

Differences in the right inferior longitudinal fasciculus but no general disruption of white matter tracts in children with autism spectrum disorder

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One of the most widely cited features of the neural phenotype of autism is reduced “integrity” of long-range white matter tracts, a claim based primarily on diffusion imaging studies. However, many prior studies have small sample sizes and/or fail to address differences in data quality between those with autism spectrum disorder (ASD) and typical participants, and there is little consensus on which tracts are affected. To overcome these problems, we scanned a large sample of children with autism ($n = 52$) and typically developing children ($n = 73$). Data quality was variable, and worse in the ASD group, with some scans unusable because of head motion artifacts. When we follow standard data analysis practices (i.e., without matching head motion between groups), we replicate the finding of lower fractional anisotropy (FA) in multiple white matter tracts. However, when we carefully match data quality between groups, all these effects disappear except in one tract, the right inferior longitudinal fasciculus (ILF). Additional analyses showed the expected developmental increases in the FA of fiber tracts within ASD and typical groups individually, demonstrating that we had sufficient statistical power to detect known group differences. Our data challenge the widely claimed general disruption of white matter tracts in autism, instead implicating only one tract, the right ILF, in the ASD phenotype.

diffusion-weighted imaging | connectivity

What is the key difference in the brains of individuals with autism that accounts for the distinctive cognitive profile of this disorder? One of the most widely claimed brain signatures of autism spectrum disorder (ASD), reported in dozens of papers that used diffusion-weighted imaging (DWI), is reduced integrity of long-range fiber tracts (1). This finding has been taken as evidence that autism is fundamentally a “disconnection” syndrome, in which the core cognitive deficits result from reduced integration of information at the neural and cognitive levels (2–5). For example, it has been argued that the characteristic deficits in social cognition and language arise because these functions require rapid integration of information across spatially distant brain areas (3, 6, 7), which would likely be affected if major white matter tracts are compromised.

Evidence for a general reduction in the “integrity” of white matter in autism has come primarily from diffusion imaging studies that report reduced directionality of the diffusion of water molecules, or fractional anisotropy (FA), and increased speed of diffusion, or mean diffusivity (MD) of many major fiber bundles. However, the literature reveals little actual agreement on the existence and direction of group differences in diffusion parameters (reviewed in ref. 1). White-matter differences have been reported in various brain regions in positive and negative directions. Possible reasons for these inconsistent findings include small sample sizes [mean of ~ 20 in each group, with 40% of studies scanning 15 or fewer participants with ASD (1)], the

heterogeneity of ASD itself, variations across studies in the age of the cohort tested, and the type of DTI analysis performed. Another potential problem that few diffusion studies of autism address or even mention is data quality. Indeed, to our knowledge, only two studies (9, 10) report quantitative analyses of the amount of motion in their DWI data. Group differences in head motion could be a serious confounding factor, given that head motion is likely to be greater in children with autism, and group differences in head motion can lead artifactually to just the effects most often reported: reduced FA in white matter tracts in ASD (11).

To address these concerns, we scanned a relatively large sample of children with and without ASD, and evaluated data quality from each participant by visual inspection of the data and quantification of head motion (11). We then excluded scans that did not reach our data quality criterion, and matched the remaining participants across groups for data quality. These data were used to determine whether people with autism do in fact show widespread differences in the known white matter tracts in ASD. We further tested the specific hypothesis that individuals with ASD show changes in one particular tract, the inferior longitudinal fasciculus (ILF), a white matter tract important for

Significance

One of the most accepted brain “signatures” of autism spectrum disorder (ASD) is a reduction in the integrity of long-range white-matter fiber tracts. Here, we assessed known white matter tracts in children with ASD by using diffusion-weighted imaging. In contrast to most prior studies, we carefully matched for head motion between groups. When data quality was matched, there was no evidence of widespread changes in white-matter tracts in the ASD group. Instead, differences were present in only one tract, the right inferior longitudinal fasciculus. These data challenge the idea that widespread changes in white-matter integrity are a signature of ASD and highlight the importance of matching for data quality in future diffusion studies of ASD and other clinical disorders.

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*Although reductions in FA are often used to argue for reduced “integrity” of white matter tracts, the precise anatomical correlates of reduced FA are not clear (8). In the present paper, we therefore interpret reduced FA in ASD to show only differences in white matter, without assuming that such differences constitute reductions in the integrity of those tracts.

Results

A total of 21.3% of our diffusion scans on children with ASD and 11.3% of the scans on typical children do not meet even our more liberal threshold for usable data quality (*Methods* provides details on how data quality was assessed and quantified). Not surprisingly, the scans from children with ASD have significantly lower data quality than those from the typically developing (TD) children on each of our four measures of head motion/data quality (P values in Fig. 1). When these bad scans are excluded from the analysis (leaving $n = 40$ in the ASD group and $n = 71$ TD children; Fig. 1, “all scans without visible artifacts in FA maps”), and age, intelligence quotient (IQ), and sex are controlled for, we find significantly lower FA in many tracts (Fig. 2, column A), with a significant group-by-tract interaction [$F(17, 1,836) = 2.73, P = 0.001$] and a main effect of group just short of significance [$F(1, 108) = 3.10, P = 0.08$]. These results qualitatively resemble prior findings in the literature. However, data quality was significantly lower in the ASD group (Fig. 1), a situation we have shown can lead to spurious group differences in FA (11).

To equalize data quality across groups, we therefore identified two subsets of our data matched across groups for age, IQ, sex,

and five measures of head motion and data quality. One subset of the data used a relatively liberal threshold for data inclusion (the absence of visible artifacts in the raw FA maps); this cohort enabled us to preserve a larger number of subjects (called from here on the main cohort). A second subset of the scans used a more stringent threshold for data quality (the absence of visible artifacts in raw DWI images) and a correspondingly smaller number of subjects (called from here on the stringent cohort). Fig. 1 provides details of the demographics in each group for each analysis.

Testing for Changes in FA, MD, and Radial Diffusivity in ASD in the Main Cohort.

The main question of this study was whether

Main Cohort. The main question of this study was whether widespread differences in major white matter tracts in autism are found when data quality is matched between ASD and typical participants (*Methods* provides details on how these white matter tracts were identified and assessed). The data from our main cohort (ASD, $n = 40$; TD, $n = 43$) provide no evidence for this hypothesis. A two-way ANOVA on FA as a function of group (ASD vs. TD) by tract found no main effect of group [$F(1, 81) = 0.591$, $P = 0.444$], and no group-by-tract interaction [$F(17, 1,377) = 1.358$, $P = 0.149$]. Post hoc comparisons of FA in each tract individually (Fig. 2) found that only one tract was significantly different between groups: the right ILF (rILF), which showed lower FA in the ASD group [$t(81) = 3.119$, $P = 0.003$].

	pIQ (K-bit)	Age (years)	SRS (total)	ADOS (CS)	Translation	Rotatation	Benner Score	% Bad Slices	
	All Scans before quality control measures								
Image Quality	ASD (n = 52) (8 girls; 75 scans)	107.4 (16.4)	8.88 (1.84)	78.9 (9.11)	7.35 (1.67)	1.179 (.6790)	.0112 (.0080)	.1185 (.1256)	.2635 (.5512)
	TD (n = 73) (15 girls; 115 scans)	117.4 (16.3)	8.64 (1.93)	46.7 (7.28)	-	.8494 (.4370)	.0068 (.0048)	.0605 (.1001)	.0881 (.2139)
	p value	.001	.397	<.001	-	<.001	<.001	.001	.002
Matching	All Scans without visible artifacts in FA maps								
	ASD (n = 40) (5 girls; 59 scans)	106.9 (17.6)	8.98 (1.81)	78.9 (9.11)	7.35 (1.67)	.8691 (.0905)	.0075 (.0070)	.0801 (.1394)	.0921 (.2448)
	TD (n = 71) (14 girls; 102 scans)	117.8 (14.7)	8.62 (1.94)	46.7 (7.28)	-	.7451 (.2752)	.0055 (.0028)	.0402 (.0829)	.0447 (.0991)
	p value	.001	.352	<.001	-	.013	<.001	.016	.016
Image Quality	Matched Scans without visible artifacts in FA maps (Main Cohort)								
	ASD (n = 40) (5 girls)	106.9 (17.6)	8.98 (1.81)	78.9 (9.11)	7.35 (1.67)	.8730 (.3639)	.0077 (.0044)	.0808 (.1298)	.0962 (.1567)
	TD (n = 43) (8 girls)	110.8 (14.3)	8.90 (1.87)	46.2 (6.51)	-	.8285 (.3041)	.0067 (.0034)	.0730 (.1103)	.0699 (.1261)
	p value	.271	.854	<.001	-	.545	.263	.767	.401
Matching	All Scans without visible artifacts in raw DWI images								
	ASD (n = 17) (5 girls; 19 scans)	107.6 (18.3)	9.32 (1.41)	78.9 (8.30)	7.00 (1.58)	.6553 (.1767)	.0048 (.0019)	.0065 (.0282)	.0037 (.0163)
	TD (n = 42) (8 girls; 50 scans)	117.5 (12.8)	8.92 (2.03)	45.9 (6.82)	-	.6560 (.2428)	.0041 (.0013)	.0091 (.0233)	.0149 (.0452)
	p value	.021	.431	<.001	-	.990	.042	.489	.219
Image Quality	Matched Scans without visible artifacts in raw DWI images (Stringent Cohort)								
	ASD (n = 17) (5 girls)	107.6 (18.3)	9.22 (1.46)	78.9 (8.30)	7.00 (1.58)	.6649 (.1815)	.0050 (.0019)	.0072 (.0300)	.0042 (.0173)
	TD (n = 21) (5 girls)	113.4 (12.3)	9.18 (2.11)	45.9 (6.94)	-	.6980 (.2826)	.0043 (.0014)	.0096 (.0265)	.0085 (.0201)
	p value	.260	.937	<.001	-	.677	.283	.801	.467

Fig. 1. The steps taken to ensure acceptable data quality across all scans and data quality matching between groups. During “image quality” steps, subsets of data were selected based on visual inspection of each scan for artifacts in raw DWIs or FA maps. During “matching” steps, subsets of data were selected that enabled us to match ASD and TD groups for age, IQ, sex, and data quality measures. *P* values show the significance of the differences between the ASD and TD groups on the indicated dimensions for each column. Black-outlined rectangles denote the two cohorts of participants analyzed: the main cohort (*Middle*) and the stringent cohort (*Bottom*).

age group-by-tract interaction [$F(17, 646) = 0.929, P = 0.539$]. These effects reflect widespread increases in the FA of white-matter tracts with age, much like the findings seen in the typical group (Fig. S1, *Right*).

Stringent cohort. In the stringent cohort, we had 20 typical participants in each age group matched for head motion and IQ (mean ages, 10.29 y for older group and 6.96 y for younger group). A two-way ANOVA on FA as a function of age group and tract found a main effect of age group [$F(1, 38) = 4.209, P = 0.04$] but no age group-by-tract interaction [$F(17, 646) = 1.27, P = 0.208$]. The same analysis for ASD participants in the stringent cohort identified only eight children in each age group (older mean age, 10.34; younger mean age, 7.94) that could be matched for motion and IQ. Despite the small number of subjects, a two-way ANOVA on FA as a function of age group found a main effect of group [$F(1, 14) = 8.73, P = 0.010$], but no age group-by-tract interaction [$F(17, 646) = 0.717, P = 0.784$].

In sum, all four analyses show robust increases in FA with age. Evidently, our data are of sufficient quality, and our analyses of sufficient power, to detect known group differences in FA between groups. Note that half as much data went into the developmental analyses (because they were conducted within each group separately) compared with the main analysis comparing ASD vs. typical groups (across ages). Thus, we have substantially more power to detect differences in ASD if they exist compared with age differences, yet still we detected none (except for the predicted effect in the rILF). These results suggest that our failure to find differences between children with ASD and typical children in orthogonal analyses of the same data are unlikely to be a result of insufficient data quality or power, unless group differences in FA are substantially smaller than age differences. Note that, because no comparable prior study has reported effect sizes for the differences they report in FA between ASD and TD groups, it is not possible to determine whether our study had enough power to detect the effects reported in the prior literature.

Discussion

We used diffusion imaging in a large sample of children with and without autism to test the widespread claim that individuals with ASD show general disruption of long-range white matter tracts. Despite careful efforts to minimize head motion with the use of custom pediatric imaging coils and prior training in a mock scanner, a substantial percentage of the scans, and more in the autism group (21.3%) than the typical group (11.3%), were unusable because of head motion. When these bad scans were omitted, we replicated the standard finding that many white matter tracts show lower FA in ASD. However, because head motion strongly affects measures of diffusion (11, 19, 20), it is important to quantify this motion, exclude data not meeting a reasonable criterion of data quality, and match the remaining data for head motion/data quality across groups (10). By using these procedures (*Methods* and Fig. 1), we find no evidence for a general reduction in the integrity of white matter tracts in autism. This result is not likely caused by insufficient statistical power because our study included more subjects than most prior studies reporting such effects, and because we robustly detect the known increase in FA with age in the same data within ASD and typical groups. Further, we found a significant reduction in participants with autism in the diffusion anisotropy of the one major tract where we predicted this effect in advance: the rILF. These data argue against general changes in white matter tracts across the brain in autism, instead demonstrating a more specific effect on just the rILF.

How can our findings be reconciled with the prior literature suggesting general differences in white matter tracts in autism? One possibility is that many prior studies have been affected by head motion artifacts. Indeed, our own study found that, despite great effort to minimize head motion, it remains a substantial

problem when scanning children, and is significantly worse for children with ASD. We see no reason to think that head motion would be less severe in prior diffusion studies in children with ASD. However, only a few diffusion imaging studies of autism even mention possible differences in head motion, let alone measure it. Only two papers report any quantitative analysis of the amount of motion present in the DWI scans, or report what motion threshold was used for excluding participants (9, 10). Ten studies gathered imaging data while some participants were under general anesthesia and an additional two while participants were sleeping naturally, presumably reducing head motion. Of these studies, however, only one imaged both ASD and typical groups under anesthesia (21). Indeed, one study that imaged participants with ASD under anesthesia and typical participants while asleep concluded that at least some of their group differences were likely caused by differences in motion (22). Thus, few prior studies have adequately dealt with possible artifacts of head motion.

If ASD and TD groups did in fact differ in head motion in prior studies, could these differences account for the reported differences in FA? Consistent with this possibility, the present study also finds widespread reductions in FA when data quality is not matched between groups. Further, a parallel analysis of the present data set found that FA is correlated with head motion, and differences in head motion are sufficient to produce spurious differences in FA between groups (11). Most strikingly, when a group of TD subjects was scanned twice each, a contrast of the higher-motion scan vs. the lower-motion scan within the very same children found significant differences in FA between “groups” (11). Thus, the FA differences between TD and ASD groups previously reported could be partly or entirely a result of differences in head motion.

Several papers published in the past year highlight these concerns. In particular, the other main line of neural evidence for reduced long-range connections in autism has come from studies in which reduced correlations are found in ASD between brain regions in the time course of the functional MRI signal at rest (reviewed in ref. 23). However, three recent papers have shown that head motion artifacts can produce functional connectivity patterns resembling those reported for autism, i.e., reduced long-range connectivity and increased local connectivity (24–26), and another recent paper in adults with ASD suggests there may be very little difference between groups in functional connectivity when head motion is carefully controlled (27). Thus, much of the prior evidence for reduced long-range connectivity in autism based on resting functional studies could also be an artifact of head motion (28). One very recent paper pooled functional connectivity scans from 17 different sites and 539 people with ASD across a wide age and IQ range and used data scrubbing techniques to try to mitigate residual artifacts from head motion. Although this study found statistically significant differences in functional connectivity between those with ASD and TD children (29), important questions for the future are (i) whether comparable differences in diffusion measures of connectivity would be found in similarly large samples, and (ii) whether effect sizes so small they can only be detected with extremely large samples are theoretically significant (30). In any event, the problem with head motion in functional correlation studies that use more standard sample sizes underlines the importance of matching for head motion in diffusion studies.

Beyond the widespread failure to control for head motion in past studies, several other factors could explain some of the differences between our results and the previous literature. Although we see no reason why this should be the case, differences in analysis methods (e.g., tract-based vs. voxel-wise methods) could in principle account for some of the differences between results among previous studies, or between our results and those of previous studies (1). One might wonder in particular whether

removing from the data any scan with any images showing visible motion artifacts (even if the FA maps did not). This much more stringent data quality control removed an additional 40 scans from children with ASD and 52 scans from TD children, removing for this analysis 75.6% of the original sample from participants with ASD and 56.5% of the data from TD children. The remaining scans (ASD, $n = 17$; TD, $n = 42$) were then again explicitly matched on IQ, age, sex, and all four motion measures before the second analysis of the stringent cohort was conducted. Fig. 1 includes details on the demographics and matching of groups for both of these analyses.

Analysis of Diffusion Measures. Automated parcellation of the T1-weighted images were performed in FreeSurfer 5.1 (39) to identify gray and white matter volumes and to define specific cortical and subcortical regions in each individual (40, 41). Automated segmentation results were reviewed for quality and corrected by trained experts when necessary and then registered to each individual's diffusion images. These segmentations were then used as part of the diffusion analysis. Anatomically constrained probabilistic diffusion tractography was carried out by using the Tracts Constrained by Underlying Anatomy (TRACULA) tool within FreeSurfer (42). This algorithm for automated global probabilistic tractography estimates the posterior probability of each of 18 white-matter pathways given the diffusion-weighted MRI data of each participant. This posterior probability is modeled as the product of two terms: (i) a data likelihood term, which uses the "ball-and-stick" model of diffusion; and (ii) a pathway prior term, which incorporates prior anatomical knowledge about the pathways from a set of training subjects. There is no assumption that the pathways have the same

shape in the study subjects as in the training subjects, and thus TRACULA does not rely on perfect alignment between study and training subjects. The work of Yendiki et al. (42) provides more details on this method, as well as information on its accuracy in healthy participants and those with schizophrenia. Mean values for FA, MD, RD, and axial diffusivity (AD) were obtained for each of the tracts reconstructed by TRACULA. These mean values were computed by thresholding the pathway distributions at 20% of their maximum value, and FA, MD, RD, and AD values at each voxel in the tract were weighted by the pathway probability at that voxel. Analyses run with DWI measures from just the center of each tract did not change the results in any substantive way.

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Supporting Information

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Tract	FA (TD Group: n = 68)					FA (ASD Group: n = 40)				
	Dir.	Mean 1	Mean 2	p-value	Cohen's d	Dir.	Mean 1	Mean 2	p-value	Cohen's d
f major	↑ *	.6487	.6743	.031	.5335	↑	.6231	.6584	.062	.6080
f minor	↓	.5353	.5334	.868	.0406	↓	.5292	.5225	.625	.1557
L ATR	↑ *	.3688	.3882	.005	.6987	↑	.3709	.3859	.180	.4323
R ATR	↑ *	.3607	.3751	.044	.4980	↑	.3664	.3780	.300	.3323
L CAB	↑	.3476	.3660	.126	.3756	↑	.3626	.3768	.322	.3176
R CAB	↑ *	.3517	.3856	.005	.7061	↑	.3451	.3602	.386	.2774
L CCG	↑ *	.4553	.5102	<.001	1.182	↑	.4677	.4860	.216	.3976
R CCG	↑ *	.4186	.4676	<.001	1.036	↑ *	.4240	.4640	.005	.9408
L CST	↑ *	.5172	.5401	.046	.4928	↑ *	.5135	.5392	.050	.6384
R CST	↑ *	.4916	.5290	.001	.8467	↑ *	.5005	.5285	.036	.6881
L ILF	↑	.5048	.5235	.060	.4637	↑	.5016	.5122	.463	.2345
R ILF	↑ *	.5182	.5372	.037	.5159	↑	.5021	.5124	.421	.2570
L SLFP	↑ *	.4245	.4403	.047	.4901	↑	.4350	.4511	.092	.5463
R SLFP	↑	.4165	.4295	.132	.3697	↑	.4207	.4389	.077	.5741
L SLFT	↑ *	.4436	.4614	.024	.5616	↑	.4453	.4581	.117	.5074
R SLFT	↑ *	.4200	.4402	.009	.6548	↑	.4172	.4356	.071	.5880
L Unc	↑ *	.4019	.4282	.003	.7463	↑ *	.4103	.4340	.007	.8995
R Unc	↑ *	.3970	.4232	.003	.7418	↑ *	.4081	.4209	.024	.4322

Fig. S1. Fractional anisotropy (FA) for each tract between younger (mean 1) and older children (mean 2) from the main cohort for typical (*Left*) and autism spectrum disorder (ASD; *Right*) groups separately. Arrows indicate the direction of the difference from younger to older children (an upward arrow indicates older children have higher FA than younger children). *P* value (uncorrected for number of tracts) and Cohen *d* refer to comparisons across age groups for each tract individually; asterisks denote significant between-group differences at $P < 0.05$, uncorrected.