data quality assurance

Each participant's raw DW images were independently inspected by two trained raters (BB, FIK or QTHN), blind to group assignment, who flagged images with visible motion artifacts for removal. Final decisions regarding removal were made during a consensus group inspection. Entire scans from 4 participants were discarded (3 ASD, 1 TD) due to excessive motion (severe signal drop out in more than a third of the DW images). In the remaining participants, an average of 5.5 ± 7.1% of the ASD DW images were removed and 2.5 ± 5.3% of the TD images ($t(81) = 2.11$, $p = .04$). We quantified motion using four measures (Yendiki et al., 2014): average volume-by-volume translation, average volume-by-volume rotation, percentage of slices with signal drop-out, and signal drop-out severity (using the dropout measure defined in Benner et al., 2011). Scans with quantitative measures > 1.5 SD of the entire sample were excluded (10 ASD). The resulting groups were matched on all data quality indices (Table 1).

2.2.4. DW-MRI analyses

FreeSurfer 5.3 was used to automatically segment gray and white matter and define cortical and subcortical regions in the T1-weighted images of each individual (Fischl, 2012; Fischl et al., 2004, 2002).

DW images were preprocessed and analyzed using TRActs Constrained by UnderLying Anatomy (TRACULA; Yendiki et al., 2011), an automated global probabilistic tractography algorithm that delineates 18 major white matter pathways. Preprocessing involves registration of the images to a reference non-diffusion weighted (b = 0) volume, eddy current distortion correction and registration to individual T1-weighted anatomical scans (using FreeSurfer's bbregister function). TRACULA automatically reconstructs white matter pathways in each participant's DW-MRI space based on tract definitions from a set of training subjects, in which the pathways have been manually labeled. It fits these pathways into each participant's DW images by estimating the posterior probability of the pathway given the data. After defining 18 major tracts in each participant's DWI space, the scans are registered to standard MNI space for group-level analyses. For each participant we extracted four diffusion measures (fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity) for the eight bilateral and two interhemispheric major fiber tracts: corticospinal tract (CST), inferior longitudinal fasciculus (ILF), uncinate fasciculus (UNC), anterior thalamic radiations (ATR), cingulum – cingulate gyrus bundle (CCG), cingulum – angular bundle (CAB), superior longitudinal fasciculus – parietal terminations (SLFP), superior longitudinal fasciculus – temporal terminations (SLFT), corpus callosum – forceps major (FMajor), and corpus callosum – forceps minor (FMinor).

We investigated group differences in the relations of age with the four diffusion measures, averaged across all tracts, using ANOVA with factors for age, group and their interaction. For diffusion measures showing a significant group by age interaction (Bonferroni-corrected $p \leq .0125$), we conducted voxel-wise ANOVAs within each tract. We used false discovery rate ($p_{FDR} \leq .05$) implemented in Statistical Parametric Connectome (SPC; Meskaldji et al., 2015) to correct for multiple comparisons both across multiple tracts and within individual tracts that showed significant age by group interactions. SPC offers robust correction for comparisons of multiple fiber tracts by basing tract level p-values on voxel-wise p-values, handles collinearity across variables and is more powerful than standard correction methods in both simulated (Meskaldji et al., 2015) and real data (Fischi-Gómez et al., 2015).

Exploratory analyses: Based on prior findings of reduced asymmetry and left lateralized abnormalities in speech and language-related tracts in ASD (Fletcher et al., 2010; Joseph et al., 2014; Peeva et al., 2013), we examined the relations of age with hemispheric asymmetry. For each diffusion measure we quantified hemispheric asymmetry using a normalized asymmetry score: (R − L)/(R + L) and used ANOVA with factors for group, age and their interaction to test for group differences in the development of hemispheric asymmetry for each of the eight bilateral tracts.

3. Results

There was no significant group difference in any diffusion measure averaged across all tracts (Table 2). We observed strong age effects for fractional anisotropy, mean diffusivity and radial diffusivity. Fractional anisotropy correlated positively with age ($p = 3 \times 10^{-4}$), while both mean diffusivity and radial diffusivity inversely correlated with age (mean diffusivity: $p = 3 \times 10^{-5}$; radial diffusivity: $p = 10^{-5}$). Importantly, the relations with age differed by group for both fractional anisotropy (Age by Group interaction: $p = .005$) and axial diffusivity ($p = .002$). Fractional anisotropy was positively correlated with age in TD ($r = 0.65$, $p = 2 \times 10^{-5}$) but not ASD participants ($r = 0.08$,

Table 2
ANOVA results of diffusion measures averaged across all tracts.

	Diffusion		Laterality (R − L)/(R + L)	
	F(70)	*p*	F(70)	*p*
Fractional Anisotropy				
Group	1.5	.22	0.1	.75
Age	14.6	3×10^{-4}*	1.2	.27
Group × age	8.5	5×10^{-3}*	1.8	.19
Axial Diffusivity				
Group	0.4	.52	8×10^{-3}	.93
Age	1.6	.20	0.02	.90
Group × age	10.7	2×10^{-3}*	0.01	.91
Mean Diffusivity				
Group	2.6	.11	0.4	.53
Age	19.9	3×10^{-5}*	1.5	.23
Group × age	0.3	.56	1.1	.29
Radial Diffusivity				
Group	2.6	.11	0.7	.42
Age	22.1	10^{-5}*	1.9	.18
Group × age	1.2	.28	2.2	.14

* Significant at $p \leq .0125$ (Bonferroni-corrected for the four diffusion measures).

$p = .65$). Axial diffusivity did not correlate with age in TD ($r = 0.25$, $p = .15$) but was inversely correlated with age in ASD ($r = 0.44$, $p = .005$).

For fractional anisotropy, the group by age interaction was driven by bilateral cingulate gyrus bundle, inferior longitudinal fasciculus, superior longitudinal fasciculus – both parietal and temporal terminations and the right corticospinal tract (Fig. 1). At the voxel level, the effects were significant in anterior through middle portions of bilateral cingulate gyrus bundle, limbic portions of the left and occipital portions of bilateral inferior longitudinal fasciculus, middle portions of bilateral superior longitudinal fasciculus – both parietal and temporal terminations and right superior and middle portions of the corticospinal tract (Supplemental Fig. S1). For axial diffusivity, significant interactions were seen in an overlapping set of tracts – bilateral cingulate gyrus bundle, inferior longitudinal fasciculus, superior longitudinal fasciculus – parietal terminations, the left superior longitudinal fasciculus – temporal terminations and the right corticospinal tract – but were also seen in the left corticospinal tract, and corpus callosum – forceps major (Fig. 2).

As described above, the lack of significant group differences in diffusion measures does not reflect that the groups were the same, but rather that the direction of group differences changed with age. When we split the groups by age and compared the younger participants (8–15 years), fractional anisotropy and axial diffusivity tended to be higher in ASD than TD in the tracts showing significant group by age interactions for fractional anisotropy, while the opposite was true for older participants (16–25 years). As is shown in Supplemental Table S1, most of these split-group comparisons did not reach statistical significance.

Hemispheric asymmetry: There were no significant effects of group, age or age by group interactions for any tract with any diffusion measure (Table 2; Supplemental Table S2 provides *t*-tests of tract asymmetry for each diffusion measure in the combined groups).

4. Discussion

The present study used rigorous methods to prevent, correct and match groups for motion-related artifacts and found evidence of an altered trajectory of white matter development in ASD during the period spanning late childhood through early adulthood. While the TD group showed the expected positive relationship of age with fractional anisotropy, which is associated with myelination and regarded as a developmental biomarker (Bonekamp et al., 2007; Dennis and Thompson, 2013), in ASD, fractional anisotropy did not change with age. In parallel, in the averaged tract data, diffusion along the main axis (axial diffusivity) was inversely correlated with age in ASD, but not in TD. Radial diffusivity inversely correlated with age in both groups, consistent with increased myelination. One interpretation of these group differences in age-related white matter changes is that they reflect increased axons during late childhood in ASD that continue to myelinate over development, but are less directionally coherent, thereby offsetting fractional anisotropy increases due to myelination. Evidence of abnormal white matter development in ASD was observed primarily in association bundles (cingulate gyrus bundle, inferior longitudinal fasciculus and the superior longitudinal fasciculus – parietal and temporal terminations). The altered age-related changes of these tracts in ASD may be neuroanatomical correlates of abnormal development of the myriad cognitive, social and emotional functions they support.

The cingulate gyrus bundle is the portion of the cingulum bundle extending from anterior to posterior cingulate cortex. Communication between these regions is important for cognitive control, including recognizing errors and adjusting responses (Agam et al., 2011). Postmortem work shows abnormalities in axons underlying anterior cingulate cortex in ASD (Zikopoulos and Barbas, 2010). In *in vivo* studies of ASD, the anterior cingulate cortex shows abnormal functional MRI activation during response monitoring, abnormal functional connectivity and reduced fractional anisotropy of its underlying white matter all of which correlate with restrictive, repetitive behavior (Agam et al., 2010; Thakkar et al., 2008). This suggests that dysconnectivity of the anterior cingulate cortex contributes to behavior that is rigid, repetitive and stimulus-bound rather than flexible, controlled and responsive to contingencies. Reduced fractional anisotropy of the inferior longitudinal fasciculus, which connects occipital and temporal lobes, is associated with visuoperceptual impairment (Ortibus et al., 2012), congenital prosopagnosia (Thomas et al., 2009) and ASD (Koldewyn et al., 2014; Weigelt et al., 2012), consistent with the hypothesis that inferior longitudinal fasciculus dysconnectivity contributes to the visuoperceptual and face processing deficits seen in ASD (Barton et al., 2007). The superior longitudinal fasciculus – temporal terminations corresponds most closely to the arcuate fasciculus (Yendiki et al., 2011) and connects the key cortical regions for language, Broca's and Wernicke's areas. In ASD increased mean diffusivity of the arcuate fasciculus correlates with language impairment (Nagae et al., 2012). The superior longitudinal fasciculus – parietal terminations, which corresponds most closely to SLF III (Yendiki et al., 2011) connects the supramarginal gyrus with ventral prefrontal and premotor regions. It is associated with a range of cognitive functions including visuospatial attention (de Schotten et al., 2011), which is impaired in ASD (Keehn et al., 2010). Abnormal development of these tracts from late childhood to early adulthood in ASD may compromise the coordination of activity across brain regions and contribute to core features and cognitive deficits.

The lack of group differences in diffusion measures when averaged across the entire age span reflected that the direction of group differences depended on age. Examination of the scatter plots (Figs. 1 and 2) and *post-hoc* comparisons of the groups divided by age (Supplemental Table S1) revealed that in younger participants fractional anisotropy and axial diffusivity tended to be higher in ASD than TD, while the opposite was true in older participants. The pattern is consistent with prior work showing higher fractional anisotropy in young children with ASD compared with TD controls (Ben Bashat et al., 2007; Billeci et al., 2012; Solso et al., 2016; Weinstein et al., 2011) and lower fractional anisotropy in older children and adults (Ikuta et al., 2014; Keller et al., 2007; Shukla et al., 2011b, 2011a; Thakkar et al., 2008). Since fractional anisotropy and axial diffusivity are indirect indices of white matter microstructure and can be affected by a number of factors including myelination, the number of axons, axonal diameter and

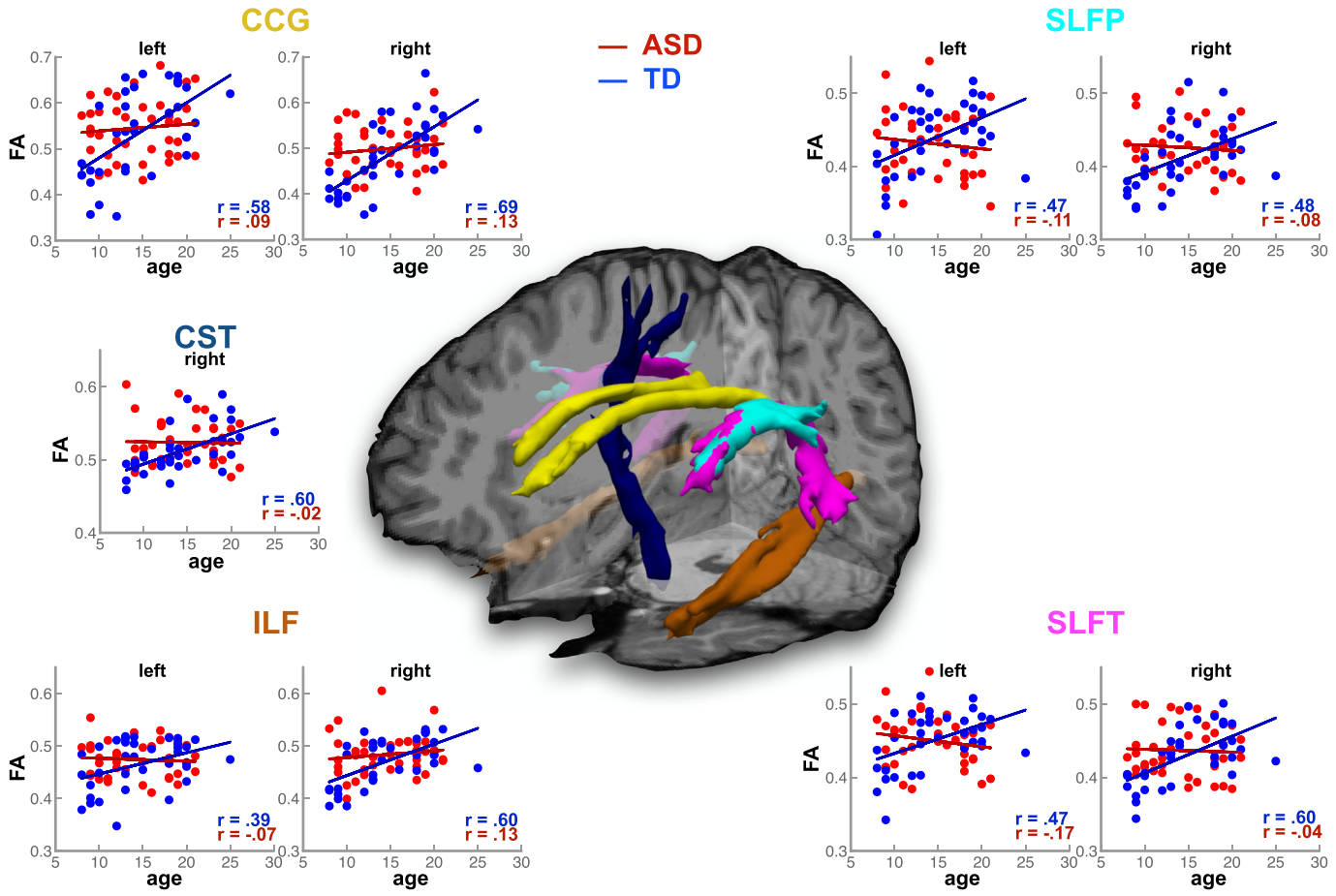

Fig. 1. Tracts showing significant group differences in the relations of age with fractional anisotropy. Fractional anisotropy increases with age in TD (blue) but not in ASD (red) participants in bilateral cingulate gyrus bundle (CCG), right corticospinal tract (CST), bilateral inferior longitudinal fasciculus (ILF), bilateral superior longitudinal fasciculus – temporal terminations (SLFT) and parietal terminations (SLFP). Y-axes show fractional anisotropy values averaged along each tract.

coherence of axon orientation (Beaulieu, 2002; Jones et al., 2013) it is not possible to definitively ascribe group differences in development to a particular white matter property. However, evidence from a post-mortem study indicates that during childhood, there is an excess of cortical neurons in ASD (Courchesne et al., 2011), which would be expected to increase axon number (Ringo, 1991), and consequently fractional anisotropy, to the degree that the axons are directionally coherent. Lower fractional anisotropy in adolescents and adults with ASD has been attributed to reduced directional coherence of axons, fewer or thinner axons and/or decreased myelination, (Ikuta et al., 2014; Keller et al., 2007; Shukla et al., 2010, 2011b), the latter of which is consistent with postmortem work (Zikopoulos and Barbas, 2010).

Regardless of the underlying causes, our findings raise an important methodological point. Depending on the age range of the sample, DW-MRI studies may have valid findings of increased, decreased or no difference in diffusion measures in ASD. Given the variable rates of white matter development across tracts (Lebel et al., 2008) and the different manifestations of abnormal connectivity based on developmental stage, studies of group differences should either account for age effects or sample from a narrow age range. An important limitation of the present study is that it is cross-sectional. A longitudinal approach would be valuable to document age-related changes *within* individuals and how they correspond to the development of age appropriate social and cognitive functions. Importantly, these changes may differ by tract. Although our interpretations focused on average patterns of age-related changes, our data is consistent with the literature in showing variability across tracts (Lebel et al., 2008), particularly for axial diffusivity. In addition, an examination of the scatterplots of fractional anisotropy for TD suggests that nonlinear models may provide a better fit of its relations with age in some tracts (Fig. 1). Since our focus was on comparing groups rather than characterizing typical development across tracts, and the ASD data did not significantly deviate from linearity, we used linear models. Another limitation is that our sample was comprised of relatively high functioning individuals with ASD and it is not known whether our findings would generalize to individuals with intellectual disability.

Our findings of reduced age-related increases in fractional anisotropy are consistent with previous cross-sectional studies of ASD showing *i*) greater frontal white matter fractional anisotropy and less increase with age in toddlers (Solso et al., 2016), *ii*) no age-related fractional anisotropy increases across adolescence in paracentral lobule and superior frontal gyrus white matter (Cheng et al., 2010) and *iii*) no increase in fractional anisotropy from childhood to adulthood in superior temporal gyrus white matter (Lee et al., 2007). The present study extends these findings to major association bundles from later in childhood to early adulthood. This period is characterized by synaptic proliferation, pruning and remodeling (Petanjek et al., 2011) and myelination (Benes et al., 1994) to support the specification of neuronal connections and allow more efficient communication. This prolonged period of developmental plasticity allows for the maturation of highly evolved human emotional and cognitive abilities. This body of work underscores the importance of applying a neurodevelopmental perspective to the study of ASD during childhood, adolescence, and even adulthood. We conclude that deviant age-related changes in white matter tracts continue into adulthood, may underlie impaired brain communication and contribute to the manifestations of ASD.

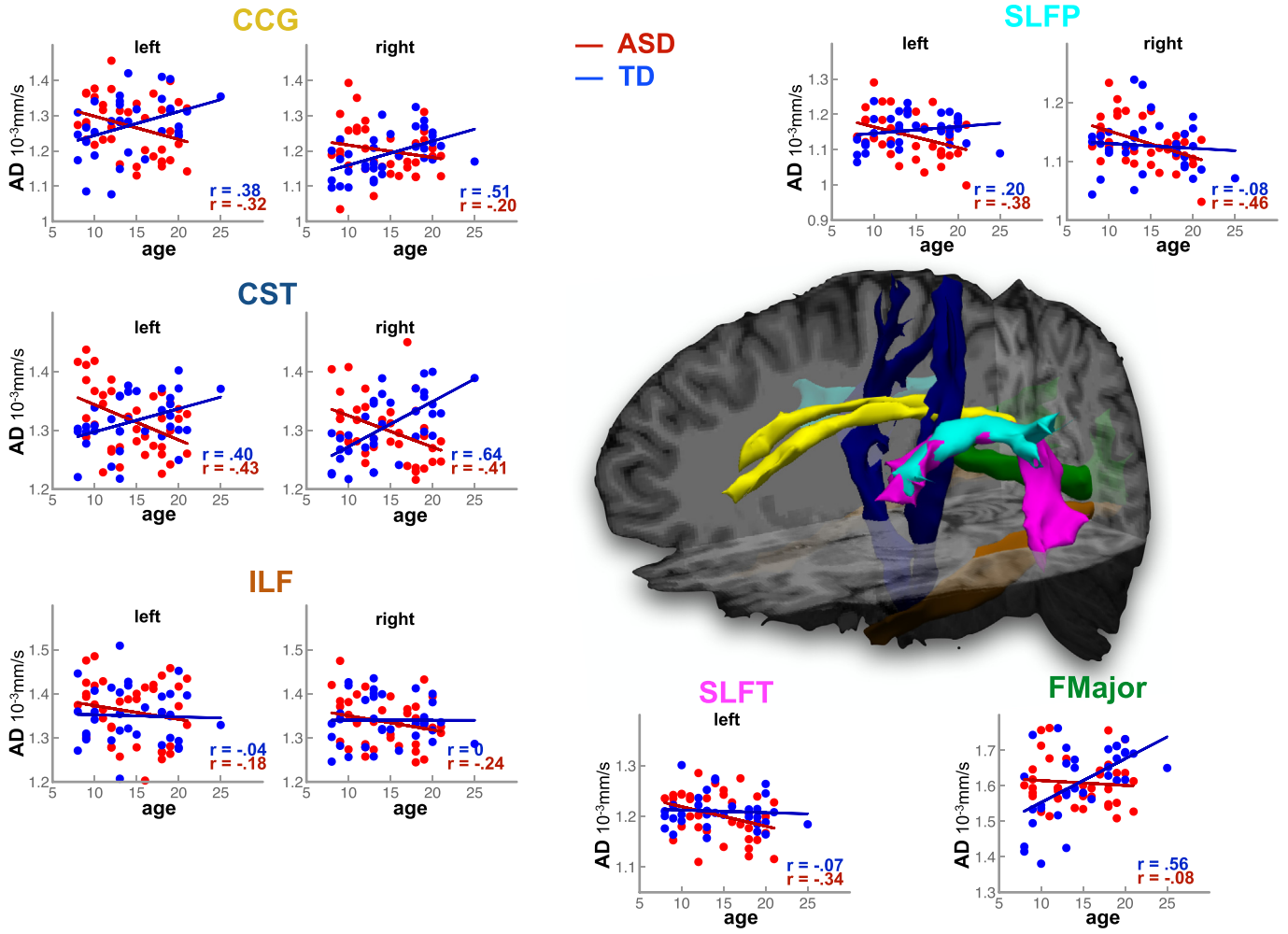

Fig. 2. Tracts showing significant group differences in the relations of age with axial diffusivity. Axial diffusivity decreases with age in in ASD (red) but not TD (blue) participants for bilateral cingulate gyrus bundle (CCG), corticospinal tract (CST), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus – parietal terminations (SLFP) and left temporal terminations (SLFT) and corpus callosum – forceps major (FMajor). Y-axes show axial diffusivity values averaged along each tract.

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Appendix A. Supplementary data

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