論　文　名

Altered white matter connectivity of ventral language networks in autism spectrum disorder: An automated fiber quantification analysis with multi-site datasets

（　自閉スペクトラム症における脳内言語ネットワークの白質微細構造の異常　）

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Altered white matter connectivity of ventral language networks in autism spectrum disorder: An automated fiber quantification analysis with multi-site datasets

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ABSTRACT

Comprehension and pragmatic deficits are prevalent in autism spectrum disorder (ASD) and are potentially linked to altered connectivity in the ventral language networks. However, previous magnetic resonance imaging studies have not sufficiently explored the microstructural abnormalities in the ventral fiber tracts underlying comprehension dysfunction in ASD. Additionally, the precise locations of white matter (WM) changes in the long tracts of patients with ASD remain poorly understood. In the current study, we applied the automated fiber-tract quantification (AFQ) method to investigate the fine-grained WM properties of the ventral language pathway and their relationships with comprehension and symptom manifestation in ASD. The analysis included diffusion/T1 weighted imaging data of 83 individuals with ASD and 83 age-matched typically developing (TD) controls. Case-control comparisons were performed on the diffusion metrics of the ventral tracts at both the global and point-wise levels. We also explored correlations between diffusion metrics, comprehension performance, and ASD traits, and conducted subgroup analyses based on age range to examine developmental moderating effects. Individuals with ASD exhibited remarkable hypoconnectivity in the ventral tracts, particularly in the temporal portions of the left inferior longitudinal fasciculus (ILF) and the inferior fronto-occipital fasciculus (IFOF). These WM abnormalities were associated with poor comprehension and more severe ASD symptoms. Furthermore, WM alterations in the ventral tract and their correlation with comprehension dysfunction were more prominent in younger children with ASD than in adolescents. These findings indicate that WM disruptions in the temporal portions of the left ILF/IFOF are most notable in ASD, potentially constituting the core neurological underpinnings of comprehension and communication deficits in autism. Moreover, impaired WM connectivity and comprehension ability in patients with ASD appear to improve with age.

1. Introduction

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder that arises in early childhood, characterized by core deficits in socio-communicative abilities and stereotypical/restricted behaviors (American Psychiatric Association, 2013). Although language deficits have been removed from the core symptoms of autism, they remain pervasive among most patients with ASD, causing various

Abbreviations: AD, axial diffusivity; ADOS-2, autism diagnostic observation schedule, second edition; AFQ, automated fiber-tract quantification; AF, arcuate fasciculus; ASD, autism spectrum disorder; AQ, autism-spectrum quotient; BET, brain extraction tool; DICOM, digital imaging and communications in medicine; DSM-IV, diagnostic and statistical manual of mental disorders IV criteria; DTI, diffusion tensor imaging; FA, fractional anisotropy; IFG, inferior frontal gyrus; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; FDR, false discovery rate; fMRI, function magnetic resonance imaging; FSL, FMRIB software library; FSIQ, full-scale intelligence quotient; MD, mean diffusivity; MNI, Montreal neurological institute; MTG, middle temporal gyrus; MRI, magnetic resonance imaging; NIfTI, the neuroimaging informatics technology initiative; RD, radial diffusivity; ROI, region of interest; STG, superior temporal gyrus; SCQ, social communication questionnaire; SLF, superior longitudinal fasciculus; TD, typically developing; UF, uncinate fasciculus; VBM, voxel-based morphometry; VCI, verbal comprehension index; WISC-IV, Wechsler intelligence scale for children, fourth edition; WM, white matter.

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difficulties in social interaction and daily living skills (Levy et al., 2010). Specifically, comprehension and pragmatic abilities are the most affected by autism (Hage et al., 2021). Moreover, a delay in language development often serves as an early warning sign in ASD detection and is more predictive than the onset of social ability or repetitive behaviors (Herlihy et al., 2015; Kalandadze et al., 2018). Therefore, uncovering the neurocognitive mechanisms underlying language disorders in ASD is critical for diagnosis, screening, and intervention.

Recently, neuroimaging studies have posited that altered brain connectivity may be the neurobiological basis for cognitive and behavioral abnormalities in ASD (Just et al., 2012; Libero et al., 2016; Rane et al., 2015). Diffusion tensor imaging (DTI) is a non-invasive neuroimaging technique widely used to explore the atypical structural connectivity of ASD *in vivo*. It characterizes the microstructural properties of white matter (WM) fibers by detecting the diffusion of water molecules in brain tissues. The integrity and orientation of white matter (WM) tracts can be evaluated using quantitative measures such as fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). FA and MD are two integrative measures commonly used in previous diffusion tensor imaging (DTI) studies. FA is widely accepted as a comprehensive measure of WM integrity and is sensitive to microstructural changes in WM (Travers et al., 2012). Decreased FA may indicate impaired axonal architecture, including alterations in myelin and axonal density (Beaulieu, 2014). MD reflects tissue damage via the mean eigenvalues of water diffusion (Beaulieu, 2014). MD effectively characterizes tissue properties, such as the cytoskeleton, tissue water content, and membrane permeability, and is closely linked to tissue injuries such as inflammation, edema, or neoplasia (Alexander et al., 2007). RD and AD are two primary directional metrics representing the perpendicular and parallel diffusivity of the tensor, respectively (Beaulieu, 2002). Notably, RD correlates with the myelination process (Song et al., 2005) and provides detailed information on axonal features (Aung et al., 2013). Therefore, we applied two commonly used summary measures (FA and MD) and one directional measure (RD) to better characterize the WM microstructural changes in ASD. Tractography, an efficient method for analyzing DTI data, can recreate the fiber tracts in the brain and evaluate the microstructural profiles of each WM tract.

Despite an increasing number of ASD studies applying tractography, findings on WM changes in language networks in ASD are inconclusive. Previous studies have suggested that individuals with ASD have reduced integrity in the ventral language networks, including the uncinate fasciculus (UF), inferior longitudinal fasciculus (ILF), and inferior fronto-occipital fasciculus (IFOF) (Andica et al., 2021; Fitzgerald et al., 2018; Lei et al., 2019). Hypoconnectivity in the ventral tracts appears to underpin comprehension and pragmatic dysfunction in individuals with ASD (Mody et al., 2013). However, while some studies have not found significant WM alterations (Hattori et al., 2019; Karahanoglu et al., 2018; Kato et al., 2019), others have reported over-connectivity in the ventral route in patients with ASD (Bode et al., 2011). The developmental stage is likely a critical factor in these inconsistent findings. Brain structural profiles show distinct patterns at different age ranges in individuals with ASD. For instance, Haghighat et al. (2021) reported that children with ASD tend to exhibit hyper-connectivity, while both hypo- and hyper-connectivity are observed in adolescents and adults. Additionally, pronounced morphological or microstructural alterations are found in childhood but not in adolescence with ASD (Ameis et al., 2011; Mizuno et al., 2019). However, given that most previous studies tend to focus on specific age groups or mixed age groups with ASD, the moderating effects of the developmental stage on brain connectivity in ASD remain to be elucidated. Thus, identifying developmental changes in microstructural alteration patterns in ASD across different age groups will help clarify the inconsistent findings in previous studies. Moreover, our recent meta-analysis of tractography studies (Li et al., 2022) indicated that existing studies on language networks in autism have focused more on the traditional dorsal pathway (such as arcuate fasciculus [AF] and superior longitudinal fasciculus [SLF]) than on the ventral tracts. The elaborate relationships between WM characteristics and language performance in ASD remain to be clarified.

Although the developmental stage of autism is a critical factor accounting for inconsistent findings, there has been insufficient concern across previous studies. Furthermore, conventional tractography only examines the microstructural properties of WM fibers globally, whereas WM changes in the autistic brain may vary along the trajectory of the tract. Automated fiber-tract quantification (AFQ) is a novel tractography approach for automatically reconstructing and segmenting each fiber tract into multiple points and extracting diffusion metrics at both pointwise and global average levels. This fine-grained analysis of specific segments can provide more precise information regarding the WM changes in patients with ASD. However, to the best of our knowledge, only a few studies have used AFQ to investigate abnormalities in WM connectivity in individuals with ASD (Libero et al., 2016; Naigles et al., 2017). These studies reported that diffusion metrics varied along focal locations in language-related tracts (such as the SLF and ILF) in autism. These findings verified the feasibility of the AFQ method for ASD research. In previous studies, Libero et al. (2016) examined the microstructural alterations of major WM tracts in ASD without specifically focusing on language performance. Naigle et al. (2017) investigated WM variability at different language levels in preschool children with ASD but did not compare these changes to typically developing (TD) controls.

In the present study, we conducted AFQ analysis to investigate detailed patterns of WM alterations in autism. Given the extensive research focused on the traditional dorsal pathway, we directed our attention to the less explored ventral tracts. Our aim was to explore both focal and widespread disruptions in ventral fibers in individuals with ASD. Additionally, we aimed to elucidate the associations between WM changes in the ventral pathway and comprehension performance through correlation analyses. Recognizing that comprehension and pragmatic problems are closely interwoven with the social communication deficits of ASD, we also examined the relationships between autistic severity and WM properties. Our third goal was to examine whether the altered pattern of WM tracts was affected by developmental stage, using subgroup analyses. We hope that AFQ can provide new insights into WM abnormalities in ASD and that information on these location-specific properties could offer a new target for speech treatment in ASD.

2. Materials and methods

2.1. Participants

We recruited participants with ASD (age range: 6–16 years) at Osaka University Hospital and University of Fukui Hospital in Japan. Pediatric neurologists made autism diagnoses based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. Symptom assessments of patients with ASD were conducted by expert clinical psychologists using the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2). TD controls were recruited from the local community via advertisements. They had no history of developmental, neurological, or psychiatric disorders and had never received special support education. Intelligence was evaluated for all participants using the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV). The verbal comprehension index (VCI) subscale of the WISC-IV was used to assess the language comprehension ability of the subjects. Three standard subtests of the VCI (similarities, vocabulary, and comprehension) were used to measure language performance on lexical category/semantic content, conceptualization, and implications. ASD traits were estimated for participants using the Social Communication Questionnaire (SCQ) at Osaka University and the Autism-Spectrum Quotient (AQ) at the University of Fukui. Participants were excluded based on the following criteria: full-scale IQ < 70 points, history of head injury or any neurological illness, or left-handedness (examined by the Edinburgh Handedness Inventory).

The current study was approved by the Ethics Committees of Osaka University and the University of Fukui (Assurance no. K22213). Written informed consent was obtained from all participants and their parents after a complete explanation of the study.

2.2. Magnetic resonance imaging acquisition

Participants underwent diffusion/T1 weighted imaging via 3-Tesla scanners at Osaka University Hospital or University of Fukui Hospital. The magnetic resonance imaging (MRI) acquisition protocols for the two sites are summarized in Table 1. As shown in Table 1, high-resolution, three-dimensional (3D), and silent T1-weighted (T1W) axial protocols were conducted at each site. Diffusion-weighted images were acquired using a single-shot spin-echo echo-planar imaging sequence with 25 (at the Osaka University) or 30 (at the University of Fukui) directional diffusion encodings ($b = 1000$ s/mm^2), as well as an acquisition without diffusion weighting ($b = 0$ s/mm^2). All participants underwent scans without sedation, receiving instructions about the MRI sessions and being required to stay awake. Head stabilization during scanning was carefully considered using cushions and foam pillows at both institutions.

2.3. Data pre-processing

First, all raw digital imaging and communications in medicine (DICOM) images were converted into the neuroimaging informatics technology initiative (NIfTI) format using the MRIcron software (https://www.nitrc.org/projects/mricron/). Data quality was checked using the MANGO toolbox (v4.1; https://mangoviewer.com/mango.html), and scans with artifacts or distortions were excluded.

Routine preprocessing procedures for the diffusion datasets were conducted using the FMRIB Software Library (FSL) (v5.0.9; https://www.fmrib.ox.ac.uk/fsl). First, the diffusion-weighted images were aligned to the b0 image to maximize frame normalization. Second, eddy-current distortion and head motion were corrected using a rigid-body alignment to minimize data noise. Third, non-brain structures were removed using a Brain Extraction Tool (BET). Simultaneously, a brain mask was generated to restrict the operational range of the diffusion algorithm. Specifically, a more stringent fractional intensity threshold (0.5) was applied during brain extraction to rigorously address truncation artifacts, which commonly occur at the brain-skull interface. Finally, the diffusion tensor model was fitted using the DTIFIT command to obtain the diffusion metrics (fractional anisotropy [FA], mean diffusivity [MD], axial diffusivity [AD], and radial diffusivity [RD]) and s0 images (T2 images without diffusion weighting).

The preprocessing of T1-weighted images comprised two steps. (1) Non-brain structures were removed using the BET function in the FSL. (2) The anterior commissure-posterior commissure (AC-PC) plane was aligned using the mrAnatAverageAcpcNifti command in the VistaSoft package (v1.0; https://github.com/vistalab/vistasoft). The resulting T1 images were used as references for realigning the diffusion-weighted images (aligning T1 images to S0 images) to reduce the displacement of DTI data.

Table 1
Site-specific scanning protocol.

Site	*Osaka Univ. 1*		*Osaka Univ. 2*		*Univ. of Fukui*	
No. of subjects	38 ASD; 34 TD		10 ASD; 11 TD		35 ASD; 38 TD	
Scan parameters	T1	DTI	T1	DTI	T1	DTI
Scanner	Discovery MR 750w 3.0T		Signa Architect 3.0T		Discovery MR 750w 3.0T	
Head coil	24ch		48ch		32ch	
TR (ms)	880	12,000	876.332	6000	6.38	8400
TE (ms)	0.016	75	0.02	75	1.99	84.2
FA (Def)	5	–	5	–	11	–
FOV (mm^2)	240	128 × 128	100	128 × 128	256	256 × 256
Acquisition Matrix	240 × 240	256 × 256	256 × 256	256 × 256	256 × 256	256 × 256
Number of Slices	480	59	480	50	172	64
Voxel Dimension (mm^3)	1.0 × 1.0 × 1.0	–	0.94 × 0.94 × 0.50	–	1.0 × 1.0 × 1.0	–
Slice Thickness (mm)	–	3	–	3	–	2
Number of Directions		25		25		30
b value (s)		0 / 1000		0 / 1000		0 / 1000

TR, repetition time; TE, echo time; FA, flip angle; FOV, field of view; DTI, diffusion tensor imaging.

2.4. Automated fiber quantification

The preprocessed datasets were further analyzed using AFQ software (https://github.com/yeatmanlab/AFQ), an open-source MATLAB toolkit that can automatically reconstruct and segment the main fiber tracts in the individual brain.

The standard AFQ pipeline involves six main steps (Yeatman et al., 2012). (1) Deterministic fiber tractography across the entire brain using a streamlined tracking algorithm. Termination criteria for fiber tracking were: FA value <0.2 and turning angle >30 degrees. (2) Tract segmentation using waypoint regions of interest (ROIs) (Wakana et al., 2007). The waypoint ROIs were in the MNI space and transformed into the individual's native space based on non-linear transformation to minimize the heterogeneity across individual brains. (3) Fiber refinement based on the probabilistic tract atlas (Hua et al., 2008). Fibers passing through the low-probability voxels were expurgated as non-proposed tracts. (4) Tract cleaning using iterative procedure. Fibers with deviated properties (fiber length > mean length + 4 SDs; distance from the tract core > 5 SDs) were filtered out as outliers for each fiber group. (5) Fiber clipping based on the two waypoint ROIs of each fiber bundle. The central trajectory of each fiber group was defined as the tract core, which was more consistent across individuals. (6) Tract quantification and metrics extraction. Clipped fibers were resampled into 100 equidistant nodes, and the diffusion metrics (including FA, MD, AD, and RD) at each node were calculated via spline interpolation. The mean measurements of the fiber core were computed using the weighted average across the entire fiber bundle.

We applied FA, MD, and RD to evaluate the WM connectivity for each participant's brain at point-wise and global levels. Additionally, we focused on three ventral WM tracts in the bilateral hemisphere (IFOF, ILF, and UF). These fiber tracts are consistently considered the ventral pathway of language networks and are critical for comprehension processing from visual to meaning (Friederici, 2020; Hagoort, 2019).

2.5. Statistical analysis

First, we compared the demographic and clinical characteristics of the ASD and TD groups using two-sample *t*-tests. Second, before starting the statistical analyses of the diffusion metrics, we performed a harmonization process to correct the site-specific effects introduced by the different imaging parameters in the multisite datasets. The FA, MD, and RD values for each subject were harmonized using the ComBat method in MATLAB (Fortin et al., 2017). Age, sex, full-scale intelligence quotient (FSIQ), and VCI were included as covariates in the ComBat harmonization model to control for potential confounding effects. Third, we performed between-group comparisons of corrected FA, MD, and RD values at the entire tract and point-wise levels using two-sample *t*-tests. In the point-wise analysis, false discovery rate (FDR) correction was applied for multiple comparisons. Only significant differences observed

at more than three adjacent nodes were reported as effective results (Banfi et al., 2019). Fourth, we evaluated the relationships between the mean diffusion metrics in each tract and the four main cognitive indices and ADOS scores in the ASD group using Pearson's correlations. Additionally, further correlation analyses were performed between the diffusion profiles of significantly altered fiber segments and the VCI/ADOS scores in individuals with ASD. Finally, to investigate the moderating effects of developmental stage, we divided the participants into children (age range: $6.0 \leqq$ years < 12.0) and adolescents (age range: $12.0 \leqq$ years < 18.0) as done previously (Haghighat et al., 2021; Holiga et al., 2019; Lee et al., 2017), and conducted two-sample *t*-tests and correlation analyses at the subgroup level.

All statistical analyses were performed using Jeffreys's Amazing Statistics Program (JASP) (v.0.17.3; https://jasp-stats.org). The statistical significance of the point-wise analysis was set at $p < 0.05$ with FDR correction or $p < 0.01$ without correction (Helwegen et al., 2023). For other statistical tests, $p < 0.05$ was considered the significance level.

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of the participants are summarized in Table 2. AFQ analyses involved datasets from 83 individuals with ASD (mean age: 11.03 ± 2.18 years, 47 children, 36 adolescents) and 83 TD controls (mean age: 10.57 ± 2.33 years, 56 children, 27 adolescents). There was no significant difference in age and sex between the ASD and TD subjects ($p > 0.05$). The ASD group showed prominent autistic traits compared to the TD group in the SCQ and AQ (SCQ: $p < 0.001$, $T = 7.862$; AQ: $p < 0.001$, $T = 9.915$). Fifty-three patients with ASD were assessed using the ADOS-2 scale (mean score: 10.12 ± 4.21). Subjects with ASD exhibited significantly poorer performance on FSIQ ($p < 0.001$, $T = -4.118$) and four main cognitive indices (PRI: $p = 0.014$, $T = -2.474$; PSI: $p = 0.002$, $T = -3.139$; WMI: $p < 0.001$, $T = -3.355$; VCI: $p = 0.003$, $T = -3.032$) compared to TD participants. Notably, in the subgroup analysis, children with ASD showed significantly lower scores than TD controls on the PSI, WMI, and the comprehension subtest of the VCI (PSI: $p = 0.002$, $T = -3.251$; WMI: $p < 0.001$, $T = -3.587$; VCI-Comprehension: $p = 0.035$, $T = -2.143$). However, in the adolescent group, the case-control differences tended to be attenuated, and no statistical significance remained in most cognitive indices or any of the VCI subscales (detailed information is provided in Table 2).

3.2. Group comparative analyses on diffusion metrics

We successfully identified the target fiber tracts (bilateral UF, ILF, and IFOF) in both groups using AFQ. We then applied ComBat harmonization to the diffusion metrics (FA, MD, and RD) for each tract, including age, sex, FSIQ, and VCI as confounding covariates. To confirm the harmonization effect, we compared the inter-site differences of diffusion profiles at each fiber tract before and after applying the ComBat process via ANOVA analysis. The site effects in all DTI metrics were successfully removed by the ComBat method (detailed information is provided in Supplementary Table 1). Then, group comparison analyses of FA, MD, and RD were performed at the global-tract and point-wise levels.

3.2.1. Group differences at the global-tract level

At the global tract level, compared with TD controls, individuals with ASD showed significantly higher MD in the left IFOF ($p = 0.035$, $T = 2.124$) and left ILF ($p = 0.027$, $T = 2.235$) (Fig. 1A). In the subgroup analyses, children with ASD had a significantly increased MD in the left IFOF ($p = 0.038$, $T = 2.103$), while no significant alteration was found in the adolescent group (Fig. 1B and C). For the mean FA of each fiber tract, despite subjects with ASD exhibiting a decreasing tendency, the group

Table 2
Demographic and clinical characteristics of the participants.

	ASD	TD	*p*- value	*T*-value
Subjects (*n*)	83	83	–	–
Osaka Univ. (*n*)	48	45	–	–
Univ. of Fukui(*n*)	35	38	–	–
Sex (*n.* male / female)	77 / 6	74 / 9	–	–
Age (*years*)	11.03 (2.18)	10.57 (2.33)	0.132	1.515
FSIQ	97.77 (14.83)	106.61 (11.59)	< 0.001**	−4.118
PRI	99.40 (18.37)	105.72 (13.40)	0.014*	−2.474
PSI	92.84 (18.99)	100.90 (12.69)	0.002**	−3.139
WMI	94.44 (19.66)	103.30 (12.84)	< 0.001**	−3.355
VCI-total	99.35 (17.49)	107.35 (14.16)	0.003**	−3.032
VCI-Similarities	11.0 (3.81)	11.16 (2.81)	0.778	−0.282
VCI-Vocabulary	10.11 (5.13)	11.59 (3.12)	0.049*	−1.984
VCI-Comprehension	9.44 (4.03)	11.03 (2.95)	0.010**	−2.607
ADOS-total	10.12 (4.21)	–	–	–
SCQ-total (*Osaka*)	11.91 (8.01)	1.81 (1.98)	<0.001**	7.862
AQ-total (*Fukui*)	18.86 (6.37)	6.58 (5.12)	<0.001**	9.915
Subgroup of age range				
Children group (*n*, $6.0 \leqq y < 12.0$)	47	56	–	–
FSIQ	96.70 (13.89)	106.39 (12.99)	<0.001**	−3.654
PRI	101.55 (14.88)	106.53 (14.30)	0.095	−1.688
PSI	94.06 (12.90)	101.86 (10.83)	0.002**	−3.251
WMI	92.43 (16.26)	103.53 (14.38)	<0.001**	−3.587
VCI-total	97.98 (17.62)	105.61 (14.93)	0.019*	−2.379
VCI-Similarities	10.87 (4.53)	10.95 (2.96)	0.920	−0.101
VCI-Vocabulary	10.28 (6.21)	11.76 (3.25)	0.171	−1.381
VCI-comprehension	9.24 (4.15)	10.93 (3.12)	0.035*	−2.143
Adolescents group (*n*, $12.0 \leqq y < 18.0$)	36	27	–	–
FSIQ	99.17 (16.07)	106.07 (8.35)	0.046*	−2.035
PRI	96.51 (22.12)	104.19 (11.61)	0.107	−1.635
PSI	91.20 (25.08)	99.07 (15.68)	0.158	−1.429
WMI	97.14 (23.45)	102.85 (9.49)	0.239	−1.190
VCI-total	101.14 (17.39)	109.48 (12.77)	0.040*	−2.102
VCI-Similarities	11.18 (2.61)	11.63 (2.45)	0.537	−0.621
VCI-Vocabulary	9.88 (3.25)	11.21 (2.88)	0.143	−1.486
VCI-comprehension	9.71 (3.90)	11.26 (2.60)	0.126	−1.556

ASD, autism spectrum disorders; TD, typically developing; FSIQ, full scale intelligence quotient; PRI, perceptual reasoning index; PSI, processing speed index; WMI, working memory index; VCI, verbal comprehension index; ADOS, autism diagnostic observation schedule; SCQ, social communication questionnaire; AQ, autism-spectrum quotient; *$p < 0.05$, ** $p < 0.01$.

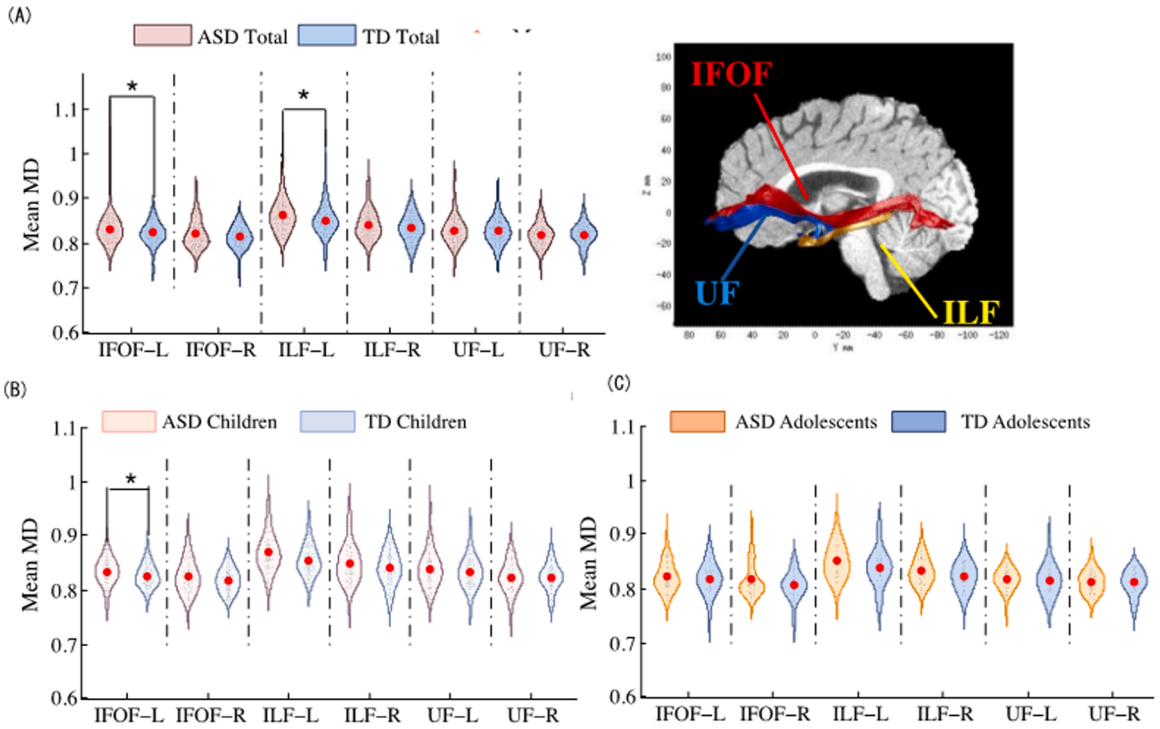

Fig. 1. Group comparisons of mean MD profiles at the global tract level.
(A) Group differences in tract-level MD profiles between all ASD and TD subjects (pink for ASD and blue for TD). The ASD group showed a significantly increased MD in the left IFOF and ILF. (B) Subgroup analysis of children in tract-level MD profiles (light pink for children with ASD and light blue for TD children). Children with ASD showed increased MD in the left IFOF. (C) Subgroup analysis of adolescents in tract-level MD profiles (orange for adolescents with ASD and cyan blue for TD adolescents). No significant group differences were observed between the TD adolescents and those with ASD. ASD, Autism spectrum disorder; TD, Typically developing; MD, Mean diffusivity; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; UF, uncinate fasciculus; R, right; L, left. * indicates a statistically significant difference between groups, $p < 0.05$.

difference failed to reach significance (details in Supplementary Fig. 1). Meanwhile, no significant case-control differences were observed in the mean RD of each ventral tract (Supplementary Fig. 2).

3.2.2. *Group differences at the point-wise level*

In point-wise analyses, we applied a relatively liberal significance level ($p < 0.01$ without correction) due to the difficulty in achieving statistically significant results that could survive FDR correction. We found that patients with ASD presented with significant MD elevation ($p < 0.01$ without correction) in two regions (*node.* 50–55, 76–79) of the left ILF compared to TD controls (Fig. 2A). According to point-wise comparison of the FA profiles, we observed a significant FA reduction ($p < 0.01$ without correction) in a small area of the left IFOF (*node.* 70–72) in the ASD group relative to that in the TD group (Fig. 2B). These results indicate that the temporal lobe positions (Ivanova et al., 2016) of the left IFOF/ILF tend to show more significant alterations in autistic brains.

3.3. *Correlation analyses between diffusion metrics and cognitive assessments in ASD*

3.3.1. *Relationships between diffusion metrics and comprehension performance*

First, we examined the relationships between the mean diffusion

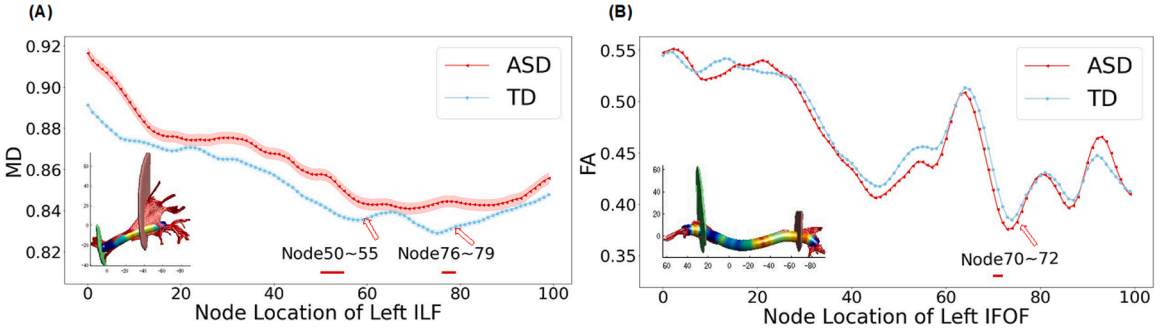

Fig. 2. Point-wise comparison of diffusion profiles between ASD and TD groups. The red line indicates the ASD group, the blue line indicates the TD group, and the red bars at the bottom represent fiber segments with significant group differences. Rendering of diffusion metrics (FA/MD) for the target fiber tract of one subject is displayed in the lower left corner of each plane to provide a visualization of the tract properties.
(A) Significantly increased MD values in the temporal lobe portions of the left ILF (*node.* 50–55 and *node.* 76–79) in the ASD group *($p < 0.01$ without correction)*. (B) Significantly decreased FA values in the temporal component of the left IFOF (*node.* 70–72) in the ASD group *($p < 0.01$ without correction)*. ASD, Autism spectrum disorder; TD, Typically developing; FA, Fractional anisotropy; MD, Mean diffusivity; IFOF, Inferior fronto-occipital fasciculus; ILF, Inferior longitudinal fasciculus.

measurements (FA, MD, RD) in each fiber tract and the four main cognitive indices (VCI, PRI, PSI, WMI) within the ASD group. There were significantly negative correlations between VCI scores and mean MD of the left ILF ($r = -0.237$, $p = 0.035$; Fig. 3A), whereas no significant correlations were found between the other core cognitive scales and diffusion metrics (details in Supplementary Table 2). In the subgroup analyses, the children group showed pronounced correlations between the MD or RD in the left ILF and VCI (MD: $r = -0.420$, $p = 0.006$, Fig. 3B; RD: $r = -0.304$, $p = 0.049$; Fig. 3C), while no significant correlations remained in the adolescent group.

Additionally, we conducted correlation analyses of the diffusion metrics and the three core subtests of the VCI scale (similarities, vocabulary, and comprehension). The ASD group exhibited significant negative correlations between the comprehension score and mean MD of the left ILF ($r = -0.241$, $p = 0.036$, Fig. 4A). According to the subgroup analyses, within the children group, the comprehension score was negatively related to the average MD in the bilateral ILF (left: $r = -0.498$, $p < 0.001$; right: $r = -0.371$, $p = 0.016$, Fig. 4B) and mean RD in the left ILF ($r = -0.370$, $p = 0.016$), while no significant relationship was observed in adolescents (Fig. 4C). Moreover, the relationships between the other two subtests of the VCI and the MD of the left ILF also showed a trend towards significance in the children group (Similarities: $r = -0.298$, $p = 0.056$; Vocabulary: $r = -0.302$, $p = 0.052$; details in Supplementary Fig. 3B).

Moreover, we conducted further correlation analyses between the VCI scores and average diffusion metrics of the fiber segments that showed significant case-control differences in the point-wise comparison. In the total group, no significant correlations were found between the segmental fiber microstructure and the total or any subtest of the VCI scale (details in Supplementary Table 3). However, strong correlations were achieved in the subgroup analyses. The VCI total score was negatively correlated with the mean MD of *node.* 50–55 in the left ILF within the children group ($r = -0.470$, $p = 0.001$ without correction; Fig. 5A). Additionally, for the VCI subtests, more significant negative correlations were observed between the comprehension score and the mean MD of *node.* 50–55 ($r = -0.577$, $p < 0.001$ without correction, Fig. 5B) and *node.* 76–79 ($r = -0.495$, $p = 0.002$ without correction, Fig. 5B) in the left ILF in children with ASD. In contrast, no significant correlations were found between the VCI scores and the point-wise diffusion profiles in the adolescent group (details in Supplementary Table 4).

3.3.2. *Relationships between diffusion metrics and ASD symptom measures*

We computed the correlations between the diffusion profiles of each tract and the ADOS-2 scores at the whole-group and subgroup levels. In the correlation analyses of the total group, we found that the ADOS-2 scores were positively correlated with the mean RD in the left ILF and left IFOF (left ILF: $r = 0.287$, $p = 0.043$; left IFOF: $r = 0.292$, $p = 0.040$, Fig. 6A). According to the subgroup analyses, ADOS-2 scores showed a significantly positive correlation with the average MD in the left IFOF in the children group ($r = 0.443$, $p = 0.014$; Fig. 6B). Moreover, in the adolescent group, the ADOS-2 scores were negatively related to the mean FA in the left IFOF ($r = -0.512$, $p = 0.021$; Fig. 6C) and left ILF ($r = -0.537$, $p = 0.012$; Fig. 6C).These findings indicate that lower connectivity in the ILF and IFOF is closely associated with worse clinical symptoms of autism. Furthermore, in the point-wise correlation analyses, we did not find any significant associations between the diffusion metrics of any fiber segment and the ADOS-2 scores (details in Supplementary Table 6).

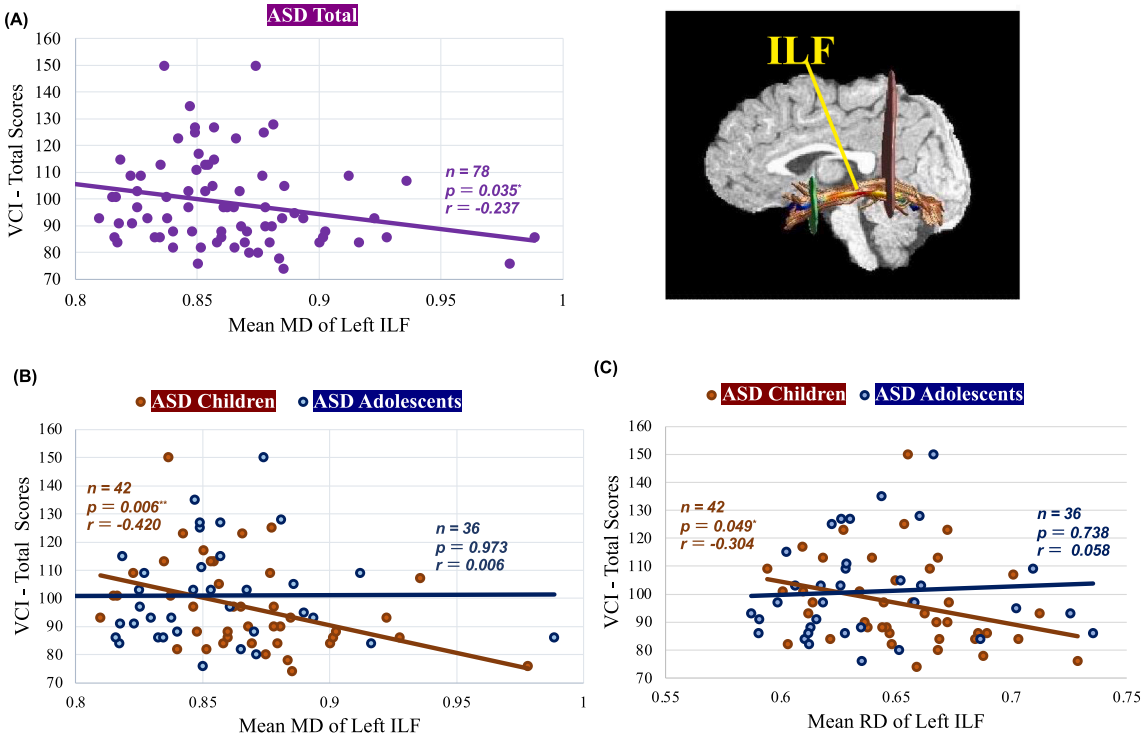

Fig. 3. Correlations between diffusion profiles of ILF and full-scale VCI scores in ASD.
(A) Correlation between the mean MD of the left ILF and full-scale VCI scores in all subjects with ASD (significant negative correlation: $r = -0.237$, $p = 0.035$). (B) Subgroup analysis of the correlations between the mean MD of the left ILF and full-scale VCI scores (brown for children with ASD, blue for adolescents with ASD). A significant negative correlation was observed in children with ASD ($r = -0.420$, $p = 0.006$), whereas no significant correlation was observed in adolescents with ASD. (C) Subgroup analysis of the correlations between the mean RD of the left ILF and full-scale VCI scores (brown for children with ASD, blue for adolescents with ASD). A significant negative correlation was observed in children with ASD ($r = -0.304$, $p = 0.049$), while no significant correlation was observed in adolescents with ASD. VCI: Verbal comprehension index; MD, Mean diffusivity; RD: Radial diffusivity; ILF, Inferior longitudinal fasciculus; ASD, Autism spectrum disorder. *$p < 0.05$, ** $p < 0.01$.

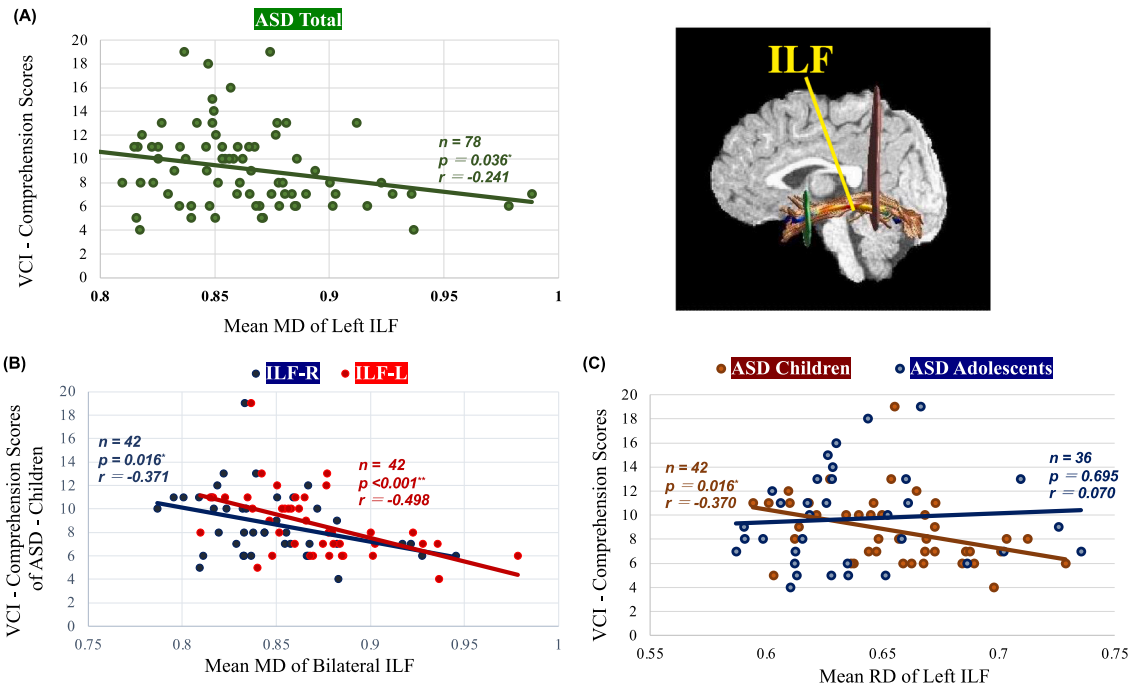

Fig. 4. Correlations between diffusion profiles of ILF and comprehension scores in ASD.
(A) Correlation between the mean MD of the left ILF and comprehension subtest scores in all subjects with ASD (significant negative correlation: $r = -0.241$, $p = 0.036$). (B) Correlations between the mean MD of the bilateral ILF (red for left ILF, blue for right ILF), and comprehension subtest scores in children with ASD (left ILF: $r = -0.498$, $p < 0.001$; right ILF: $r = -0.371$, $p = 0.016$). (C) Subgroup analysis of the correlations between the mean RD of the left ILF and comprehension scores (brown for children with ASD, blue for adolescents with ASD). A significant negative correlation was observed in children with ASD ($r = -0.370$, $p = 0.016$), while no significant correlation was observed in adolescents with ASD. VCI: Verbal comprehension index; MD, Mean diffusivity; RD: Radial diffusivity; ILF, Inferior longitudinal fasciculus; ASD, Autism spectrum disorder. *$p < 0.05$, ** $p < 0.01$.

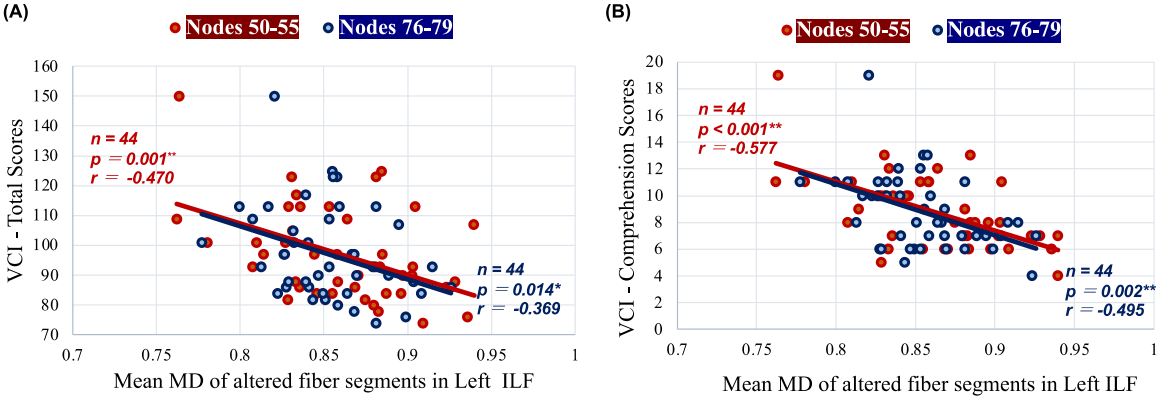

Fig. 5. Correlations between diffusion profiles of altered fiber segments in the left ILF and VCI scores in ASD children.
(A) Correlations between the mean MD of the altered fiber segments in the left ILF (red for nodes 50–55, blue for nodes 76–79) and full-scale VCI scores in children with ASD (nodes 50–55: $r = -0.470$, $p = 0.001$; nodes 76–79: $r = -0.369$, $p = 0.014$). (B) Correlations between the mean MD of the altered fiber segments in the left ILF (red for nodes 50–55, blue for nodes 76–79) and comprehension subtest scores in children with ASD (nodes 50–55: $r = -0.577$, $p < 0.001$; nodes 76–79: $r = -0.495$, $p = 0.002$). Significance was set at $p < 0.01$ without correction. VCI: Verbal Comprehension Index; MD: Mean Diffusivity; ILF: Inferior Longitudinal Fasciculus.

4. Discussion

In the current study, we investigated the precise patterns of WM abnormalities in patients with ASD using the AFQ and explored their associations with the severity of language comprehension disability and autistic traits. First, according to the cognitive assessment results, we discerned that individuals with ASD tended to show more deficits in high-level comprehension ability than in elementary lexical processing. Second, we found that subjects with ASD had impaired connectivity in the left IFOF/ILF, with particularly pronounced alterations observed in the temporal segments of these tracts. These findings indicate that WM changes may vary depending on the specific fiber location in the autistic brain. Moreover, decreased connectivity, indicated by elevated MD and RD, in the bilateral ILF was related to lower comprehension scores in children with ASD. In particular, the temporal portions of the left ILF showed relatively stronger correlations with comprehension ability in younger individuals with ASD. Additionally, compromised integrity of the left IFOF/ILF, characterized by elevated MD and RD or reduced FA, was associated with increased severity of ASD traits. These results suggest that the left IFOF and ILF, especially their temporal portions, play a pivotal role in the neuropathology of ASD, potentially underpinning comprehension disability and clinical manifestations in autism.

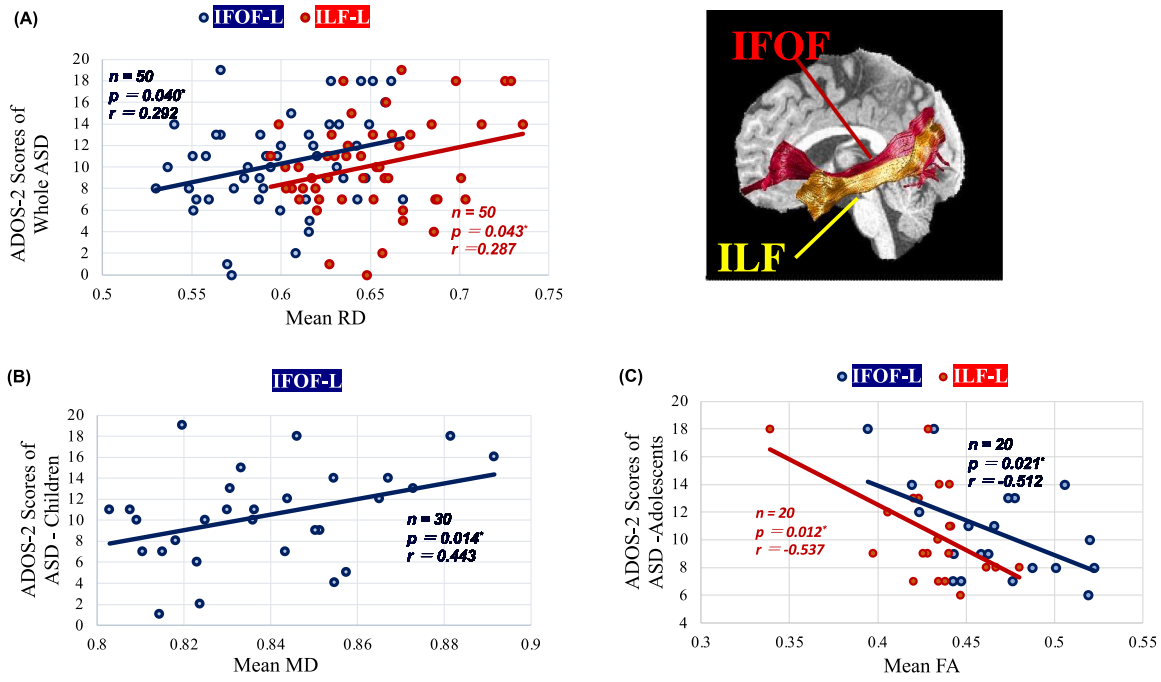

Fig. 6. Correlations between diffusion profiles of ventral tracts and ADOS-2 scores in ASD.
(A) Correlation between the mean RD of the left ILF/IFOF (red, left ILF; blue, left IFOF) and ADOS-2 scores in ASD group (left ILF: $r = 0.287$, $p = 0.043$; left IFOF: $r = 0.292$, $p = 0.040$). (B) Correlation between the mean MD of the left IFOF and ADOS-2 scores in children with ASD (significant positive correlation: $r = 0.443$, $p = 0.014$). (C) Correlations between the mean MD of the left ILF/IFOF (red, left ILF; blue, left IFOF) and ADOS-2 scores in adolescents with ASD (left ILF: $r = -0.537$, $p = 0.012$; left IFOF: $r = -0.512$, $p = 0.021$). ADOS-2, Autism Diagnostic Observation Schedule, second edition; RD: Radial diffusivity; MD, Mean diffusivity; ILF, Inferior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus; ASD, Autism spectrum disorder. $^*p < 0.05$.

Subgroup analyses revealed that younger ASD cohorts manifested more conspicuous comprehension difficulties and WM alterations than adolescents. In children with ASD, reduced integrity of the ILF was significantly correlated with poorer comprehension performance. However, this significant correlation disappeared in the adolescent group. We speculate that WM alterations in the ventral tract and their relationship with comprehension ability may be dynamic in autism throughout development. Our findings provide more refined and focal information on the comprehension and WM characteristics of autism.

4.1. *Altered structural connectivity in ventral language networks of ASD*

Our findings of reduced integrity in the left IFOF/ILF in patients with ASD are consistent with several systematic reviews of DTI studies (Ameis and Catani, 2015; Vissers et al., 2012). Our recent meta-analysis (Li et al., 2022) synthesized 33 tractography studies that demonstrated elevated MD in ventral language networks in autism. These findings provide further evidence that ASD is a disconnection syndrome that involves atypical brain connectivity (Geschwind and Levitt, 2007; Mohammad-Rezazadeh et al., 2016). Moreover, morphological abnormalities in the ventral route in autism have also been validated using structural MRI. For example, several meta-analyses of VBM studies have reported reduced volume and density of the ILF/IFOF in patients with ASD (Duerden et al., 2012; Nickl-Jockschat et al., 2012). These microstructural and morphological alterations in ASD may arise from aberrant brain maturation. Emerging evidence suggests that children with ASD exhibit exaggerated synaptic pruning (Rafiee et al., 2022) and deficient axonal myelination (Galvez-Contreras et al., 2020). However, the specific pathophysiological underpinnings of these MRI alterations in the autistic brain remain poorly understood and require elucidation in future studies utilizing multimodal methodologies.

Notably, the IFOF and ILF are long-range association tracts, and microstructural abnormalities in the autistic brain may vary along the white matter trajectory. Our point-wise level analysis verified that the temporal lobe portions of the left IFOF/ILF tend to show more prominent underconnectivity in autism. As described by Geschwind and Levitt (2007), the disconnection between multimodal higher-order association cortices in the temporal-frontal lobe is considered a key point in autism. In previous MRI studies, functional and morphological alterations in the temporal regions were most pervasively observed in patients with ASD. For instance, a recent meta-analysis of fMRI studies (Herringshaw et al., 2016) indicated that participants with ASD exhibited concurrent hypoactivation in the middle temporal gyrus (MTG) and superior temporal gyrus (STG) during many language tasks, including lexical processing, sentence comprehension, and pragmatic language processing paradigms. Xiao et al. (2023) combined the analysis of resting-state fMRI and eye-tracking data, suggesting that the atypical functional connectivity of superior temporal regions with other cortical regions is the core neural mechanism underlying communication and language deficits in ASD. Several systematic reviews on the neuroanatomical characteristics of ASD have consistently indicated that the superior temporal sulcus and Wernicke area are core regions most commonly affected in ASD (Khandan Khadem-Reza et al., 2023; Liu et al., 2020).

Additionally, we did not detect any significant group differences in the UF, although this is a ventral tract involved in verbal communication and often reported to have abnormalities in prior ASD studies (Catani et al., 2016; Jung et al., 2019). Previous findings on the microstructural alterations of the UF in the autistic brain are inconsistent. Some studies have reported reduced integrity in the UF in individuals with ASD (Andica et al., 2021; Cheon et al., 2011) while others have found no significant differences between case-control groups (Libero et al., 2016; Boets et al., 2018; Kato et al., 2019). These inconsistencies may result from individual variation and distinctive trajectories in the WM development. Several lifespan studies have investigated the developmental trajectories of major fiber tracts in the healthy brain, suggesting that the UF tends to mature later than other association tracts (such as the ILF or IFOF) (Lebel et al., 2012, 2008). Moreover, diffusion parameter changes in WM maturation show large personal differences, with greater

individual discrepancies in the UF than in other ventral tracts (Lebel and Beaulieu, 2011). Thus, we speculate that the longer developmental course and larger individual variation likely contribute to the discrepant findings in prior research. The microstructural anomalies of the UF in ASD remain to be elaborated in future studies using larger sample sizes or long-term longitudinal designs.

Furthermore, our study revealed that the microstructural disturbances of the ventral tracts in ASD were more pronounced in MD than in FA. Similar trends have been noted in previous DTI studies involving children with ASD, where MD exhibited a remarkable increase, whereas FA did not reach statistical significance (Ameis et al., 2011; Groen et al., 2011). These discrepancies may stem from distinct neurobiological underpinnings of FA and MD. MD represents the average rate of a molecule's diffusion movement and is sensitive to the maturation processes of cellular membranes, such as changes in the cytoskeleton, tissue water content, and membrane permeability (Beaulieu, 2014). FA is regarded as a composite measure of WM integrity and reflects the directional dependence of diffusion (Alexander et al., 2007). FA is associated with numerous neural fiber factors and is easily affected by many unrelated effects (Tournier, 2019). The ambiguous biological interpretations of FA may have resulted in the absence of statistical significance regarding FA changes in our results. Although the precise neurobiological meaning of diffusion metrics remains unclear, FA and MD remain the most prominent diffusion markers for detecting disruptions in white matter maturation. Moreover, recent studies have suggested that atypical WM maturation processes, such as abnormal myelination and decreased oligodendrocyte generation, are the primary causes of aberrant neural connectivity in autism (Galvez-Contreras et al., 2020). Therefore, illustrating the neurobiological distinctions underlying FA and MD through more specific histological studies could provide crucial insights into the etiology and precision of autism therapy.

4.2. WM changes of ventral pathway associated with hallmark of ASD

In the correlation analysis, the diffusion profiles in the IFOF/ILF were significantly related to VCI, particularly the comprehension subtest scores, but not to other cognitive indices such as PRI, PSI, and WMI. Notably, we found that the temporal segments of the left ILF exhibited more remarkable correlations with comprehension performance in children with ASD. These results reveal noteworthy and specific associations between verbal comprehension performance and WM integrity of the IFOF/ILF (especially the temporal portions) in patients with autism. The ILF and IFOF serve as primary fibers in the ventral language pathway and support comprehension processes in a natural social environment (Kljajevic, 2014). The IFOF has extensive branching in the occipital, temporal, and frontal lobes, connecting critical regions for semantic and syntactic processing, such as the STG/MTG (BA22), IFG (BA45), and pars triangular/orbitalis (BA47) (Martensson et al., 2013; Sarubbo et al., 2013; Thiebaut de Schotten et al., 2012; Young et al., 2021). Disruptions in the IFOF may result in various problems in semantic categorization, contextual comprehension, and pragmatic information extraction, which are critical for social communication (Friederici, 2015; Friederici and Gierhan, 2013; Hage et al., 2021). Our results showed notable correlations between the diffusion properties of the left IFOF and ADOS-2 scores in subjects with ASD. Similarly, a previous study observed that decreased FA in the IFOF was related to heightened autistic traits as assessed by the AQ (Roine et al., 2015). These findings suggest that under-connectivity in the IFOF may contribute to the more severe clinical symptoms of ASD.

The ILF connects the occipital lobe with the temporal pole and projects into crucial regions for visual-linguistic information mapping and verbal declarative memory, such as the posterior occipitotemporal regions, fusiform gyrus, and superior/inferior temporal gyrus (Herbet et al., 2018; Latini et al., 2017; Martino et al., 2011). Impairments in the ILF may cause difficulties in object naming, lexical-semantic access, and visual-linguistic integration (Gil-Robles et al., 2013; Mandonnet et al., 2007; O'Rourke and de Diego Balaguer, 2020). We found that reduced integrity of the ILF correlated with lower comprehension performance and higher ADOS scores in subjects with ASD. In line with our findings, a previous study on children with ASD with varying linguistic levels suggested that the low language-ability group exhibited diminished integrity in the bilateral ILF compared to the high language-ability group (Nagile et al., 2017). Another study reported that reduced FA in the right ILF was related to decreased phonological working memory ability in individuals with ASD, which is critical for reading and listening comprehension processing (Lu et al., 2016). Additionally, Mills et al. (2013) reported that greater integrity of the ILF significantly contributes to better morphological and narrative performance, which are critical for social communication. Moreover, a few studies have examined the relationships between the microstructure in the ventral stream and the social communication subscale of autistic assessment (Cheon et al., 2011; Poustka et al., 2012). Cheon et al. (2011) reported remarkable correlations between the diffusion properties of the left ILF and the ADOS social scores. Overall, microstructural alterations in the ILF and IFOF may cause comprehension and pragmatic difficulties frequently observed in ASD, leading to verbal communication and social interaction deficits in autism.

4.3. Developmental moderating effects on the autistic brain

Our subgroup analysis revealed that adolescents with ASD showed improved comprehension ability and fewer IFOF/ILF abnormalities than children with ASD. These results indicate that ASD manifests as a dynamic developmental syndrome, wherein comprehension deficits and impaired WM connectivity may be alleviated through ongoing brain development. Our findings align with previous research indicating an accelerated maturation of WM in individuals with ASD during early years, followed by a decreased maturation rate in late childhood and adolescence, ultimately resulting in subtle WM changes in adults (Girault and Piven, 2020; Karahanoglu et al., 2018). This atypical developmental trajectory is particularly prominent in the temporal and frontal lobes of autistic brains (Cascio et al., 2013; McFadden and Minshew, 2013). Moreover, the cortical development of ASD follows a similar pattern, undergoing three distinct phases: overgrowth in early childhood, a period of stagnant growth until adolescence, and eventually a few alterations in later adulthood (Courchesne et al., 2004; Nunes et al., 2020; Zielinski et al., 2014). Khundrakpam et al. (2017) reported that case-control differences in cortical thickness were maximal around ten years of age but did not show statistical significance during the pubertal stage. The narrowing gap may be due to neural maturation within the typical brain, gradually catching up with that in the autistic brain (Courchesne et al., 2011), and adolescence seems to be a turning point in group differences (Lange et al., 2015). Therefore, we posit that the atypical developmental patterns observed in the autistic brain likely account for our results regarding diminishing WM alterations in adolescents with ASD.

Notably, although the diffusion profiles in the ventral tracts tend to normalize with age, neural abnormalities may not completely disappear. Aberrant brain development in ASD could prompt belated neural circuit reorganization involving processes that attempt to prune excessively altered axon connections, synapses, and neurons to enhance neural circuit function (Courchesne et al., 2011). Dysregulated connection formation and neural activity may persistently affect long-term manifestations of autism. Previous resting-state fMRI studies examining intrinsic functional connectivity have consistently revealed abnormal connectivity in autistic brains during childhood (Di Martino et al., 2011; Uddin et al., 2013a) and adulthood (Cherkassky et al., 2006; Mueller et al., 2013). However, the nature and direction of connectivity differences in ASD likely vary depending on the developmental stage (Ecker et al., 2015), with adolescents and adults with autism exhibiting underconnectivity, whereas younger children appear to exhibit over-connectivity (Uddin et al., 2013b). The structural and functional

maturation trajectory and developmental moderating effects in autistic brains need further clarification using long-term longitudinal studies. Uncovering the developmental framework of the autistic brain has the potential to provide a more comprehensive understanding of the neurobiology of autism.

In the clinical setting, we noted that the severity and profile of symptoms in individuals with ASD tend to be more heterogeneous with age, which may result from the enhanced influence of environmental factors (Ecker et al., 2015). The amplified degree of interindividual variability during development may have led to the lack of case-control differences observed in the adolescent group in the present study. Nevertheless, less is known about how the heterogeneity in brain characteristics and clinical symptoms of individuals with ASD changes across developmental stages, which requires detailed elaboration in future studies.

4.4. Limitations

Our study has some unavoidable limitations. First, we applied a relatively liberal significance level to our point-wise analysis. Although we utilized the FDR method to correct the statistical bias from multiple comparisons, hardly any results survived the FDR correction. The lenient statistical threshold may affect the persuasion of the point-wise results. We believe that we will be able to determine whether these findings are justifiable with larger and more homogeneous samples in future studies. Second, although we revealed relatively detailed WM changes in ASD through point-wise level analysis, specifying the exact anatomical coordinates for these damaged nodes remains challenging. This is a common limitation across previous AFQ studies (Dou et al., 2020; Xu et al., 2022; Zhang et al., 2019) because the fiber segmentation and quantification are processed in individual native space, and only the central portion of the fiber tract is analyzed (Yeatman et al.,2012). Advanced algorithms to provide more accurate node landmarks are desirable for future studies. Third, although we controlled for sex differences between groups, the large numeral gap between sexes might have biased the results. The effects of sex on brain structure and function should be carefully considered in future studies on ASD. Finally, the current study did not include low-intellectual or non-verbal subjects with ASD, who represent an extreme part of the autism spectrum. These individuals exhibit more complex patterns of language deficits that extend beyond comprehension abilities to include severe impairments in speech production, with some cases lacking all spoken language (Tager-Flusberg and Kasari, 2013). Additionally, a recent DTI study reported that non-verbal autism likely has a distinctive pattern of WM changes compared to verbal ASD, showing more remarkable disruption in the ventral stream (Olive et al., 2022). However, it should be noted that the WM microstructure alterations in non-verbal or low-intellectual ASD remain less focused and under-researched. The neurological basis of language deficits in these extreme cases of ASD is a crucial topic for future studies to uncover the complete picture of the neuropathology underlying autism.

5. Conclusions

We explored WM alterations in the ventral language pathway in autism using global-tract and specific-location analyses via the relatively novel tractography method, AFQ. To the best of our knowledge, AFQ has rarely been employed to investigate WM changes in language networks in ASD, and the relatively large-scale datasets used here present a remarkable advantage. Participants with ASD exhibited pronounced underconnectivity in the left IFOF and ILF. Specifically, the temporal portions of the left IFOF/ILF showed more remarkable disturbances that were likely the core impaired regions of the autistic brain. Additionally, these WM changes in the ventral route were closely related to comprehension difficulties and symptom severity in autism, which may constitute the neurological underpinnings of social communication deficits in ASD. Atypical WM features were more notable in younger children with ASD than in adolescents. This finding suggests that WM disturbances in autism are not static and may be alleviated with age owing to developmental and environmental moderating effects. Our findings provide detailed information on the neurobiological mechanisms underlying comprehension and pragmatic deficits in autism. We expect that our study will address the research gaps in language development studies on ASD and contribute novel insights into behavioral interventions for autism. Finally, age-related WM alterations and their impact on language and social communication in autism should be elaborated in future long-term longitudinal studies involving larger and more diverse cohorts.

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Ethical approval

The current study was approved by the Ethics Committees of Osaka University and the University of Fukui (Assurance no. K22213).

Consent to participant

Written informed consent was obtained from all participants and their parents after a complete explanation of the study.

CRediT authorship contribution statement

Min Li: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Maya Izumoto:** Data curation. **Yide Wang:** Data curation. **Yoko Kato:** Data curation. **Yoshiko Iwatani:** Writing – review & editing, Supervision. **Ikuko Hirata:** Writing – original draft, Supervision. **Yoshifumi Mizuno:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Data curation. **Masaya Tachibana:** Writing – review & editing, Supervision, Resources. **Ikuko Mohri:** Supervision. **Kuriko Kagitani-Shimono:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Data availability

The data and codes supporting this article are available to interested researchers upon reasonable request from the corresponding author after approval from the Research Ethics Committee.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2024.120731.

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