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The loss of asymmetry and reduced interhemispheric connectivity in adolescents with autism: A study using diffusion spectrum imaging tractography

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Evidence from neuroimaging and neurobiological studies suggests that abnormalities in cortical–cortical connectivity involving both local and long-distance scales may be related to autism. The present study analyzed the microstructural integrity of the long-range connectivity related to social cognition and language processing with diffusion tractography among adolescents with autism compared with neurotypical adolescents. Tract-specific analyses were used to study the long-range connectivity responsible for integrating social cognition and language processing. Specifically, three pairs of association fibers and three portions of callosal fiber tracts were analyzed. Generalized fractional anisotropy (GFA) values were measured along individual targeted fiber tracts to investigate alterations in microstructure integrity. The asymmetry patterns were also assessed in three pairs of association fibers. In neurotypical participants, we found a consistent leftward asymmetry in three pairs of association fibers. However, adolescents with autism did not demonstrate such asymmetry. Moreover, adolescents with autism had significantly lower mean GFA in three callosal fiber tracts than neurotypical participants. The loss of leftward asymmetry and reduction of interhemispheric connection in adolescents with autism suggest alterations of the long-range connectivity involved in social cognition and language processing. Our results warrant further investigation by combining developmental and neurocognitive data.

1. Introduction

Autism is a common, multi-factorial, highly heritable, clinically heterogeneous neuro-developmental disorder that is diagnosed along severities related to the core impairments in social reciprocity and communication, as well as stereotyped and repetitive behaviors (Caronna et al., 2008). In the past few decades, several psychological theories have been proposed to explain the psychopathology of autism (Boucher, 2009). Evidence from neuroimaging and neurobiological studies suggests that the autistic disorder might be related to abnormalities in the cortical–cortical connectivity involving both local and long-distance scales (Courchesne and Pierce, 2005; Minshew and Williams, 2007). Aberrant connectivity theories based on information processing perspectives such as diffuse underconnectivity (Just et al., 2004) and a "globally underconnected and locally overconnected" brain (Belmonte et al., 2004; Baron-Cohen and Belmonte, 2005) have also been proposed.

Recently, researchers have applied diffusion tensor imaging (DTI) to obtain information about the white matter connectivity in individuals with autism (Barnea-Goraly et al., 2004; Alexander et al., 2007; Lee et al., 2007; Catani et al., 2008; Sundaram et al., 2008; Thakkar et al., 2008; Pugliese et al., 2009). DTI permits an examination of the microstructure integrity of white matter in terms of scalars derived from the diffusion tensor. One of the widely used scalars is

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fractional anisotropy (FA), a measure that reflects the directional anisotropy of water molecular diffusion (Basser, 1995). A higher FA value reflects a higher fiber density, larger axonal diameter, and more consistent myelination in the white matter (Johansen-Berg and Behrens, 2009). Many DTI studies, based either on regions of interest (ROI) approaches or voxel-based morphometry, have shown significantly reduced FA in the white matter adjacent to brain regions involved in the social cognition or language processing, such as the fusiform gyrus, the superior temporal sulcus, the ventromedial prefrontal cortex (Barnea-Goraly et al., 2004), the anterior cingulate cortex (Thakkar et al., 2008), the superior temporal gyrus, and the temporal stem (Lee et al., 2007). Taken together, these findings revealed abnormal white matter microstructure in various regions relevant to the core impairments of autism (Lee et al., 2007; Muller, 2007; Sundaram et al., 2008), suggesting that alterations of local connectivity might contribute to the pathology of autism.

With the advance of diffusion tractography, some studies have examined the microstructure integrity of long-range connectivity in autism. Conturo et al. (2008) found a normal size and shape but reduced FA of the hippocampo-fusiform and amygdalo-fusiform pathways in individuals with autism. In individuals with Asperger's disorder, Catani et al. (2008) found significantly lower FA in the intracerebellar fibers, while Pugliese et al. (2009) reported no significant differences in FA for limbic white matter tracts, i.e., the cingulum bundles and fornix, compared with healthy participants. Given the above reports, it is still unclear how the long-range connectivity specifically involved in the core impairments is altered in autism.

Given that deficits in social cognition and language processing are central to autism, that the fronto-temporal regions are responsible for most social and language processing, and that altered local connectivity in autistic brains is mostly found in the frontal and temporal lobes, it is plausible that the three major long-range fiber tracts connecting the frontal and temporal lobes, namely the cingulum (CG), arcuate fasciculus (AF), and uncinate fasciculus (UF), might be related to the neurostructural characteristics of autism. Results from neurocognitive studies have demonstrated that these three fiber tracts are involved in social or language functions. For example, CG is associated with empathic cognition and social behaviors (Wang et al., 2004), AF is responsible for the functions of language comprehension and expression (Vernooij et al., 2007), and UF is related to episodic memory and autonoetic awareness (Kubicki et al., 2002).

Therefore, the present study aimed to use diffusion tractography to analyze the microstructural integrity of the three pairs of association fibers, namely the bilateral CG, AF, and UF. In addition, the asymmetry patterns of these three pairs of association fibers were also analyzed. Moreover, we analyzed the long-range interhemispheric connections between the bilateral UF, i.e., the callosal fiber tracts connecting the bilateral orbitofrontal lobes, and between the bilateral AF, i.e., the callosal fiber tracts connecting the bilateral inferior frontal gyri and bilateral superior temporal gyri. We hypothesized that the long-range connectivity of the networks involved in social cognition and language processing is altered in autism, which could be revealed by diffusion tractography analyses.

2. Methods

2.1. Participants

We assessed 15 Taiwanese male adolescents with autism, aged 14 to 17, as well as 15 neurotypical control participants who were matched to the patients on age and full-scale intelligence quotient (IQ) (see Table 1). All participants were right-handed, as assessed with the Edinburgh Inventory (Oldfield, 1971). Participants with autism were clinically diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) and International Classification of Diseases-10 (ICD-10) criteria by senior child psychiatrists (Dr. S.S. Gau and Dr. W.T. Soong) experienced in autism assessments and treatments. Among them, all were clinically diagnosed to be high-functioning autistic disorder.

The mothers were interviewed with the Chinese version of the Autism Diagnostic Interview-Revised (ADI-R) (Rutter et al., 2003; Gau et al., 2009), confirming the diagnoses of autism and providing information about past and current autistic behavioral symptoms for their children. All 15 participants with autism met the ADI-R criteria of autism. The Chinese version of ADI-R, translated into Chinese by S.S. Gau et al. (2009), has been approved by Western Psychological Services.

The present study was approved by the Research Ethics Committee at the National Taiwan University Hospital (Clinical Trials gov. number: NCT00494754). The procedures and purpose of the study were clearly explained to the participants and their parents; the confidentiality of participants' information was assured. Written informed consent was obtained from the participants and their parents.

2.2. Magnetic Resonance Imaging (MRI) data acquisition

All images were acquired on a 3 T MRI system (Trio, Siemens, Erlangen, Germany). Head movement was restricted with expandable foam cushions. To obtain an anatomical reference, high-resolution T1-weighted Magnetic Resonance (MR) images were acquired covering the whole head with a magnetization-prepared rapid gradient echo (MPRAGE) sequence, repetition time (TR)/echo time (TE) = 2530/3.4 ms, slice thickness = 1.0 mm, 256 × 256 acquisition matrix, and field of view (FOV) = 25 × 25 cm in coronal view. Multiple trans-axial T2-weighted MR images were acquired with TR/TE = 5920/102 ms, slice thickness = 3.9 mm, flip angle = 150°, 256 × 256 acquisition matrix and FOV = 25 × 25 cm.

A pulsed-gradient spin-echo diffusion echo-planar imaging (EPI) sequence with a twice-refocused balanced echo being used to acquire the diffusion-weighted images in trans-axial view (Reese et al., 2003). The diffusion-encoding scheme used in this study followed the framework of diffusion spectrum imaging (DSI) in which diffusion-weighted images were acquired with diffusion gradients of different b values corresponding to the grid points filled within a sphere in the 3D diffusion-encoding space (q-space) (Wedeen et al., 2005). To reduce the scan time, we only acquired half-sphere DSI data, as performed by Hagmann et al. (2008) and Granziera et al. (2009). Specifically, the DSI data were acquired with 102 diffusion-encoding directions corresponding to grid points filled in the half sphere of the q-space with a radius of three units. For the first 12 participants (six with autism and six neurotypical), the b_{max} of 6000 s mm^{-2}, TR/TE = 9100/142 ms, and isotropic spatial resolution of 2.7 mm were prescribed. For the next 18 participants (nine with autism and nine neurotypical), the b_{max} of 4000 s mm^{-2}, TR/TE = 9600/130 ms, and isotropic spatial resolution of 2.5 mm were prescribed.

To correct for image distortion due to magnetic susceptibility, field maps were obtained by acquiring five EPI images with five TE values

Table 1
The age and intelligence levels of the participants.

	Autism (n = 15)		Neurotypical (n = 15)		P
	Mean	S.D.	Mean	S.D.	
Age, in years	15.2	1.0	15.0	0.8	0.54
Full-scale IQ	108.4	7.3	110.6	10.2	0.49
Verbal IQ	107.8	10.9	113.6	9.1	0.12
Performance IQ	108.2	11.4	105.4	12.9	0.53
Verbal comprehension index	107.8	11.1	114.5	9.2	0.08
Perceptual organization index	111.4	14.5	107.1	12.3	0.38
Freedom from distractibility index	105.6	13.3	107.9	13.2	0.65

Neurotypical = healthy comparison adolescents; S.D. = standard deviation.