Corpus Callosum Volumes in Toddlers With Autism Spectrum Disorders: Gender-Associated Differences and Clinical Correlations

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Abstract

Background: Gender differences in clinical features is a prominent feature of autism spectrum disorder (ASD), and the corpus callosum (CC) is the largest commissural tract connecting the left and right hemispheres associated with autism symptoms. This study aimed to analyze the relationship between gender-associated clinical features and CC size in children aged 2-4 years.

Methods: A prospective study of 100 children aged 2-4 years, including 50 cases with ASD (ASD group) and 50 cases with typically developing (TD group) who were matched with equivalent samples of ASD, were recruited with assessments of demographic data (gender, age, and body mass index [BMI]), clinical features (full-scale/verbal/performance IQ, ADOS, and ADI-R), and CC size measured by Structural Magnetic Resonance Imaging. SPSS version 22 was used to analyze the data.

Results: The mid-posterior CC (MPCC), anterior-middle CC (AMCC), and total CC (TCC) volumes in ASD were higher than that in TD, and the significance these sub-regions volumes between ASD-Females and ASD-Males was existed in ASD group (all $P < 0.05$). Analogously, the mean of verbal IQ score in ASD-Males was significantly higher than in ASD-Females, but the scores of ADOS communication (AC) and ADOS total (AT) were lower in ASD-Males (all $P < 0.05$). AC and AT scores were significantly and positively related to MPCC, AMCC and TCC volumes (all $P < 0.05$), but verbal IQ score was significantly and negatively associated with MPCC, AMCC and TCC volumes (all $P < 0.05$). In ASD-Males and -Females, both AC and AT scores increase with the change of MPCC, AMCC and TCC volumes, but VIQ decline.

Conclusion: The language ability, including communication and verbal IQ, of ASD aged 2-4 years old has gender differences, which may be related to the CC size, especially the MPCC and AMCC.

Background

Autism spectrum disorder (ASD) is characterized by impaired social interactions and communication skills, and are often accompanied by restricted interests and/or repetitive behaviors[1]. Despite the exact etiopathogenesis of idiopathic ASD has not been fully elucidated, recent evidences suggest an interaction between genetic liability and environmental influences in producing early alteration of brain development[2]. ASDs represent a substantial economic burden, mainly due to the provision of support to adults who cannot function independently, which results in higher health-care and school costs and loss of income for caregivers[3]. In 2009, the National Institutes of Health listed ASD as the second public enemy of health, after cancer. The incidence of ASD in China is about 1.53%, ranking first among children with mental disability[4, 5]. Interestingly, ASD is the preponderance of male cases. On average, the male to female ratio is estimated to be 4.3:1, This striking gender difference has aroused strong concerns among scholars who have made attempt to explore the pathogenesis of ASD based on it.

In recent decades, modern neuroimaging technologies have developed rapidly, and is widely used in the research field of brain function related to ASD. With the deepening of research, most scholars believed that ASD is mainly a structural and functional obstacle in a certain brain area, and they hope to achieve spatial positioning[6]. Structural Magnetic Resonance Imaging (sMRI) studies of ASD patients have consistently reported abnormalities in total brain volume as well as in grey and white matter volume of discrete brain

regions[7-9]. Specifically, the abnormally large brains frequently described in ASD toddlers can negatively impact on large-scale structural and functional cerebral connectivity. To date, the widely accepted theory for the pathogenesis of ASD is the imbalance between the long- and short-distance connection. Among long-distance white matter structures, the corpus callosum (CC) is the largest commissural tract connecting the left and right hemispheres and it is thought to be involved in the integration of neural information across distant brain regions. The CC has been considered to play a crucial role in the pathogenesis of ASD frequently, because problems with processing of multiple source of sensory information are common in ASD patients and are possible sustained by the specific combination of a local over-connectivity and a long distance under connectivity[10]. To explore the brain-behavior relationship, the possible correlation between CC volume and ASD clinical features has been investigated in some studies[11]. However, there have been few reports on gender differences in CC structures and their association with the core clinical phenotypes of the disorder. Furthermore, evidence regarding brain volume differences in older children and adolescents with ASD is mixed, although differences in brain volume may be smaller than in toddlerhood[12]. Considering that children younger than 2 years are undergoing myelination process, which may affect the accuracy of sMRI measurement. Therefore, it is meaningful and interesting to clarify the relationship among gender, clinical characteristics and CC size in children with ASD at early stage.

In this study, we used sMRI and a post-processing brain-segmentation software to measure the total and subdivided CC volumes in ASD toddlers aged 2 - 4 years. Our aim was to investigate the difference in CC size between males and females, and its correlation with the clinical features of ASD.

Methods

Ethical approval

This study was approved by the Research Ethics Committee of Children's Hospital of Chongqing Medical University (IRB number: [2018] Ethical Review [Research] No. [82]). All parents of subjects gave written informed consent after they had been informed of the possible risk and benefit in the research and assured of the security and privacy concerning the children’s medical records.

Participants

All participants were recruited at the child healthcare department of Children's Hospital of Chongqing Medical University, a tertiary hospital and National Children's Medical Center in China, from May 2018 to January 2020. ASD was rigorously diagnosed according to the DSM-5 criteria[13] or ICD-10 criteria[14], and confirmed by Autism Diagnostic Observation Schedule (ADOS)[15] and Autism Diagnostic Interview-Revised (ADI-R)[16] administrated by two independent expert psychologists. ASD patients were included if their age was between 2 and 4 years and their performance intelligence quotient (IQ) $\geq$ 50. Exclusion criteria included other neurological disorders, genetic conditions, structural brain abnormalities and the presence of any MRI contraindications (e.g. metal implants, braces, claustrophobia). Considering that demographic data (age, gender, and BMI) may influence the MRI acquisition parameters[17, 18], we used careful individual matching for demographic data between ASD and typically developing (TD) to overcome this limitation. The TD group was composed of healthy children aged 2 - 4 years, and the number was the same as the ASD group. The TD group was selected so as to meet the same

exclusionary criteria as the ASD patients. The resulting 14 females with ASD (ASD-Females) were individually matched for age and for BMI with 17 females with TD (TD-Females). Similarly, the 36 males with ASD (ASD-Males) were individually matched for age and for BMI with 33 males with TD (TD-Males).

Clinical features assessment

A standardized symptom evaluation were performed in ASD and TD patients through a variety of tests, depending on chronological age, productive language skills and functioning level. ADOS consists of four module: communication, social interaction, play and imagination, each containing a schedule of activities designed for children or adults at a particular developmental and language level, ranging from non-verbal to verbally fluent persons[19]. Considering the language ability of children aged 2-4, we performed two domains including social interaction (designed for pre-verbal children or children with only single words) and communication (children with consistent phrase speech), and calculate the combined social-communication score. ADI-R was used as a clinical diagnostic evaluation scale: the scoring standards and methods were divided into three subscales of social, language and stereotypes due to different items. Generally, they were scored in four levels from 0 to 3, and the score was calculated according to the corresponding rules, and the diagnosis was made according to the corresponding threshold score[20]. Participants received a standardized evaluation of cognitive abilities through a variety of tests, depending on chronological age, productive language skills and functioning level of subjects. WISC-IV was performed to assess the IQ including verbal and non-verbal subscales[21]. To standardize the data, IQ was prorated from verbal and performance subscales using an algorithm developed by Schoenberg et al[22] that produces an estimated IQ score highly correlated with a full-scale IQ (FSIQ) obtained by administering the complete test.

MRI data acquisition

Each subject's MR data were obtained by a 3 Tesla MR-scanner (Achieva, Philips, The Netherlands) with an 8-channel head coil. The child's head was fixed with a sponge cushion before scanning. Children who can cooperate to the MRI examination can be awake to complete accompanied by a guardian. While most of the children under the age of 4 need to be sedative, intravenous or chloral hydrate oral for sedation could be performed according to the guardian's choice . After the evaluation by a anesthesiologist, propofol could be given intravenously (induction dose: 2mg/kg, plus 1mg/kg if necessary). Oral sedatives should undergo sleep deprivation for a certain period of time. Oral 10% chloral hydrate 0.5ml/kg, with the maximum dose ≤10ml.

Each case underwent routine MR scan with the sequences including axial T1WI, T2W1, T2FLAIR and sagittal T2WI, to exclude obvious organic neurological disease. The parameters of the routine MRI sequences were the following: axial T1WI: inversion recovery sequence (IR), repetition time (TR),2000ms, echo time (TE), 20ms; Axial T2WI: turbo field echo sequence (TFE), TR, 3500ms, TE, 80ms; T2FLAIR sequence: TR, 8000ms,TE, 125ms; All axial scanning field of view (FOV): 230×191×143 (mm^3), slice thickness, 5mm, interval, 1mm, total of 20 layers. After routine MR scan, a sagittal three-dimensional SPGR sequence(3D-SPGR) was performed for The T1-weighted images were acquired using. The parameters of the sequence were the following: TR, 7.7 ms; TE, 3.8 ms; flip angle, 8°; FOV, 256×256; voxel size, 1mm×1mm×1mm; slice thickness, 1 mm; total time: 155 seconds.

MRI image analysis

Routine sequence images were analyzed and reported by an attending physician and confirmed by a professor from the radiology department. Post-processing of the original 3D-SPGR images were performed by a professional trained attending physician. The volumes of corpus callosum were calculated by using FREESURFER v6.0(http://surfer.nmr.mgh.harvard.ed u/). The CC were further divided into five anatomical sub-regions (ACC, AMCC, MCC, MPCC, and PCC) as shown in Figure 1. FREESURFER software is well-documented and freely for download. The technical details of these procedures were described in the publication by Fischl (2012)[23]. We processed each subject's MRI data by the steps of the Freesurfeer, with manual correction when needed. Then we got the volume of each subregion of CC, and total CC (TCC) volume was calculated as the sum of these five segment volumes for each study participant.

Statistical analysis

Statistical analysis was performed by using the Statistical Package for Social Sciences (SPSS) software. The normal distribution of the data was evaluated with the Shapiro-Wilk test, and all values with normal distribution were presented as Mean ± standard deviation (SD). The statistical analyses of the CC size were performed using the analysis of variance (ANOVA) test. The statistical analyses were univariate because each test was performed on a single variable compared between the groups. When the ANOVA tests were applied on correlated variables, such as the volume of CC sub-regions and ADOS sub-scores, the significance level was corrected for multiple comparisons using Monte Carlo simulations[24]. Categorical variables were presented as numbers and percentages, and Chi-square test was used in comparison of categorical data. The Pearson's correlation index was used to test linear relationships between the CC size and autistic symptoms. In statistical analysis, a $P<0.05$ was considered statistically significant.

Results

Demographic data

The demographic data of participants were shown in Table 1. In ASD group, the chronological age and BMI were 32.1±6.1 months, 21.0±5.0 kg/m^2, respectively. Among them, 14 cases (28%) were females, and 36 cases (72%) were males. Chronological age and BMI between different genders were not statistically significant ($P>0.05$) in both ASD and TD groups. Furthermore, there was no statistical difference in demographic data (gender, chronological age and BMI) between the two groups ($P>0.05$).

We evaluated cognitive profile in the ASD and TD groups based on gender differences. The mean of FSIQ, verbal IQ (VIQ) and performance IQ (PIQ) scores were significantly higher (FSIQ: 109.5 versus 100; VIQ: 107.9 versus 99.6; PIQ: 106.1 versus 93.0; $P < 0.05$ for all) in TD group than ASD group. The mean of VIQ score in ASD-Males were significantly higher (VIQ: 106.3 versus 90.2, $P < 0.05$) than in ASD-Females. However, there was no statistical difference in cognitive profile between TD-Males and TD-Females.

Table 1 Demographic characteristics of participants

Variables		Total (N=100)		ASD (N=50)		TD (N=50)		P_{Total}	P_{ASD}	P_{TD}
		ASD	TD	Males	Females	Males	Females			
Gender	n(%)	-	-	36 (72)	14 (28)	33 (66)	17 (34)	0.517	-	-
BMI (kg/m^2)	Mean ± SD	21.0 ± 5.0	21.1 ± 4.0	20.9 ± 5.5	21.5 ± 3.6	21.5 ± 4.6	21.4 ± 2,7	0.641	0.686	0.911
	Range	14.5 - 31.2	16.1 - 30.5	14.5 - 36.2	16.1 - 27.3	16.1 - 34.5	18.0 - 27.9			
Age (months)	Mean ± SD	32.1 ± 6.1	33.2 ± 5.7	32.4 ± 6.6	31.9 ± 4.7	32.6 ± 5.5	33.1 ± 6.0	0.414	0.450	0.698
	Range	24 – 47	25 - 45	24 - 49	25 - 39	25 - 45	27 - 43			
Cognitive variables										
FSIQ	Mean ± SD	100.0 ± 11.2	109.5 ± 5.9	97.3 ± 11.1	92.29 ± 9.9	109.5 ± 6.4	110.7 ± 4.3	0.000	0.150	0.536
	Range	74 - 121	97 - 119	77 - 121	76 - 104	97 - 121	99 - 116			
VIQ	Mean ± SD	99.6 ± 10.9	107.9 ± 6.5	106.3 ± 6.4	90.2 ± 8.7	107.7 ± 7.4	108.3 ± 4.8	0.000	0.000	0.754
	Range	78 - 118	96 - 122	83 - 118	78 - 106	96 - 122	101 - 116			
PIQ	Mean ± SD	93.0 ± 9.7	106.1 ± 4.4	96.4 ± 9.1	93.9 ± 11.2	105.6 ± 4.6	106.7 ± 3.1	0.000	0.426	0.480
	Range	74 - 113	97- 120	94 - 118	89 - 113	96 - 113	104 - 120			

ASD, autism spectrum disorder; TD, typically developing; SD, standard deviation ; BMI, body mass index; FSIQ, full - scale intelligence quotient; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient.

CC size

We calculated the CC size in children by using FREESURFER v6.0, and tried to investigate the differences in the volume of CC and its sub-regions between ASD and TD groups. A series of 2 × 2 ANCOVA analyses, with five sub-regions and TCC volumes as dependent variables, gender as fixed factors, and age and BMI as covariates revealed no significant effect of gender on all these measures or their interaction (all $P > 0.05$). No significant differences in PCC, MCC and ACC volumes ($P = 0.410$, $P= 0.926$ and $P = 0.909$, respectively) were observed between ASD and TD groups, but MPCC, AMCC and TCC volumes in ASD group was higher (MPCC: [0.39±0.07] cm^3 versus [0.31±0.03] cm^3; AMCC: [0.48 ± 0.09] cm3 versus [0.40 ± 0.07] cm3; TCC: [2.71 ± 0.28] cm^3 versus [2.52 ± 0.20] cm^3; $P < 0.05$ for all) than that in TD group (Table 2).

We compared the CC size between ASD and TD groups according to gender differences. As depicted in Figure 2, The MPCC, AMCC and TCC volumes of ASD-Females were significantly higher than that of ASD-Males and TD-Females ($P < 0.05$), but the difference of CC size between TD-Males and TD-Females was not statistically significant ($P > 0.05$). There was no statistically significant difference in ACC, MCC and PCC volumes among ASD-Female, ASD-Male, TD-Female, and TD-Male (all $P > 0.05$).

Table 2 CC size in ASD and TD groups (mean ± SD)

Variables	ASD (n=50)	TD (n=50)	*t*	P value
PCC	0.70 ± 0.10	0.68 ± 0.11	- 0.827	0.410
MPCC	0.39 ± 0.07	0.31 ± 0.03	- 6.889	0.000
MCC	0.41 ± 0.06	0.41 ± 0.04	- 0.093	0.926
ACC	0.71 ± 0.08	0.72 ± 0.09	- 0.114	0.909
AMCC	0.48 ± 0.09	0.40 ± 0.07	- 4.654	0.000
TCC	2.71 ± 0.28	2.52 ± 0.20	- 3.879	0.000

All values are in cubic centimeters and correspond to the sum of the corresponding values for the left and right hemisphere. PCC, posterior corpus callosum; MPCC, mid-posterior corpus callosum; MCC, middle corpus callosum; ACC, anterior corpus callosum; AMCC, anterior-middle corpus callosum; TCC, Total corpus callosum.

Autistic symptoms

The differences of autistic symptoms between genders in ASD were depicted in Table 3. ASD-Males and ASD-Females did not differ in severity of autism as measured with scores at the AS and ADI-R ($P = 0.092$ and $P=0.887$, respectively). However, there were gender differences in the scores of AT and AC (both $P < 0.05$), with lower scores in males than in females.

Table 3 Relationship between gender differences and autistic symptoms in ASD group

Variables		Males (n=36)	Females (n=14)	*t*	P value
AS	Mean ± SD	6.5 ± 1.4	7.2 ± 1.1	1.721	0.092
	Range	5 – 9	7 - 9		
AC	Mean ± SD	5.9 ± 1.6	7.5 ± 1.0	3.379	0.000
	Range	4 – 9	7 - 9		
AT	Mean ± SD	12.4 ± 2.5	14.7 ± 1.9	3.029	0.004
	Range	8 – 18	11 - 18		
ADI - R	Mean ± SD	2.4 ± 0.7	2.4 ± 0.7	0.143	0.887
	Range	1 – 3	1 - 3		

ADOS,Autism Diagnostic Observation Schedule; AS, ADOS social; AC, ADOS communication; AT, ADOS total; ADI - R, Autism Diagnostic Interview-Revised; SD, standard deviation.

Correlation between the volumes of CC and clinical features

The severity of clinical features of ASD was judged according to the scores of clinical assessment scales including AC, AS, AT, ADI-R, VIQ, PIQ and FSIQ. Table 4 showed the correlation between the clinical features and CC size. There were significant and positive correlations between AC score and MPCC volume ($r = 0.693$; $n = 50$; $P < 0.01$), as well as among AC score and ACC, AMCC, TCC volumes ($r = 0.412$, 0.625 and 0.859, respectively; all $P < 0.01$), with higher MPCC, ACC, AMCC and TCC volume being associated with more serious symptom levels. Furthermore, the scores of AS and AT were also positively related to MPCC, AMCC and TCC volumes (all $P < 0.01$). In terms of IQ, VIQ score was significantly and negatively associated with MPCC, AMCC and TCC volumes ($r = -0.576$, -0.471 and -0.635, respectively; all $P < 0.01$). FSIQ score was also significantly and negatively associated with ACC, AMCC, TCC volumes ($r = -0.494$, -0.525 and -0.679, respectively; all $P < 0.01$).

According to the above results, we could preliminarily judge that the gender differences of AC, AT and VIQ in ASD may be related to MPCC, AMCC and TCC volumes. Therefore, we observed divergent effects of MPCC, AMCC and TCC volumes on some clinical features (AC, AT and VIQ) in ASD by gender grouping, as seen in Figure 3. The effects of MPCC, AMCC and TCC volumes were more homogenous on AC, AT and VIQ. In males and females, both AC and AT scores increase with the change of MPCC, AMCC and TCC volumes, but VIQ decline.

Table 4 Correlations between the CC size and clinical assessment scale in ASD group

	AC	AS	AT	ADI - R	VIQ	PIQ	FSIQ
PCC	0.191	0.081	0.209	0.041	-0.176	-0.132	-0.415**
MPCC	0.673**	0.466**	0.656**	0.198	-0.576**	-0.038	-0.494**
MCC	0.045	0.086	0.048	0.147	-0.010	0.021	-0.175
ACC	0.412**	0.160	0.340*	0.059	-0.252	0.006	-0.290*
AMCC	0.625**	0.448**	0.632**	0.133	-0.471**	-0.023	-0.525**
TCC	0.859**	0.629**	0.858**	0.366**	-0.635**	0.048	-0.679**

All values in the table are ‘r’, *P < 0.05, **P < 0.01.

Discussion

To our knowledge, this study is the first of its kind to examine sex differences in CC anatomy in ASD aged 2-4 years. In this study, increases in TCC volume and several of its subdivisions were observed in ASD patients supporting that autism is a disorder of connectivity involving inter- and intra-hemispheric communications with possible alterations of intra-cortical connections. We also found that the MPCC, AMCC and TCC volumes were significantly higher in ASD-Females than in ASD-Males. For clinical features, AC and AT in ASD-Females were

higher than in ASD-Males, but the VIQ was lower than in ASD-Males. In ASD group, AC and AT increase with the change of MPCC, AMCC and TCC volumes, but VIQ decline. Based on these results, we can preliminarily conclude that ASD-Females have more severe symptoms than ASD-Males, which may be related to the higher MPCC, AMCC and TCC volumes.

The CC is the largest commissural white matter pathway connecting the left and right hemispheres with more than 300 million fibers, and plays a crucial role in communicating perceptual, cognitive, learned and volitional information and its alterations might affect the interhemispheric integration of these functions[25]. Several investigations have reported the CC regional alterations in ASD, but the results were controversial. To date, most studies supported the reductions of TCC and several of its subdivisions (ACC, PCC, or MCC)[26-28] in ASD, While some researchers presented the contrary results. In a recent study, Giuliano et al[10] found no significant volumetric differences in TCC and in its sub-regions between ASD and TD groups, but the TCC volume in younger ASD-Males subjects was found significantly larger with respect to matched TD. And Elia et al[29] also held the different conclusions that there was no significant differences in TCC volume between ASD and TD groups. Another research [30]also found an increase in CC volume at 6 and 12 months of age in infants who later developed ASD, relative to age-matching TD infants, most likely due to study design and the failure to control for known confounding factors such as gender and age[26]. The discrepancies observed in CC size studies in ASD could be most likely due to the study design and the failure to control for known confounding factors such as gender and age[26]. Shiino et al[31] reported that the TCC volume in females were bigger than males in adults. In our study, we investigated the CC volumes in a group of toddlers, and focused on the differences between males and females. The results showed that the MPCC, AMCC and TCC volumes increased in ASD. In addition, The MPCC, AMCC and TCC volumes of ASD-Females were significantly higher than that of ASD-Males, while the difference was not found between TD-Males and TD-Females. Our results corresponded to the theory of atypical CC growth trajectory in ASD, which is characterized by a greater development in early ages, followed by a slower rate of growth in subsequent ages, resulting in smaller CC in adolescent and adult patients. Although the real physiological foundation of CC size increase in younger ASD patients has not been made clear, a compensatory mechanism was generally accepted. That is, the CC size increases to compensate for the decreased functional interhemispheric connection. This could also explain the gender difference of CC size in this study, because the larger CC size was parallel with the more clinical severity in ASD-Females compared with ASD-Males.

As sex is known to affect human brain development, disorders that are likely to have a genetic or neurodevelopmental origin may affect the male brain differently from the female brain. ASD is at least three times more prevalent in males than in females, and biological sex may be an important source of heterogeneity in ASD presentation[32]. In terms of clinical features and cognitive abilities, findings have been inconsistent. A meta-analysis suggested lower levels of repetitive and restricted behaviors and interests in females and comparable levels of social communication difficulties in males and females (age range: toddler to adult), while gender difference in the severity of repetitive and stereotyped impairments was seen from 6 years onwards [33]. Frazier et al[34] reported that females with ASD had greater social communication impairment, lower levels of restricted interests, lower cognitive ability, weaker adaptive skills, and greater externalizing problems relative to males (age range: 4-18 years). Another study examined sex differences in ASD symptom among toddlers (18-35 months) and preschoolers (36-72 months), and showed that females diagnosed with

ASD displayed greater social communication deficits within the toddler group, but these differences were not corroborated within the preschool group. In our study, we found that males had lower AT and AC scores than females in severity of ASD as measured by ADOS, but this difference did not appear in ADI-R (age range: 2-4 years). We also investigated the cognitive abilities in ASD of different genders, and found that the VIQ in males were significantly higher than in the females. The association with IQ has long been taken as having etiological implications, such as a higher liability threshold for females to develop autism. IQ reductions mediated greater social impairment and reduced adaptive behavior in females with ASD, but did not mediate reductions in restricted interests or increases in irritability[34]. In many samples, lower IQ has been modestly but significantly associated with higher levels of ASD symptom severity[35]. Therefore, variation in cognitive ability and age may be the potential source of heterogeneity in individuals with ASD[36].

Previous studies in ASD patients have revealed a negative correlation between CC thickness and IQ in the pediatric population, it revealed a reduced CC size may be linked to a lower IQ[37]. While another studies revealed a positive correlation in adult samples[10], suggesting the relationship between CC morphology and clinical features changes during brain maturation. In our study, the significant and positive correlations were found between some domains of the ADOS (AS, AC, and AT) and MPCC, AMCC, and TCC volumes. The higher MPCC, AMCC and TCC volumes were associated with more serious symptom levels. In terms of IQ, VIQ score was significantly, negatively associated with MPCC, AMCC and TCC volumes. This result suggested that communication and VIQ abilities were closely related to MPCC and AMCC volumes. Furthermore, we also found that the effects of the MPCC, AMCC and TCC volumes were more homogenous on AC, AT and VIQ scores, both AC and AT scores increase with the change of MPCC, AMCC and TCC volumes, but VIQ decline in males and females. These results suggested that the CC and its sub-regions volumes measurement might be helpful for early diagnosis and evaluation of ASD.

The present study was limited by its small sample size, and replication studies with larger samples are warranted to confirm these findings. In addition, the use of subjective testing for symptoms, such as ADOS, ADI-R and WISC-IV, to evaluate clinical features does not provide accurate assessment of these abnormalities and objective tools or laboratory tests would allow more specific and precise measurements of cognitive and sensory deficits. Furthermore, this study was based on a cross-sectional design, and the developmental trend of CC size in ASD could not be obtained. A longitudinal follow-up research is needed to provide more imaging information of CC and their correlations with the clinical features, which could shed light on the anatomical and physiological foundations of ASD.

Conclusion

We conducted the assessments of CC sub-regions volumes and clinical features in toddlers with ASD controls. The MPCC, AMCC and TCC volumes were higher in ASD than in TD. ASD-Females and ASD-Males, which may cause differences in the clinical features between males and females. Compared with ASD-Males, ASD-Females had higher MPCC, AMCC and TCC volumes, which were correlated with lower communication and VIQ abilities. These findings systematically summarized the relationship among CC size, gender, and clinical feature in children aged 2-4 years with ASD, supporting the hypothesis of impaired interhemispheric connectivity. Future longitudinal studies that combine multimodal imaging techniques (e.g. structural MRI, diffusion weighted imaging, resting-state functional MRI) with genetic and molecular testing may help to

elucidate CC neuroanatomical underpinnings, and are conducive to early diagnosis and prompt interference for ASD patient.

Abbreviations

ASD: autism spectrum disorder; CC: corpus callosum; ACC: anterior corpus callosum; AMCC: mid-anterior corpus callosum; MCC: middle corpus callosum; MPCC: mid-posterior corpus callosum: PCC: posterior corpus callosum; TCC: total corpus callosum.

Declarations

Ethics approval and consent to participate

All procedures performed in this study involving human participants were in accordance with the relevant guidelines and regulations approved by the Institutional Research Ethics Board of Chongqing Children's Hospital (IRB No. [2018] Ethical Review [Research] No. [82]) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to publication

Not applicable

Availability of data and material

The datasets generated during and analysed during the current study are not publicly available due to that we are conducting more in-depth analysis of other aspects of the data but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Yun Zhang drafted the manuscript, Yun Zhang, Ke Zhang and Cui Song collected the data, Bin Qin and Longlun Wang analyzed the data, Jie Chen, Jinhua Cai and Tingyu Li critically reviewed the manuscript. All authors approved the final manuscript as submitted.

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Figures

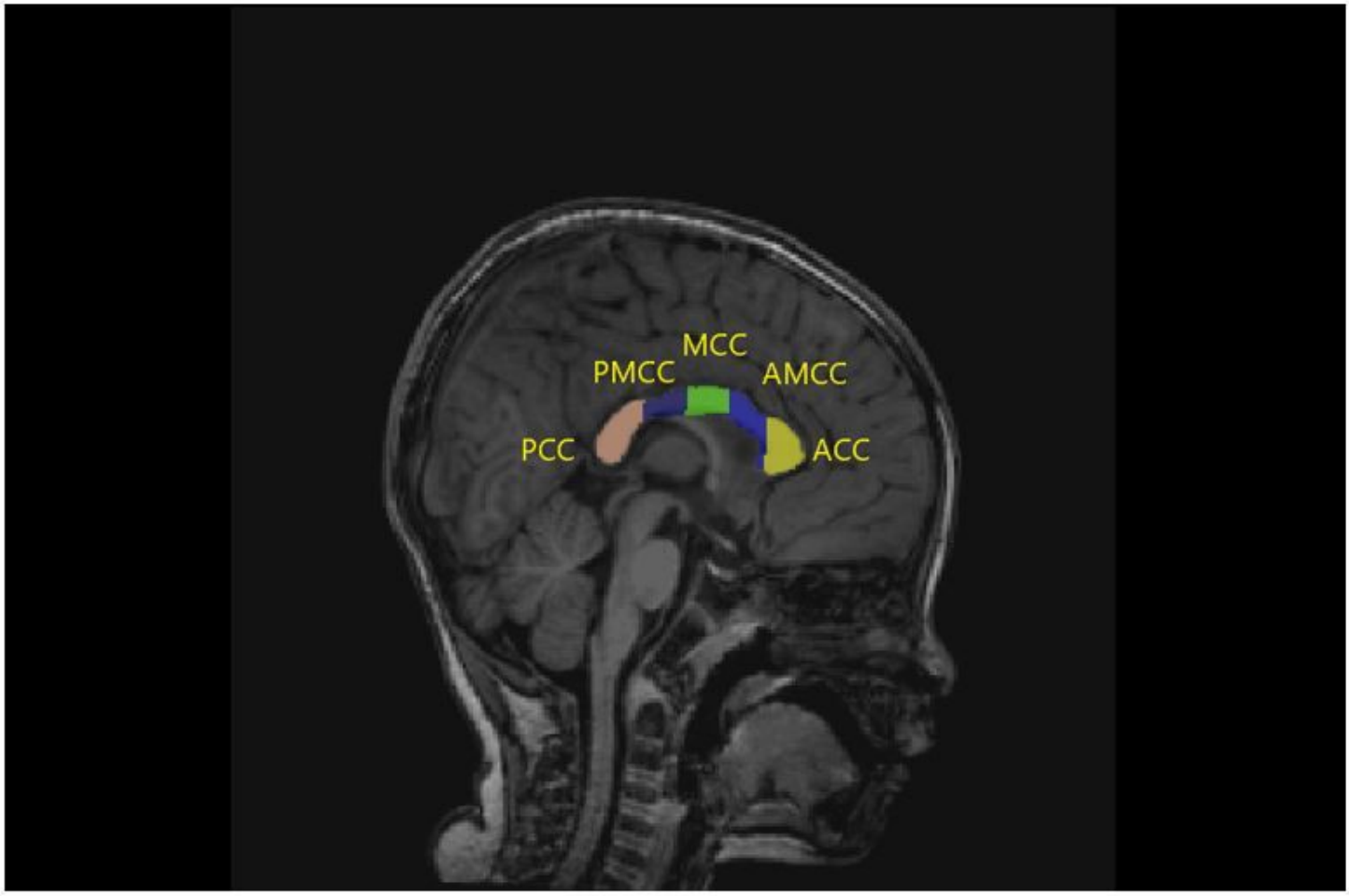
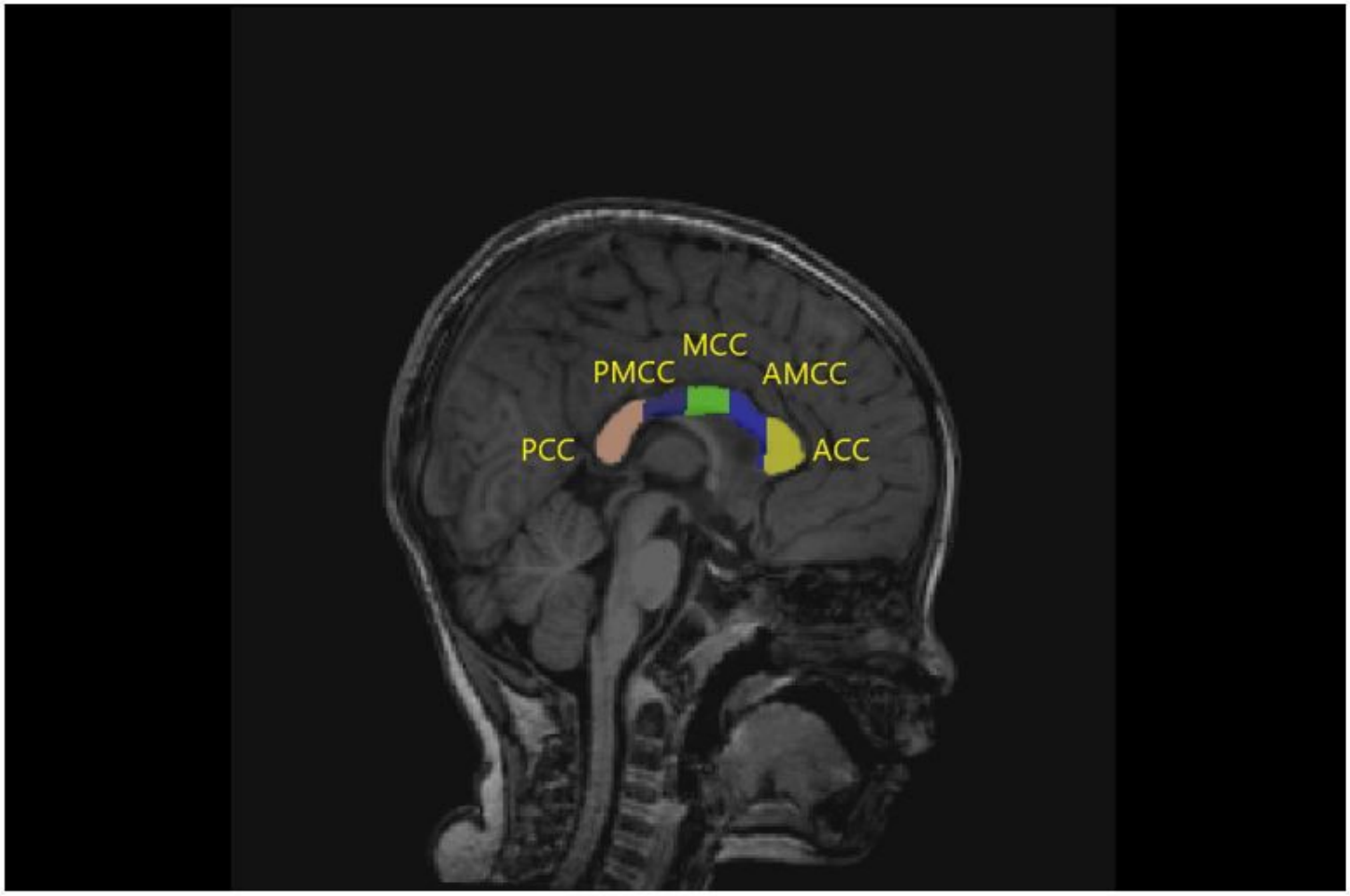


Figure 1

Sub-regions division of the CC. According to the Freesurfer suite, the CC was divided into five sub-regions in a mid-sagittal slice. PCC, posterior corpus callosum; MPCC, mid-posterior corpus callosum; MCC, middle corpus callosum; ACC, anterior corpus callosum; AMCC, anterior-middle corpus callosum; TCC, total corpus callosum.



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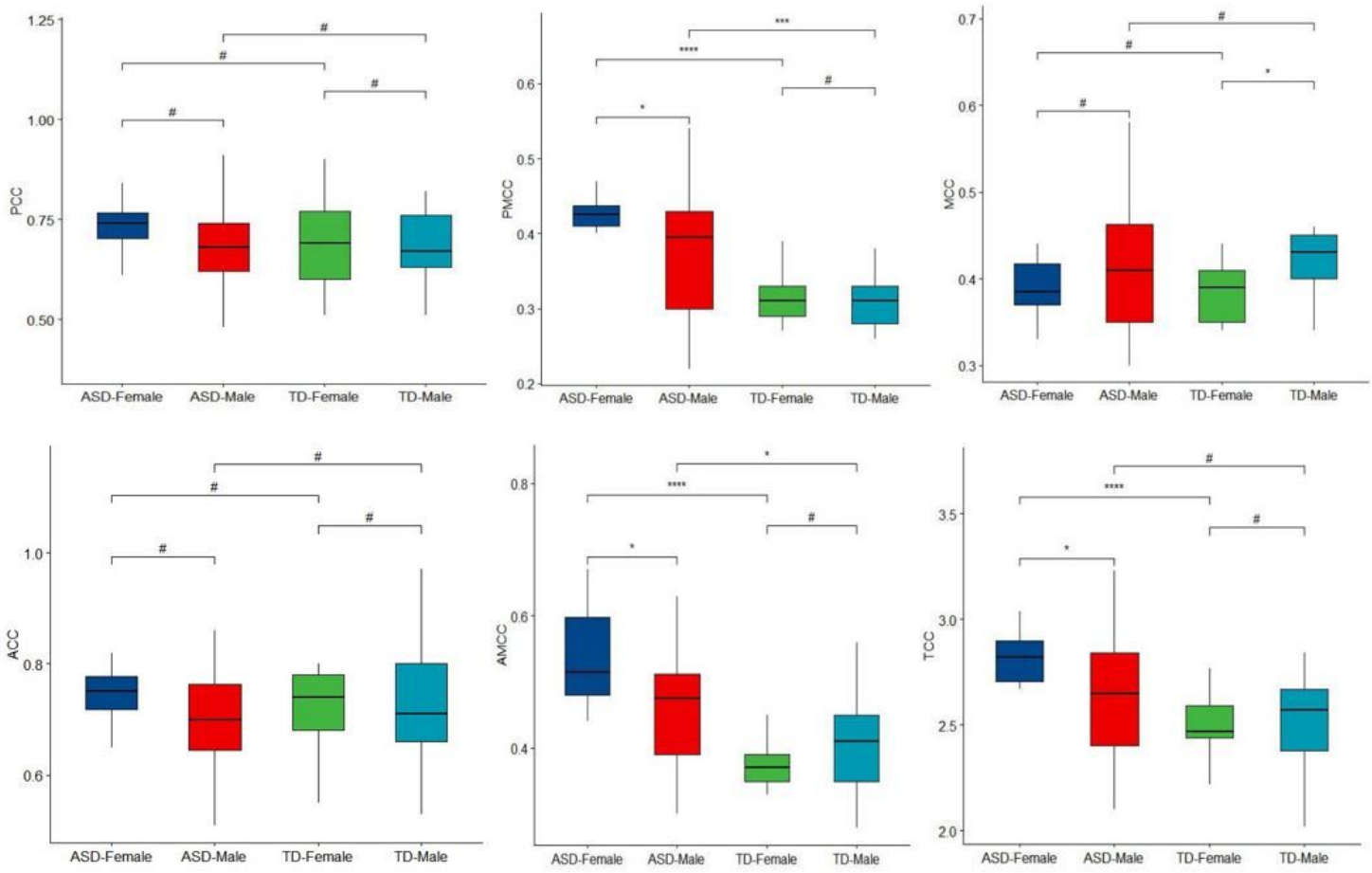
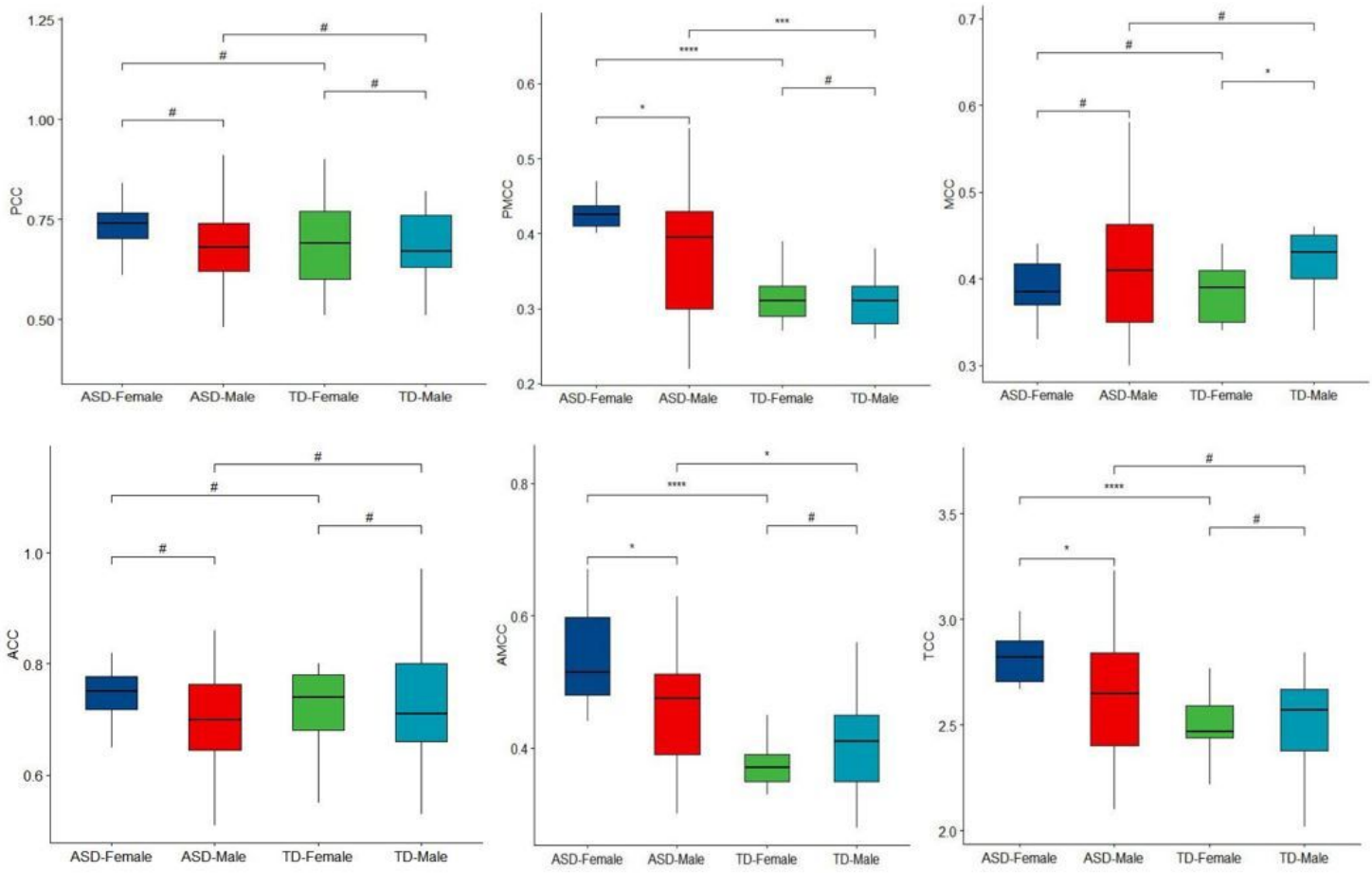


Figure 2

CC size between males and females in ASD and TD groups. For the ANCOVA two-by-two analyses, the following P values are depicted: *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001, #P > 0.05. In corpus callosum, comparative analysis showed a relative increase in the volumes of MPCC, AMCC and TCC in females compared to males.



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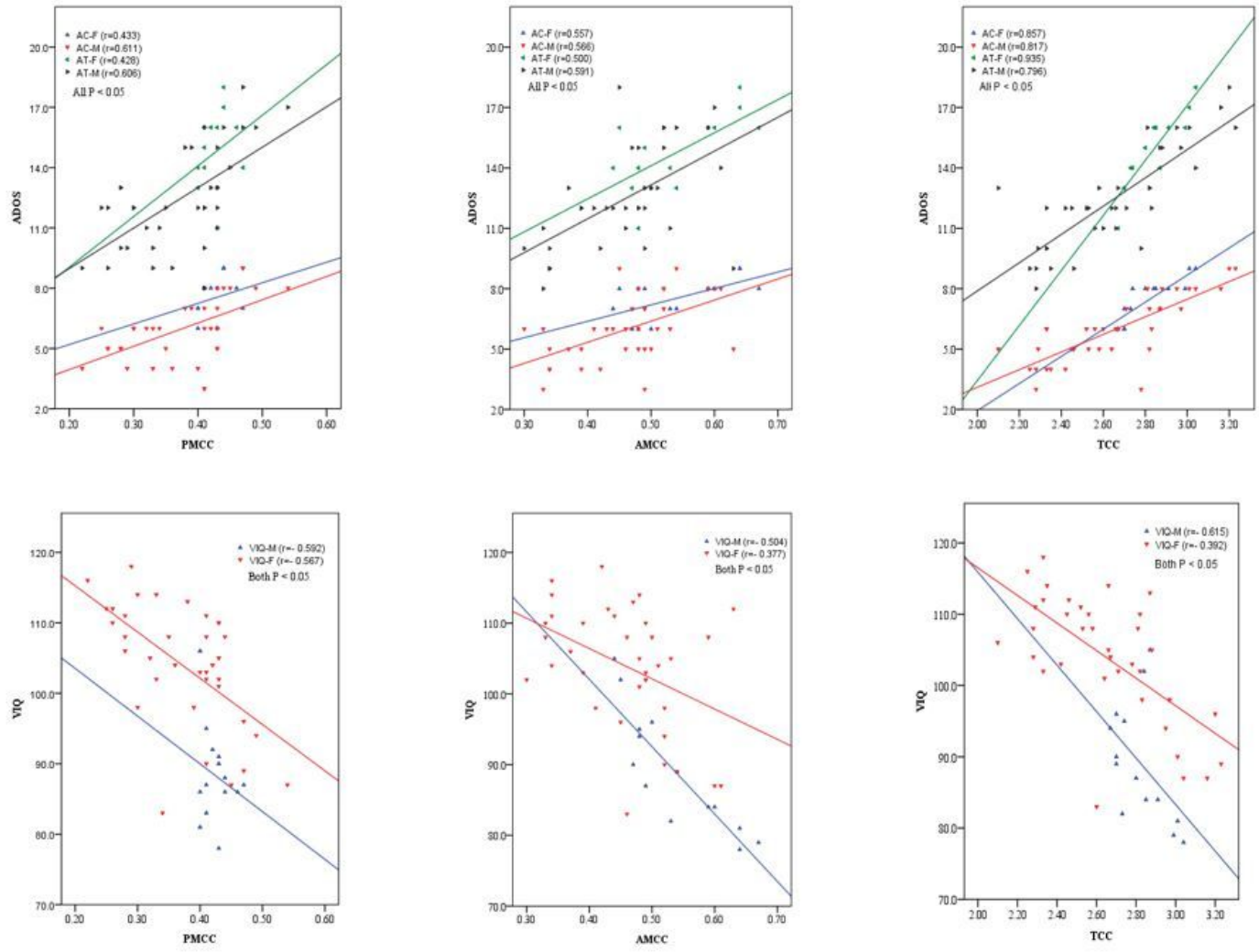
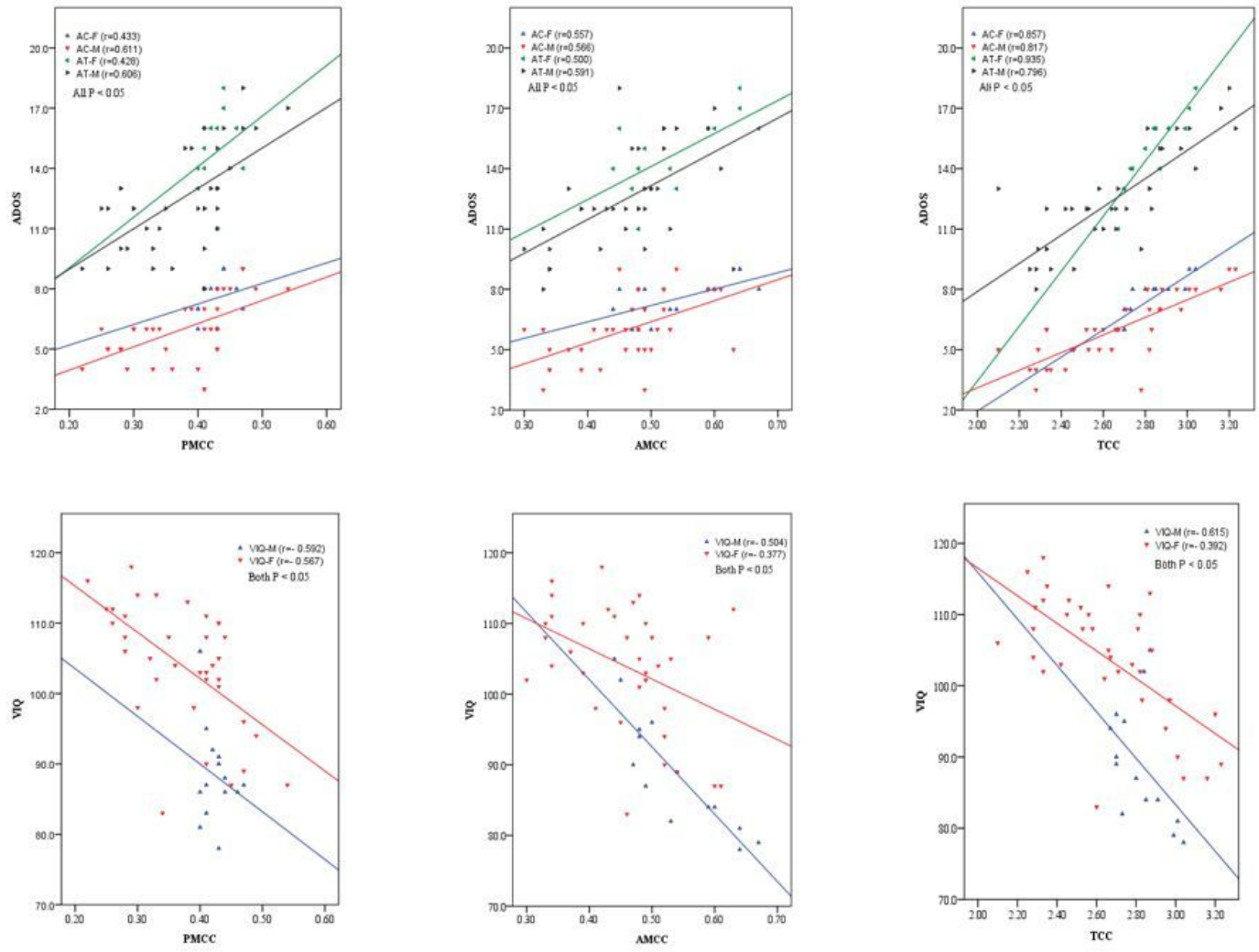


Figure 3

Correlations between clinical features (AC, AT and VIQ) and the partial CC size (MPCC, AMCC and TCC) based on gender division. Both AC and AT increase with MPCC, AMCC and TCC, but VIQ decline, with similar trends in ASD-Males and ASD-Females. AC-F, ADOS communication of females; AC-M, ADOS communication of males;AT-F, ADOS total of females; AT-M, ADOS total of males; VIQ-M, verbal IQ of males; VIQ-F, verbal IQ of females.



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