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The value of diffusion tensor imaging for differentiating autism spectrum disorder with language delay from developmental language disorder among toddlers

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Abstract

Background: Impaired language function is frequently observed as an initial sign in people with autism spectrum disorder (ASD). However, clinically, the early stages of ASD are difficult to distinguish from those of developmental language disorder (DLD).

Objective: To evaluate the ability of diffusion tensor imaging (DTI) parameters for language-related white matter tracts (arcuate fasciculus) to differentiate ASD from DLD among toddlers.

Materials and methods: We included 16 ASD toddlers with language delay and 18 DLD toddlers in this study. Magnetic resonance imaging sequences included T2-weighted imaging (T2WI), T1 3-dimensional magnetization-prepared rapid acquisition gradient-echo (3D MP-RAGE), and DTI. Tractography was performed using Neuro 3D in the Siemens Syngo Workstation, and fractional anisotropy (FA), average fiber length (AFL), tract volume (TV), and number of voxels (NV) were automatically calculated. Data were then analyzed using IBM SPSS Statistics 22.

Results: The ASD group exhibited significantly lower FA values, as well as significantly higher TV and NV values compared with the DLD group. With age as the covariate, analysis of covariance revealed different significances in TV and NV. Analysis of variance for AFL revealed no significant differences between the 2 groups.

Conclusion: DTI parameters of arcuate fasciculus were useful for differentiating ASD with language delay from DLD among toddlers. DTI has the potential to provide an objective and effective method for aiding early diagnosis, early intervention and improving long-term outcomes of ASD.

Abbreviations: ASD = autism spectrum disorder, 3D MP-RAGE = 3-dimensional magnetization-prepared rapid acquisition gradient-echo, AFL = average fiber length, DLD = developmental language disorder, DTI = diffusion tensor imaging, FA = fractional anisotropy, NV = number of voxels, T2WI = T2-weighted imaging, TV = tract volume.

Keywords: autism spectrum disorder, developmental language disorder, diffusion tensor imaging, language-related white matter tract, toddler

1. Introduction

Autism, Asperger's syndrome, Rett syndrome and disorder—not otherwise specified (PDD-NOS) are a group of neurodevelopmental pathologies known collectively as autism spectrum disorder (ASD). ASD is characterized by severe impairment in reciprocal social interactions and communication skills, and the presence of restricted, stereotypical behavior.[1] Impaired language function is frequently observed as an initial sign in people with ASD. The incidence of ASD has steadily increased in recent years, and international epidemiological surveys have reported an incidence of ASD ranging from 60/10,000 to 100/10,000 people.[2,3]

The mechanisms underlying ASD remain largely unknown. In recent years, methods for evaluating the behavioral characteristics of children with ASD have been based on several rating-scale instruments and qualitative analysis of the complexity of affecting factors.[4,5] The commonly used scales include Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision (DSM), Childhood Autism Rating Scale (CARS), and Autism Behavior Checklist (ABC). The initial presentation of ASD with language delay is similar to that of developmental language disorder (DLD), and the 2 disorders are difficult to be differentiated clinically. Because ASD and DLD require substantially different treatment, the development of objective and sensitive methods for diagnosing ASD in the early stages in clinical practice is an important research area.

As a well-developed theory of the mechanisms underlying ASD, the weak central coherence theory was devised by Frith in 1994,[6] and has become widely accepted in recent decades.[7–9]

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The symptoms of ASD have been hypothesized to be caused by changes in brain connectivity. This connectivity involves white matter tracts that link discrete grey matter regions into integrated neural circuits. The arcuate fasciculus (AF) is an important language-related white matter tract connecting the frontal expressive language area with the posterior temporoparietal receptive language areas, forming the substrate of the dorsal language pathway.

Diffusion tensor imaging (DTI) is a noninvasive, highly sensitive method for delineating WM tracts and providing indirect quantitative measures of WM integrity. Wakana and Smits reported a method for examining the AF.[10,11] Although a number of studies have examined language-related white matter tracts using DTI, relatively few DTI studies have been conducted with young children. Given the importance of early intervention in ASD, finding efficient methods for early diagnosis is an urgent research aim. As an objective method, DTI may provide an important tool for assisting in the clinical diagnosis of ASD. In the present study, we focused on AF and hypothesize that the imaging features of AF may be different between ASD toddlers with language delay and DLD toddlers. DTI was used to investigate AF alterations of ASD and DLD.

2. Materials and methods

2.1. Subjects

We examined 16 toddlers with ASD with language delay (11 males, 5 females; mean age 2.41 ± 0.58 years, range 1.42–3.25 years), and 18 toddlers with DLD (11 males, 7 females; mean age 2.46 ± 0.63 years, range 1.25–3.83 years). Diagnosis of toddlers with ASD was conducted by 2 experienced neuropsychologists using the Autism Behavior Checklist-ABC. This scale has 5 subscales: Irritability, Lethargy-Social Withdrawal, Stereotypic Behavior, Hyperactivity, and Speech Disorder. All ASD toddlers exhibited an ABC score of at least 30 (average ABC score 49.9 ± 8.0) and presented clinical symptoms of stereotypes, communication disorders, and/or language regression. The ABC scores of all DLD toddlers were less than 30, with an average ABC score of 22.9 ± 3.8. The 2 groups were well matched in terms of age, gender, and handedness. The assessment of language function was based on the Expressive Language and Receptive Language subsets of the Chinese Version of the Psycho-Educational Profile (C-PEP). The C-PEP scale not only evaluates children with ASD and DLA but also develops individualized training programs for clinicians and parents. It includes 95 functional development scales and 44 pathological scales. This study used this scale to assess the language function. Mean intelligence quotient (IQ) was measured using the Wechsler Intelligence Scale for Children (WISC), which include 14 subtests. Toddlers with hypoxic-ischemic brain damage (HIBD), brain trauma and other congenital or acquired defects were excluded. This study was approved by the local institutional review board, and informed consent was obtained from all parents before the study began.

2.2. Magnetic resonance imaging (MRI) protocol

Magnetic resonance imaging (MRI) scans were acquired with a 3.0 T Siemens TIM Trio scanner. MRI sequences included T2-weighted imaging (T2WI), 3-dimensional magnetization-prepared rapid acquisition gradient-echo (T1 3D MP-RAGE) and single-shot echo planar (SE-EPI) imaging. The imaging parameters were as follows: T2WI: repetition time (TR) = 3220 ms, echo time (TE) = 99 ms, field of view (FOV) = 250 mm, slices = 20, slice thickness = 5.0 mm. T1 3D MP-RAGE: TR = 1900 ms, TE = 2.5 ms, FOV = 250 mm, slices = 176, slice thickness = 1.0 mm, and bandwidth = 170. DTI: TR = 5500 ms, TE = 92 ms, FOV = 260 mm, matrix = 128 × 128, 20 diffusion encoding directions, slice thickness = 3.0 mm, and variable b-values between 0 and 1000 s/mm^2. Toddlers were sedated using chloral hydrate (0.5 g in 10 mL) during MRI scanning.

3. Data analysis

For tractography, post-processing was performed using Neuro 3D in the Siemens Syngo Workstation. Tractography of the AF was performed by 2 raters. After fusing the images between T1 3D MP-RAGE and DTI, the AF was tracked by placing a seed region of interest (ROI) in the green triangular-shaped periventricular white matter on the encoded tensor map in the coronal plane, and a target ROI in the posterior temporal lobe, shown as a blue narrow strip structure lateral to the splenium of the corpus callosum. Using this method, we performed tract reconstruction of the AF separately (Fig. 1A and Fig. 1B). Fractional anisotropy (FA), average fiber length (AFL), tract volume (TV) and number of voxels (NV) were then automatically calculated.

Statistical analysis was performed using IBM SPSS v22 statistical software. Pearson's Chi-square test and independent sample *t* tests were used to compare gender, age, and IQ, and expressive language (EL) and receptive language (RL) scores, respectively. Inter-group differences in the DTI parameters of AF were analyzed using analysis of variance (ANOVA). We considered *P* values $<.05$ to indicate a significant difference.

4. Results

After T2WI acquisition, 1 toddler diagnosed with ASD who had gray matter heterotopias and 1 toddler with leukomalacia were excluded from the DLD group. In addition, 1 DLD toddler was excluded owing to failure to fuse images between T1 3D MP-RAGE and DTI. Finally, 15 ASD toddlers (11 males, 4 females; mean age 2.40 ± 0.60 years, range 1.42–3.25 years) and 16 DLD toddlers (10 males, 6 females; mean age 2.46 ± 0.67 years, range 1.25–3.83 years) were included.

As shown in Table 1, Pearson's Chi-square tests and independent sample *t* tests revealed no significant differences in gender, age or verbal IQ between the 2 groups. The ABC score of ASD group was significantly higher than that in DLD group ($P < .05$). However, the DLD group exhibited higher scores than the ASD group in terms of performance IQ, EL, and RL. As shown in Table 2, the ANOVA revealed that the ASD group exhibited significantly lower FA values ($F = 8.560$, $P < .05$), as well as significantly higher TV values ($F = 8.158$, $P = .008$) and NV values ($F = 12.00$, $P = .002$) compared with the DLD group. With age as the covariate, an analysis of covariance revealed significance differences in TV ($F = 10.373$, $P = .003$) and NV ($F = 14.84$, $P = .001$). ANOVA for AFL revealed no significant differences between the 2 groups ($F = 2.158$, $P > .05$).

5. Discussion

Autism and related pervasive developmental disorders PDDs have typical neuropsychiatric characteristics, including impaired social interaction and communication skills, as well as repetitive behaviors.[12] Approximately 20/10,000 children are

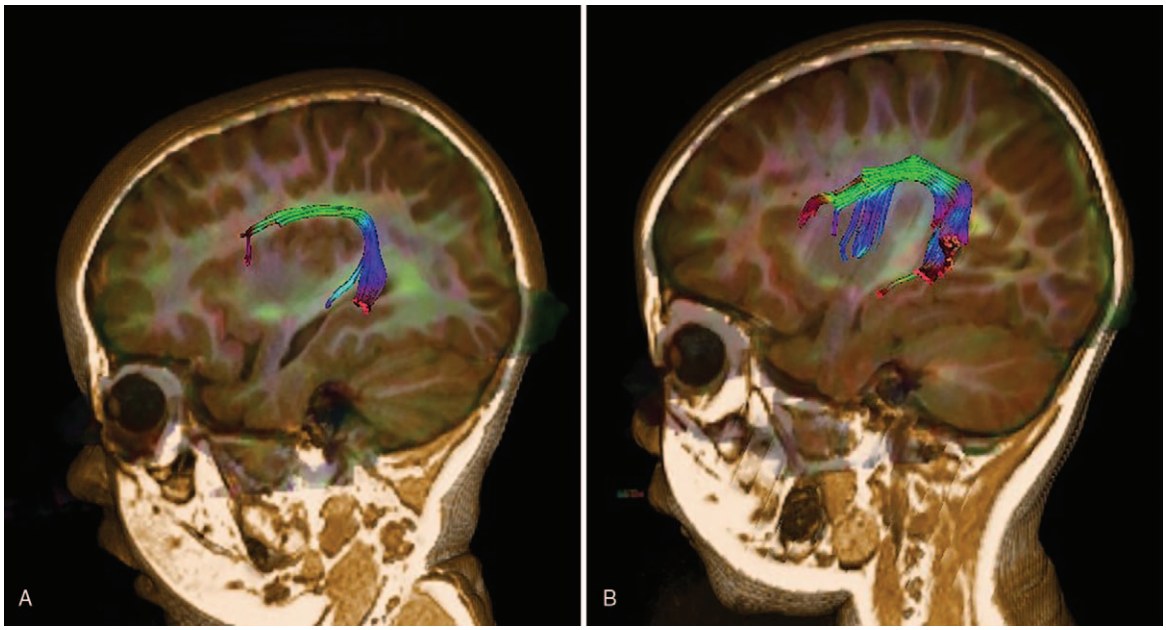

Figure 1. Three-dimensional (3D) tract reconstruction of the AF superimposed on sagittal T1 volume: (A) AF of a toddler with autism spectrum disorder with language delay; (B) AF of a toddler with developmental language disorder. AF = arcuate fasciculus.

affected by ASD, and early symptoms can be identified from 1 to 3 years of age.[13]

Prominent theories of the mechanisms underlying ASD include impeded plasticity, excitation and inhibition dysregulation, mirror neurons, and theory of mind (ToM). The impeded plasticity theory proposes that both hypo- and hyper-connectivity exist in the brains of ASD children.[14,15] Similar to this theory, Frith and Happe hypothesized the involvement of "weak central coherence" in ASD, implicating impairments in the connections between different brain regions in the disorder.[6] ASD children have no organic problems in listening and speaking, but they do not respond normally to the information they hear, which is consistent with this hypothesis. White matter tracts play a critical role in neural connectivity. Disruption of the long-range white matter tracts that mediate connectivity within systems may be an important pathogenic factor contributing to core social impairments in ASD. Language delay is not the most common symptom of ASD but is the most common reason for hospitalization.[16,17] In the present study, we focused on the AF, a language-related white matter tract that has been studied since the 19th century, which connects the frontal expressive language area with the posterior temporoparietal receptive language areas.[18]

DTI can be used to examine both the macrostructure and microstructure of white matter tracts noninvasively in the brain, enabling assessment of the AF separately with the method described by Wakana et al[10] using both a seed and target ROI. Although methods using DTI to study of ASD have developed rapidly in the past decade, the early stages of ASD have received relatively little attention from DTI studies. Given the importance of early intervention in ASD, efficient methods for early diagnosis could be valuable. The clinical manifestations of ASD with language delay in the early stages among toddlers are similar to those of developmental language disorder (DLD), and differentiation is typically not possible using clinical methods alone. The current results suggest the presence of considerable differences in several DTI parameters between ASD and DLD, which could be helpful for the diagnosis of ASD.

The present study revealed that the ASD group had significantly lower FA values compared with the DLD group, consistent with the majority of previous research on ASD. There are several possible reasons for decreased FA values, including decreased myelination, decreased axonal density (a decrease in the number of axons in the AF with an increase in intra-axonal space), decreased organization of fibers, and increased tortuosity,[19–23] all of which have been confirmed in animal experiments.[24,25] The current results also suggest that toddlers with ASD exhibited significantly higher TV values and NV values than those with DLD. There are several potential explanations for these findings. Previous evidence suggests that the elimination and formation of synapses is a continuous process.[26,27] Dysregulation of synaptic pruning is reported to be responsible for the high local connectivity and low long-range connectivity observed in the brains of people with ASD,[28–30] and this erroneous or invalid connectivity may be involved in the neural mechanisms underlying higher TV and NV values. There is

Table 1

Participant characteristics for autism spectrum disorder (ASD) and developmental language disorders (DLD).

Characteristics	ASD (n = 15)	DLD (n = 16)	*P* value
Gender, male/female	11/4	10/6	.52
Age, mean	2.49 ± 0.60	2.46 ± 0.67	.80
Age, range	1.42–3.25	1.25–3.83	
C-PEP			
EL	30.50 ± 10.39	46.31 ± 6.93	<.001
RL	33.79 ± 15.34	59.13 ± 7.21	<.001
VIQ	81.21 ± 18.96	102.56 ± 15.39	.001
PIQ	95.00 ± 14.06	103.13 ± 11.89	.086
ABC score	49.9 ± 8.0	22.9 ± 3.8	<.001

C-PEP = Chinese version of the psychoeducational profile; EL = expressive language; RL = receptive language; VIQ = verbal intelligence quotient; PIQ = performance intelligence quotient.

Table 2

Diffusion tensor imaging parameters of arcuate fasciculus comparison between autism spectrum disorders (ASD) and developmental language disorders (DLD).

	ASD (n = 15)		DLD (n = 16)		ANOVA		ANOVA[a]	
	Mean	SD	Mean	SD	F	*P* value	F	*P* value
	Range		Range					
FA	376.10	18.1	400.65	27.35	8.560	.007	8.561	.007
	343.75.–408.78		344.13–450.85					
AFL	87.50	10.38	80.71	14.80	2.158	.153	2.673	.113
	78.95–120.06		53.03–107.40					
TV	5206.26	2093.38	3306.79	1590.48	8.158	.008	10.373	.003
	2204.51–10829.45		1024.11–7257.18					
NV	322.73	129.68	183.19	92.76	12.00	.002	14.84	.001
	137–673		70–451					

ANOVA = analysis of variance, ANCOVA = analysis of covariance. ANOVA[a] = ANOVA completed using age as a covariate.

currently no clear consensus regarding this issue, despite the abundance of research on white matter tracts with DTI in recent decades. In addition to different research objectives, methods, and MRI scanners, these different results may have been affected by the dynamic and interconnected development of the white matter across the lifespan. Several previous studies reported that brain growth in children with ASD, particularly in the first 2 to 4 years of life, differs from that of typically developing children.[29,31–34]

Once diagnosed, ASD children should receive individualized treatment. The most widely used treatment is comprehensive rehabilitation therapy. For example, the C-PEP scale can be used to develop an individualized training program. Then, long-term follow-up assessment should be performed and the training program should be timely adjusted according to the efficacy of rehabilitation training. In addition, a systematic review by Serafini G et al[35] suggests that repetitive transcranial magnetic stimulation can enhance cognitive performance in treatment-resistant depression by specifically stimulating a functional brain region associated with neuropsychiatric disease, for example, the left dorsolateral prefrontal cortex. That is to say, the interaction between brain functional regions can be enhanced by stimulation, which is consistent with the theoretical basis of this study.

The present study involved several limitations that should be considered. First, the number of subjects in our sample was small. Due to the small sample size, this paper only studied the role of DTI parameters in identifying ASD and DLD. The upper/lower limit of DTI parameters for quantitative diagnosis of ASD was not obtained. Second, the diagnostic scale we used was relatively simple, and ASD children with language retardation, language deviancy, as well as other types of language disorders were ignored. In addition, other cognitive functions were not taken into consideration and were not well controlled. Thus, future studies with larger samples and more comprehensive scales are needed. Further research should be conducted to determine the brain areas involved in social interactions and communication skills related to neural connectivity, including longitudinal studies of the developmental trajectory of neural microstructure in people with ASD.

6. Conclusion

The current results demonstrate that the DTI parameters of AF, an important language-related white matter tract, in ASD toddlers with language delay are different from those in DLD toddlers, which are valuable for differentiating ASD with language delay from DLD among toddlers. DTI may provide an objective and effective method to aid clinical diagnosis and therapy in the early stages of ASD, and improve prognosis. However, further study with larger sample size is needed to determine the upper/lower limit of DTI parameters and to make quantitative diagnosis of ASD.

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Author contributions

KL and LZ were responsible for the study's design. RM contributed to the acquisition of neuroimaging sequences. YY and DL conducted the clinical data collection. LZ wrote the first draft of the manuscript. LZ, XLQ, and NZ analyzed the neuroimaging data. ZL and KL were responsible for statistical analysis. KL assisted in revising the overall manuscript. All authors read and approved the final manuscript.

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