Reduced Hemispheric Asymmetry of White Matter Microstructure in Autism Spectrum Disorder

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Objective: Many past studies have suggested atypical functional and anatomical hemispheric asymmetries in autism spectrum disorder (ASD). However, almost all of these have examined only language-related asymmetries. Here, we conduct a comprehensive investigation of microstructural asymmetries across a large number of fiber tracts in ASD.

Method: We used diffusion tensor imaging for a comprehensive investigation of anatomical white matter asymmetries across the entire white matter skeleton, using tract-based spatial statistics in 41 children and adolescents with ASD and a matched group of 44 typically developing (TD) participants.

Results: We found significant asymmetries in the TD group, being rightward for fractional anisotropy and leftward for mean diffusivity (with concordant asymmetries for radial and axial diffusivity). These asymmetries were significantly reduced in the group with ASD: in whole brain analysis for fractional anisotropy, and in a region where several major association and projection tracts travel in close proximity within occipital white matter for mean diffusivity, axial diffusivity, and radial diffusivity. No correlations between global white matter asymmetry and age or socio-communicative abilities were detected.

Conclusion: Our findings in TD children and adolescents can be interpreted as reflecting different processing modes (more integrative in the right and more specialized in the left hemisphere). These asymmetries and the "division of labor" between hemispheres implied by them appear to be diminished in autism spectrum disorder.

Key words: autism, diffusion tensor imaging, MRI, white matter, asymmetry

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Brain development is characterized by emerging functional lateralization and specialization of the cerebral hemispheres, accompanied by changes in asymmetries at the genomic,[1,2] cellular,[3,4] and macrostructural[5] levels. The latter include volumetric distributions of gray and white matter,[6,7] especially in areas associated with language.[8] Language has long been known to be predominantly controlled by the left hemisphere in most individuals.[9] Moreover, the Sylvian fissure and perisylvian regions surrounding it have been found to be morphologically asymmetric, with clinical implications for deviations from typical asymmetry.[10-12] However, asymmetries in white matter are not as well characterized.[13,14]

In the past decade, diffusion tensor imaging (DTI) has become a method of choice in the study of white matter organization in vivo. DTI detects the rate of water diffusion along multiple orientations and generates indices of white matter structure based on the diffusion tensor at each voxel. Commonly examined indices of diffusion include axial diffusivity (AD), the diffusion along the principal diffusion direction within a voxel, radial diffusivity (RD), the diffusion orthogonal to the principal diffusion direction, fractional anisotropy (FA), an index of the directional preference for diffusion in the axial relative to the radial direction, and mean diffusivity (MD), the mean diffusion regardless of direction. The tensor-based model has known limitations, particularly in its ability to resolve complex fiber crossings, and results are often nonspecific with regard to the underlying cellular differences.[15-17] Nonetheless, DTI is able to reliably localize group differences in white matter structure so long as results are interpreted with caution.[15-18] DTI studies in healthy adults have found hemispheric differences in white matter microstructure, with rightward asymmetry of AD and FA in the frontal and parietal lobes but leftward asymmetry in the temporal and occipital lobes.[19,20] In both left- and right-handed adults, white matter FA in the precentral gyrus was found to be greater contralateral than ipsilateral to the dominant hand.[21]

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by sociocommunicative deficits. Behavioral and observational findings suggest atypical asymmetries in ASD in many respects. For example, using retrospective video analysis, Esposito and Venuti[22] found that infants with ASD showed greater body asymmetry when sitting, compared to typically developing (TD) infants and those with developmental delays. Ozgen *et al.*[23] reported that atypical facial asymmetries were highly predictive of diagnostic status (ASD versus TD). Such observations are supported by findings from neurophysiological and imaging studies. Infants at high risk for ASD show atypical leftward processing asymmetry during face perception, compared to low-risk infants.[24] Atypical hemispheric asymmetries in ASD have also been reported in a number of language-related

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studies, using anatomical[25-28] and functional magnetic resonance imaging (MRI).[29-31]

In a review, Lindell and Hudry[32] concluded that atypical asymmetries in ASD are tied to language impairment and primarily detected in fronto-temporal language regions. However, a recent functional connectivity MRI study using independent component analysis found that numerous functional networks were affected by atypical right-hemisphere shifts in children and adolescents with ASD,[33] including many nonlinguistic networks (executive, attentional, and sensorimotor). Comprehensive examinations of hemispheric asymmetries in ASD beyond the language system are therefore needed.

Few studies to date have examined the asymmetry of DTI indices in ASD. Fletcher *et al.*[34] observed that rightward asymmetry of RD in the arcuate fasciculus (AF), seen in male TD adolescents, was absent in a small ASD group. Although this may be consistent with one subsequent study[35] reporting absence of typical leftward asymmetry of FA in the arcuate fasciculus (as well as in the cingulum and uncinate fasciculus) in a small sample of adolescents with ASD, it is at odds with findings from younger children (4−7 years of age) of leftward asymmetry of RD within the AF in TD children that was absent in children with ASD.[28] Leftward asymmetry of AF volume, as detected in TD children, was also significantly reduced in children with ASD in this study. Finally, Lange *et al.*[36] reported marginally reversed asymmetry of tensor skewness (a potential index of crossing fibers) in the superior temporal gyrus, which was rightward in children and adults with ASD but leftward in a matched TD group. However, all of these studies largely focused on language-related tracts. No DTI study to date has provided a comprehensive investigation of microstructural asymmetries across a large number of fiber tracts in ASD. We performed such an investigation in a cohort of children and adolescents with ASD and matched TD participants. Based on previous studies (as described above), we hypothesized an overall decrease in asymmetry in children with ASD.

METHOD

Participants

Participants were recruited through clinic referrals and advertisements. Diagnosis of ASD was performed by an expert clinical psychologist according to *DSM-V* criteria, using the Autism Diagnostic Interview−Revised[37] and the Autism Diagnostic Observation Schedule.[38] Participants with a history of medical or genetic conditions (e.g., epilepsy, tuberous sclerosis, Fragile-X, Rett syndrome) were excluded. Comorbid attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, or anxiety disorder (as reported by parents on the medical history questionnaire) were not treated as exclusionary in view of the high prevalence of these diagnoses within ASD.[39] In the TD group, no children with a personal or family history of autism or personal history of any other neurological or psychiatric conditions were included. Verbal and nonverbal IQ was assessed using the Wechsler Abbreviated Scale of Intelligence,[40] and all participants had nonverbal IQ above 50. Groups were matched for sex, handedness, verbal IQ, nonverbal IQ, and age (Table 1). Total scores on the Social Responsiveness Scale (SRS)[41] were available for all ASD, and all but 2 TD participants, and were used in correlational analyses. The study protocol was approved by the University of California, San Diego and the San Diego State University institutional review boards, and informed assent and consent were obtained from all participants and their parents prior to scanning.

TABLE 1 Participant Information

		ASD (n = 41)			TD (n = 44)			
Sex	Male	32 (6 LH)			35 (6 LH)			
	Female	9 (1 LH)			9 (0 LH)			
		Mean	**(SD)**	**Range**	**Mean**	**(SD)**	**Range**	***P***
Age (y)		13.68	(2.87)	7.4−18.0	13.43	(2.75)	8.0−17.7	.68
Verbal IQ		101.21	(17.72)	70−147	105.45	(10.53)	73−126	.18
Nonverbal IQ		104.79	(18.63)	53−140	104.8	(14.0)	62−137	>.99
Full-scale IQ		102.7	(17.64)	66−141	105.41	(11.44)	79−130	.40
ADOS	Communication	3.92	(1.68)	0−8				
	Social Interaction	8.37	(2.56)	4−14				
	Repetitive Behavior	2.32	(1.51)	0−5				
ADI-R	Communication	13.95	(5.87)	2−25				
	Social Interaction	18.11	(4.99)	7−28				
	Repetitive Behavior	6.41	(2.58)	1−12				
SRS	Total	82.32	(9.17)	62−100	42.50	(4.79)	35−52	< .01
Average translation (mm)		0.81	(0.16)	0.49−1.15	0.87	(0.24)	0.49−1.71	.17
Average rotation (rad; $\times 10^{-3}$)		4.38	(1.11)	2.31−7	4.57	(1.89)	2.39−12.2	.58
% Signal dropout		0.01	(0.02)	0−0.06	0.01	(0.02)	0−0.09	.91
Signal dropout severity		1.08	(0.18)	1−1.66	1.04	(0.10)	1−1.41	.19

Note: Scores were unavailable for the following: Verbal IQ, 2 participants with autism spectrum disorder (ASD); Nonverbal IQ, 2 participants with ASD; Full Scale IQ, 1 participant with ASD; Autism Diagnostic Observation Schedule (ADOS), 3 participants with ASD; Autism Diagnostic Interview—Revised (ADI-R), 4 participants with ASD; Social Responsiveness Scale (SRS), 2 typically developing (TD) participants. LH = left-handed; rad = radians.