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Research Article

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Abnormal functional connectivity of theory of mind and mirror neuron system is associated with social deficits in autism spectrum disorder

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Abstract: Background: Theory of mind (ToM) and the mirror neuron system (MNS) have been demonstrated to be associated with social communication deficits in autism spectrum disorder (ASD). Although previous studies have investigated the functional connectivity (FC) of the two systems, few studies have systematically explored both the within- and between-network FC and the seed-based whole-brain FC of the two networks underlying the neuromechanism of the social deficit in ASD. The current study aims to investigate the abnormalities of the FC of ToM and MNS and their association with the behavioral indicators of ASD with a large-scale multi-site dataset. Methods: A total of 646 participants (298 with ASD and 348 typically developing (TD) controls) from the Autism Brain Imaging Data Exchange I were used in this study. Four ToM seeds and five MNS seeds were determined based on previous meta-analyses for the within- and between-network FC and seed-based whole-brain FC analysis. We employed the two-sample *t*-test to derive aberrant FCs and subsequently assessed their correlation with clinical measures using partial Pearson's correlation. Results: For the seed-based whole-brain analysis, compared with TD, we found that ToM and MNS showed a mixed abnormal FC pattern of both hypo- and hyper-connectivity in ASD. Specifically, hypo- and hyper-connectivity of the ToM were associated with social symptoms severity. Hyper-connectivity of the MNS showed a positive correlation with social symptoms severity. For the within- and between-network analysis, we observed atypically increased FC between the precuneus and the left the inferior parietal lobule, which was associated with social deficits in ASD. Conclusions: Our findings highlight the aberrant FC of ToM and MNS in ASD, which provides insights into the neural mechanisms underlying social communication deficits in ASD and can contribute to the development of effective interventions for ASD.

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Key words: Autism spectrum disorder; Social brain; Theory of mind; Mirror neuron system; Functional connectivity

1 Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social communication and interaction, as well as restricted and repetitive behaviors and interests (Battle, 2013). Social deficits include critical features such as impaired eye contact, limited social or emotional reciprocity, difficulties in emotional interactions, delayed expressive language, and challenges in non-verbal behaviors and

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forming peer relationships (Hobson and Meyer, 2005; 2013). Although the social deficit symptoms are well-documented, the biological mechanisms and etiology of social communication deficits in ASD are far from clear.

The social cognitive abilities, ranging from recognizing facial expressions and imitation to grasping theory of mind (ToM) and engaging in joint attention (Soares et al., 2023), rely on a network of brain regions commonly known as the "social brain" (Muller and Fishman, 2018). The ToM network is associated with the ability to attribute mental states such as beliefs, intentions, desires, and emotions to oneself and other people (Frith and Frith, 2006), which is critical for successfully interacting with others and predicting their actions. The ToM hypothesis proposes that individuals with ASD are unable to understand the mental states of others (Baron-Cohen, 1988; Baron-Cohen et al., 1994; Baron-Cohen, 2004). Previous research has shown abnormal activation of brain regions in individuals with ASD when performing ToM tasks (such as graphic and comic reasoning tasks) (Kana et al., 2009; Kana et al., 2014). Additionally, resting-state studies have revealed abnormalities in the ToM network in individuals with ASD (Assaf et al., 2010; Weng et al., 2010; Washington et al., 2014; Cheng et al., 2015). Mirror neurons are a class of neurons located within the premotor and parietal cortices (Rizzolatti and Craighero, 2004) that are activated during action observation, motor imagery, execution, and imitation (Reynolds et al., 2015). Past research indicates that ToM and the mirror neuron system (MNS) are two distinct systems in terms of both structure and function (Van Overwalle and Baetens, 2009). ToM is primarily composed of the temporoparietal junction (TPJ), posterior cingulate cortex (PCC)/precuneus (PC), and medial prefrontal cortex (mPFC) (Schurz et al., 2014; Arioli et al., 2021), while the MNS consists mainly of the inferior parietal lobule (IPL), inferior parietal lobule (IFG), and premotor cortex (PMC) (Rizzolatti and Craighero, 2004; Rizzolatti and Fabbri-Destro, 2010). Some studies propose a collaborative role, suggesting that MNS, responsible for processing lower-level information (such as action-related visual information), collaborates with ToM, which is involved in higher-level mental state inferences (Van Overwalle and Baetens, 2009; Becchio et al., 2012; Van Veluw and Chance, 2014). In 2000, Braga and Ramachandran (Brang and Ramachandran, 2010) proposed the mirror neuron theory of ASD. It has been suggested that a dysfunctional MNS might underlie the observed weaknesses in imitation performance, poor ToM skills, and impaired social cognition in autism (Williams et al., 2001).

However, attributing ASD solely to disruptions in the MNS has been considered overly hasty by some researchers. Recent research on ASD has proposed a disruption in the chain from regions responsible for lower-order information processing to those responsible for higher-order information processing (Hong et al., 2019; Todorova et al., 2019; Ilioska et al., 2023), which is consistent with previous evidence suggesting abnormal cooperation between the MNS and ToM networks. In tasks involving action observation and inference, abnormalities in MNS activation and ToM–MNS functional connectivity (FC) were observed in ASD. For instance, Libero et al.'s study found increased activation in the MNS during intention inference and irrational action judgment (Libero et al., 2014). Using a similar task paradigm, Seghatol-Eslami et al. discovered increased FC within the ToM network and between ToM and MNS networks during judgments of action rationality (Seghatol-Eslami et al., 2020). Similarly, in studies conducted by Cole et al. using video-based tasks related to intention and behavioral judgments, ASD individuals exhibited greater activation in both ToM and MNS, while FC between mPFC and MNS decreased during intention judgments (Cole et al., 2019). In a picture cartoon attribution task, Kana et al. found reduced activation and FC in both ToM and MNS during intention attribution in ASD individuals (Kana, et al., 2014). In summary, ASD shows abnormal MNS activation and disrupted ToM-MNS FC in tasks involving intention inference and irrational action. Therefore, there is a possibility of a transition barrier from MNS to ToM in ASD, while typically developing individuals demonstrate a normal transition (Van Overwalle and Baetens, 2009).

The ToM and MNS are two subnetworks of the social brain, and task-based functional magnetic resonance imaging (fMRI) investigations have consistently shown concurrent activation of both the MNS and ToM networks during cognitive tasks of a mental nature (Libero, et al., 2014; Cole, et al., 2019). ToM and MNS are related to the social skills essential for understanding the world and interacting with others (Molenberghs et al.,

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2012; Van Veluw and Chance, 2014) and have the potential to explain the social deficits seen in ASD. In detail, the ToM and MNS networks have been found to exhibit functional abnormalities (Cheng, et al., 2015; Yang and Hofmann, 2016; Müller and Fishman, 2018; Li et al., 2019), which are associated with social impairments in ASD (Li, et al., 2019; Chan and Han, 2020; Paul et al., 2021). Some studies found that the FC between the PCC/PC and anterior cingulate cortex (ACC)/mPFC was reduced in ASD (Assaf, et al., 2010; Washington, et al., 2014; Yerys et al., 2015). Some aggregated results have been obtained for MNS, such as finding that the intra-network FC is decreased (Li, et al., 2019) and the extra-network FC is increased (Fishman et al., 2015) in ASD. Moreover, resting-state fMRI (RS-fMRI) studies have revealed hyperconnectivity between the right IPL and PCC in individuals with ASD (Delbruck et al., 2019). Additionally, excessive crosstalk between the MNS and ToM networks was detected in ASD (Fishman et al., 2014). Although the interaction between the ToM and MNS has been well documented (Gallese and Goldman, 1998; De Lange et al., 2008; Liew et al., 2011; Becchio, et al., 2012) in ASD (Rizzolatti and Fabbri-Destro, 2010), few studies have systematically explored both the within- and between-network FC and the seed-based whole-brain FC of the two networks. Furthermore, the sample sizes of previous studies were small, making the findings prone to sample bias (Lombardo et al., 2019). Therefore, it is necessary to use a large sample to systematically investigate the whole-brain FC and the within- and between-network FC of these two networks in ASD.

In the current study, we utilized a large dataset from the Autism Brain Imaging Data Exchange (ABIDE), a collaborative project that aims to accelerate progress in understanding ASD by pooling and sharing neuroimaging data across multiple sites (Di Martino et al., 2014). ABIDE has considerable statistical advantages over large numbers of small sample studies and contributes significantly to the exploration of key changes in brain function (Marek et al., 2022). We aim to investigate the abnormal FC patterns of ToM and MNS, and then explore the relationships between abnormal FCs and the behavioral indicators of ASD using ABIDE. Specifically, we examined the following: 1) the abnormalities of the within- and between-network connectivity of ToM and MNS; 2) the abnormalities of the whole-brain FC of each network hub; and 3) the relationships between abnormal FC and clinical symptoms measured with three scales (i.e., the Autism Diagnostic Observation Schedule (ADOS), the Social Communication Questionnaire (SCQ), and the Social Responsiveness Scale (SRS)). These findings may provide a more comprehensive understanding of the biological mechanisms of the social cognitive difficulties in ASD and contribute to developing more effective interventions for ASD.

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2 Materials and methods

2.1 Participants

The data used in the present study were sourced from the initial ABIDE I database (http://fcon_1000.projects.nitrc.org/indi/abide/). This database encompasses data from 17 international sites, involving a total of 1112 participants whose ages range from 7 to 64 years, with a median age of 14.7 years. The participant group consisted of 539 individuals with a diagnosis of ASD and 573 typically developing controls (TDs). Comprehensive information regarding diagnostic criteria, informed consent procedures, and site-specific protocols can be accessed on the website. For our study, we included 646 participants, consisting of 298 with ASD and 348 TDs, gathered from 14 different sites. The specific exclusion criteria for the participants, which were consistent with those detailed in our previously published work (Jin et al., 2023) and can also be referred to in the participant exclusion process flowchart (Fig. S1), were as follows: 1) absence of functional or structural images; 2) lack of handedness information; 3) absence of a full-scale Intelligence Quotient (FIQ) score or a FIQ score below 70, as indicated by Floris et al. (Floris et al., 2021); 4) utilization of different scanning parameters (such as eyes open or closed, repetition time, total time points, slice number, and image matrix size) compared to other participants at the same acquisition site; 5) identification of severe artifacts or signal loss in fMRI data upon visual inspection conducted by two authors; 6) head motion exceeding 3 mm or 3°;

7) subpar spatial normalization, as determined by visual inspection conducted by two authors; 8) scanning coverage of less than 90% of the entire brain mask. Additionally, several participants were excluded to ensure the matching of ASD and TD groups across different sites in terms of sex ($p > 0.05$, chi-square test), handedness ($p > 0.05$, chi-square test), and age ($p > 0.05$, two-sample t-test). Furthermore, the OHSU site was excluded from the study due to a scanning duration of less than 5 minutes, as reported by Van Dijk et al. (Van Dijk et al., 2010). Additionally, other sites with fewer than 20 participants were also excluded, including CAL TECH, CMU_a, CMU_b, MAX_MUN_a, MAX_MUN_b, MAX_MUN_c, MAX_MUN_d, SBL, and UCLA_2. Further details regarding the demographic and clinical characteristics of the included participants can be found in Table 1.

2.2 Data preprocessing

The data preprocessing procedures were executed with the utilization of two software tools: Data Processing and Analysis for Brain Imaging (DPABI) version 5.1 (Yan et al., 2016), accessible at http://rfmri.org/dpabi, and Statistical Parametric Mapping (SPM) version 12, accessible at https://www.fil.ion.ucl.ac.uk/spm/software/spm12/. The preprocessing pipeline encompassed the following essential steps: 1) exclusion of the initial 10 time points; 2) correction for slice timing discrepancies; 3) rectification of head motion artifacts; 4) standardization of spatial coordinates through the forward transformation field derived from the unified segmentation of structural images, followed by resampling to a voxel size of $3 \times 3 \times 3$ mm^3; 5) application of spatial smoothing employing a three-dimensional isotropic Gaussian kernel with a full-width-at-half-maximum of 6 mm; 6) elimination of linear trends from the data; 7) removal of nuisance covariates, including head motion covariates based on the Friston 24-parameter model, signals from white matter, cerebrospinal fluid, and the global mean time series; 8) application of band-pass filtering in the frequency range of 0.01–0.08 Hz. The data preprocessing process aligns seamlessly with our earlier study (Jin, et al., 2023), and these meticulous preprocessing steps were rigorously undertaken to guarantee the data's quality and reliability for subsequent analyses.

2.3 Hub selection of ToM and MNS

Various studies have consistently identified key regions involved in ToM and MNS. The ToM system typically encompasses the mPFC, PC, and TPJ (Van Overwalle, 2009; Schurz, et al., 2014), and the MNS includes regions such as the supplementary motor area (SMA), IFG, and IPL (Iacoboni and Dapretto, 2006; Yang and Hofmann, 2016; Chan and Han, 2020). Thus, we determined four seeds in ToM and five seeds in MNS (Fig. 1). For the ToM network, we performed FC analyses using seeds positioned in the bilateral TPJ (left: [-53, -59, 20], right: [56, -56, 18]), the right PC [4, -55, 34], and the left mPFC [-1, 56, 24]. These coordinates were based on a prior meta-analysis (Schurz, et al., 2014), which analyzed 757 activation foci reported from 73 studies that tested 1241 participants. The MNS seeds included bilateral IFG (left: [-48, 28, -4], right: [48, 28, -4]), bilateral IPL (left: [-52, -40, 40], right: [45, -48, 54]), and left SMA [-4, 8, 54]. MNS seeds were labeled based on previous fMRI studies (Spunt et al., 2011; Libero, et al., 2014; Cole, et al., 2019) and meta-analyses (Yang and Hofmann, 2016; Chan and Han, 2020). Each region of interest (ROI) was defined as a 6 mm radius sphere centered at coordinates above the Montreal Neurology Institute (MNI), and the averaged time series of all voxels within the ROI was used for further analysis.

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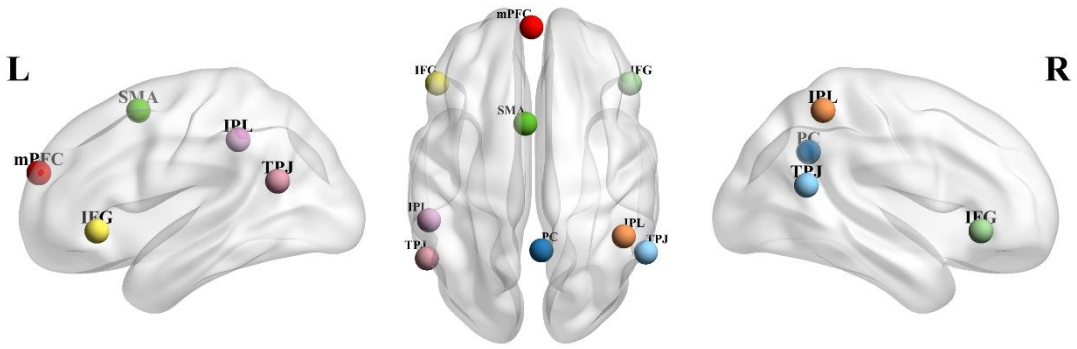

Fig. 1 Hubs of ToM and MNS.

mPFC, medial prefrontal cortex; SMA, supplementary motor area; IFG, inferior frontal gyrus; IPL, inferior parietal lobules; TPJ, temporoparietal junction; PC, precuneus; L, left; R, right. The glass brains were generated using BrainNet Viewer (http://www.nitrc.org/projects/bnv/).

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2.4 Whole-brain functional connectivity

We calculated Pearson's correlation coefficients between the seeds of ToM and MNS and all the other voxels across the brain. To ensure normality, the resultant correlation coefficients in the FC map were converted to z-scores using Fisher *r*-to-*z* transformation.

2.5 Within- and between-network functional connectivity

To measure FC within and between ToM and MNS networks, a Pearson's correlation analysis was performed between each pair of ROIs for each subject. This generated a 9 × 9 correlation matrix. Prior to the statistical analysis, correlation coefficients were transformed with Fisher *r*-to-*z* transformation. The z-scores represented FCs between ROIs.

2.6 Multi-site effect correction

To mitigate the variability arising from various sources, such as different sites, collection times, and data acquisition parameters within the ABIDE I dataset, we utilized ComBat (Fortin et al., 2017) in MATLAB version R2022a. ComBat is a data correction method available at https://github.com/Jfortin1/ComBatHarmonization (Yu et al., 2018). Notably, this method has proven its effectiveness in addressing site-related variations in multi-site resting-state fMRI datasets, as evidenced by prior research findings (Fortin, et al., 2017; Xia et al., 2019). During the ComBat correction process, diagnosis, age, sex, FIQ score, and mean framewise displacement (mFD) were considered as biologically relevant (Yang et al., 2024). Additionally, we applied a default non-parametric prior method as part of the empirical Bayes procedure.

2.7 Statistic analysis

Statistical analyses were performed using SPSS version 26.0 (https://www.ibm.com/analytics/spss-statistics-software) and DPABI version 5.1.

2.7.1 Whole-brain functional connectivity

One-sample *t*-tests with two covariates of FIQ and mFD were used to obtain the whole-brain FC patterns for each group. Two-sample *t*-tests with two covariates of FIQ and mFD were used to investigate the abnormal FCs for each ToM and MNS ROI. Gaussian random field theory (GRF) was applied to control the familywise error rate for multiple comparisons (one-sample *t*-test: GRF correction with voxel-wise $p < 0.001$, cluster-wise $p < 0.001$, two-tailed test; two-sample *t*-test: GRF correction with voxel-wise $p < 0.001$, cluster-wise $p < 0.05$,

two-tailed test). We compared the results before and after incorporating age and gender as covariates and found very tiny differences (Table S1).

2.7.2 Within- and between-network functional connectivity

One- and two-sample *t*-tests with two covariates of FIQ and mFD were used to explore within-group patterns and between-group differences of the within- and between-network FC of ToM and MNS, respectively. The significance level was set at a false discovery rate (FDR)-corrected $p < 0.05$. We compared the results before and after incorporating age and gender as covariates and found very tiny differences (Table S2).

2.7.3 Relationship between abnormal functional connectivity and clinical measures

The used clinical measures included five diagnostic scores (ADOS Communication, ADOS Social, ADOS communication + social [CS] total, Autism Diagnostic Interview - Revision (ADI-R) Social, and ADI-R Verbal) and three parent-reported scores (SRS-Total, SRS-Communication, and SCQ-Total).

We divided the seed-based whole-brain voxel-wise FC index into overconnectivity and underconnectivity. Specifically, peak FC values and coordinates of the ToM and MNS ROIs were extracted after two-sample *t*-tests. For both ToM and MNS, over- and under-connectivity indices were estimated by averaging peak FC values (Z values) for all significantly over- and under-connected clusters, respectively. Partial Pearson's correlation coefficients between FC indices and symptom severity were calculated to determine whether hypo- or hyper-connectivity patterns of ToM and MNS ROIs can reflect the typical level of social deficits observed in ASD.

For the within- and between-network FC, based on the results of two-sample *t*-tests, a Pearson's correlation analysis was performed to explore the relationship between each pair of abnormal ROI-wise FCs (Z value) and symptom severity with mFD and FIQ as covariates. The data processing framework of this study is summarized in Fig. 2.

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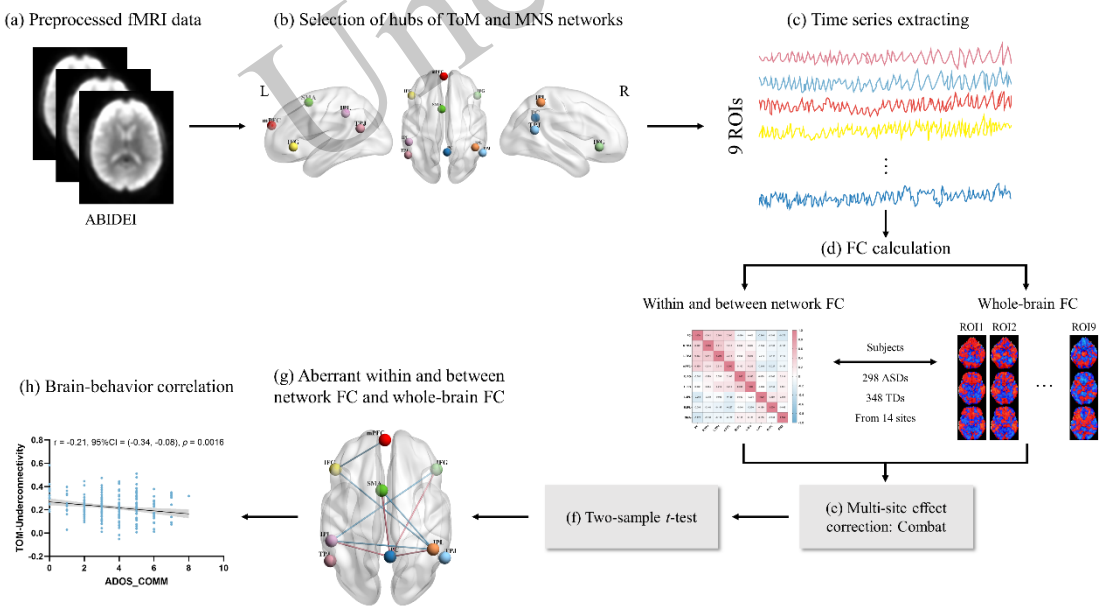

Fig. 2 Flowchart of data processing.

fMRI, functional magnetic resonance imaging; ToM, theory of mind; MNS, mirror neuron system; FC, functional connectivity.

3 Results

3.1 Demographic information

The ASD and TD groups did not significantly differ in terms of gender (p = 0.83), handedness (p = 0.24), or age (p = 0.75). However, significant differences were observed in FIQ score (p < 0.001), mFD (p < 0.001), SRS Total Scores (p<0.001), SRS Communication Score (p<0.001), and SCQ Total Scores (p<0.001; Table 1).

Table 1 Demographic characteristics for the included ASD and TD participants.

Variable	Mean (SD)		Statistics
	ASD (n=298)	TD (n=348)	
Gender (male/female)	262/36	304/44	χ^2 = 0.047, p = 0.83
Handedness (right/left/mixed)	262/32/4	319/27/2	χ^2 = 2.83, p = 0.24
Age	15.9 (6.1)	16.1 (5.6)	$t_{(644)}$ = 0.32, p = 0.75
FIQ**	106.4 (16.5)	111.2 (12.7)	$t_{(644)}$ = -4.20, p < 0.001
mFD**	0.11 (0.07)	0.09 (0.06)	$t_{(644)}$ = 3.73, p < 0.001
ADOS Scores			
Total Score (Social+Communication)	11.88 (3.77)	*NA*	*NA*
Social	8.12 (2.77)	*NA*	*NA*
Communication	3.86 (1.54)	*NA*	*NA*
ADI-R Scores			
Social	19.81 (5.30)	*NA*	*NA*
Verbal	16.01 (4.45)	*NA*	*NA*
SRS Scores			
Total Score**	89.17 (30.04)	22.13 (17.64)	U = 594.00, p < 0.001[a]
Communication**	25.30 (8.35)	9.39 (8.37)	$t_{(52)}$ = 6.92, p < 0.001
SCQ Scores			
Total Score**	18.44 (7.18)	3.33 (3.39)	U = 48.00, p < 0.001[a]

ASD, autism spectrum disorder; TD, typically developing; FIQ, full-scale intelligence quotient; mFD, mean framewise displacement; ADOS, autism diagnostic observation schedule; ADI-R, autism diagnostic interview-revised; SRS, social responsiveness scale; SCQ, Social Communication Questionnaire; NA, not available; SD, standard deviation

[a] The p value was obtained by a Mann-Whitney U test.

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3.2 Aberrant functional connectivity of ToM in ASD

For the ToM network, relative to the TD group, the ASD group exhibited weaker FC between the right TPJ and left calcarine sulcus, left medial superior frontal gyrus (SFG), and lateral aspect of the left SFG, and stronger FC between the left TPJ and the left substantia nigra pars reticulata (SNr). Furthermore, we observed the mixed pattern of both hypo- and hyper-connectivity for PC and mPFC in ToM, including the underconnectivity of the PC with the left pregenual ACC, left calcarine sulcus, left SFG, and left middle occipital gyrus (MOG), and of the mPFC with the left medial SFG, the left cuneus, and the orbital part of the right middle frontal gyrus (MFG). We observed the overconnectivity of the PC with the opercular part of the right IFG, the triangular part of the bilateral IFG, and the right superior temporal gyrus (STG), and of the mPFC with the triangular part of the right IFG. Our whole-brain FC results for ToM demonstrate patterns of both hypo- and hyper-connectivity in ASD (Fig. 3a; Table 2). However, no significant difference was found between ASD and TD groups in terms of within- and between-network FC. The within-group results of the whole-brain FC for each ToM seed are presented in Fig. S2 and Fig. S3 in the Supplemental Information (one-sample t-test: GRF correction with voxel-wise p < 0.001, cluster-wise p < 0.001, two-tailed test).

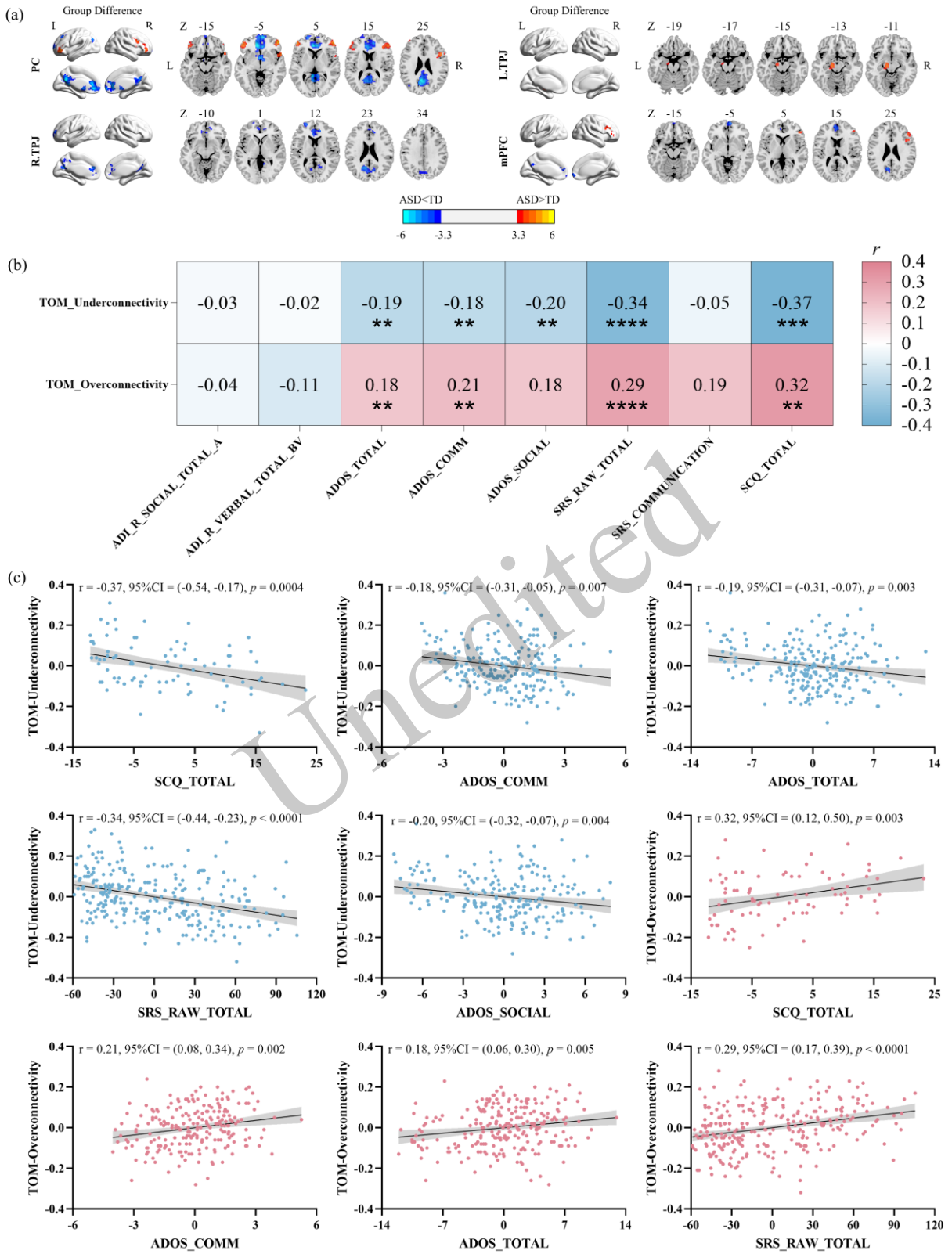

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Fig. 3 Aberrant functional connectivity and its relationship with clinical symptom scores for the ToM network. (a) Between-group difference of the whole-brain seed-based FC maps of ToM. Surface and axial maps depict significant group differences between the ASD and TD groups for each seed in ToM. Red to yellow and dark- to light-blue represent stronger and

weaker FC in the ASD group relative to the TD group, respectively (Gaussian random field theory correction with voxel-wise $p < 0.001$ and cluster-wise $p < 0.05$). (b) Partial Pearson's correlation coefficient between aberrant FC indices and clinical symptom scores (with asterisks indicating significant results surviving Bonferroni correction with significant threshold at $p < 0.00625$ (0.05/8)). (c) The relationship between aberrant FCs and clinical symptom scores. The blue and pink scatterplots show the relationship between the social symptoms and underconnectivity indices (average peak FC for all significantly underconnected clusters within the ToM network) and the overconnectivity indices (average peak FC for all significantly overconnected clusters within the ToM network), respectively. The dark grey shadings indicate 95% confidence intervals. SCQ, Social Communication Questionnaire; ADOS, Autism Diagnostic Observation Schedule; SRS, Social Responsiveness Scale. L: left hemisphere; R: right hemisphere.

Significant relationships were revealed between ADOS (Total, Communication, Social), SRS-Total, and SCQ-Total scores and abnormal FC measures. As presented in Fig. 3b-c, the results revealed that high levels of social symptoms were significantly predicted by increases in ToM-Overconnectivity (ADOS-COMM, $r = 0.21$, $p = 0.002$; ADOS-TOTAL, $r = 0.18$, $p = 0.005$; SRS-TOTAL, $r = 0.29$, $p < 0.0001$; SCQ-TOTAL, $r = 0.32$, $p = 0.003$) and decreases in ToM-Underconnectivity (ADOS-TOTAL, $r = -0.19$, $p = 0.003$; ADOS-COMM, $r = -0.18$, $p = 0.007$; ADOS-SOCIAL, $r = -0.20$, $p = 0.004$; SRS-TOTAL, $r = -0.34$, $p < 0.0001$; SCQ-TOTAL, $r = -0.37$, $p = 0.0004$).

3.3 Aberrant functional connectivity of MNS in ASD

We also detected a similar mixed pattern in the MNS network, including underconnectivity of the left IPL with the left inferior temporal gyrus (ITG) and triangular part of the left IFG, and overconnectivity of the left IFG with the right SNr, of the right IPL with the left PC and the left MFG, and of the SMA with the right PCC and the left PC (Fig. 4a; Table 2; two-sample *t*-test: GRF correction with voxel-wise $p < 0.001$, cluster-wise $p < 0.05$, two-tailed test). Additionally, we found that MNS-Overconnectivity showed a positive correlation with SRS-TOTAL scales ($r = 0.30$, $p < 0.0001$, Bonferroni corrected; Fig. 4b). The within-group results of the whole-brain FC for each MNS seed are presented in Fig. S2 and Fig. S3 in the Supplemental Information (one-sample *t*-test: GRF correction with voxel-wise $p < 0.001$, cluster-wise $p < 0.001$, two-tailed test).

The ROI-wise FC analysis revealed underconnectivity within MNS (Fig. 4c). Significant decreases in the FC of the left IPL with the right IFG, of the right IPL with the left IFG and left IPL, and of the SMA with the right IPL were observed in the ASD group compared with the TD group. Among these aberrant FCs, FC between the bilateral IPLs was negatively correlated with SCQ TOTAL scores ($r = -0.42$, $p = 0.004$, FDR-corrected) and SRS TOTAL scores ($r = -0.22$, $p = 0.01$, FDR-corrected; Fig. 4d).

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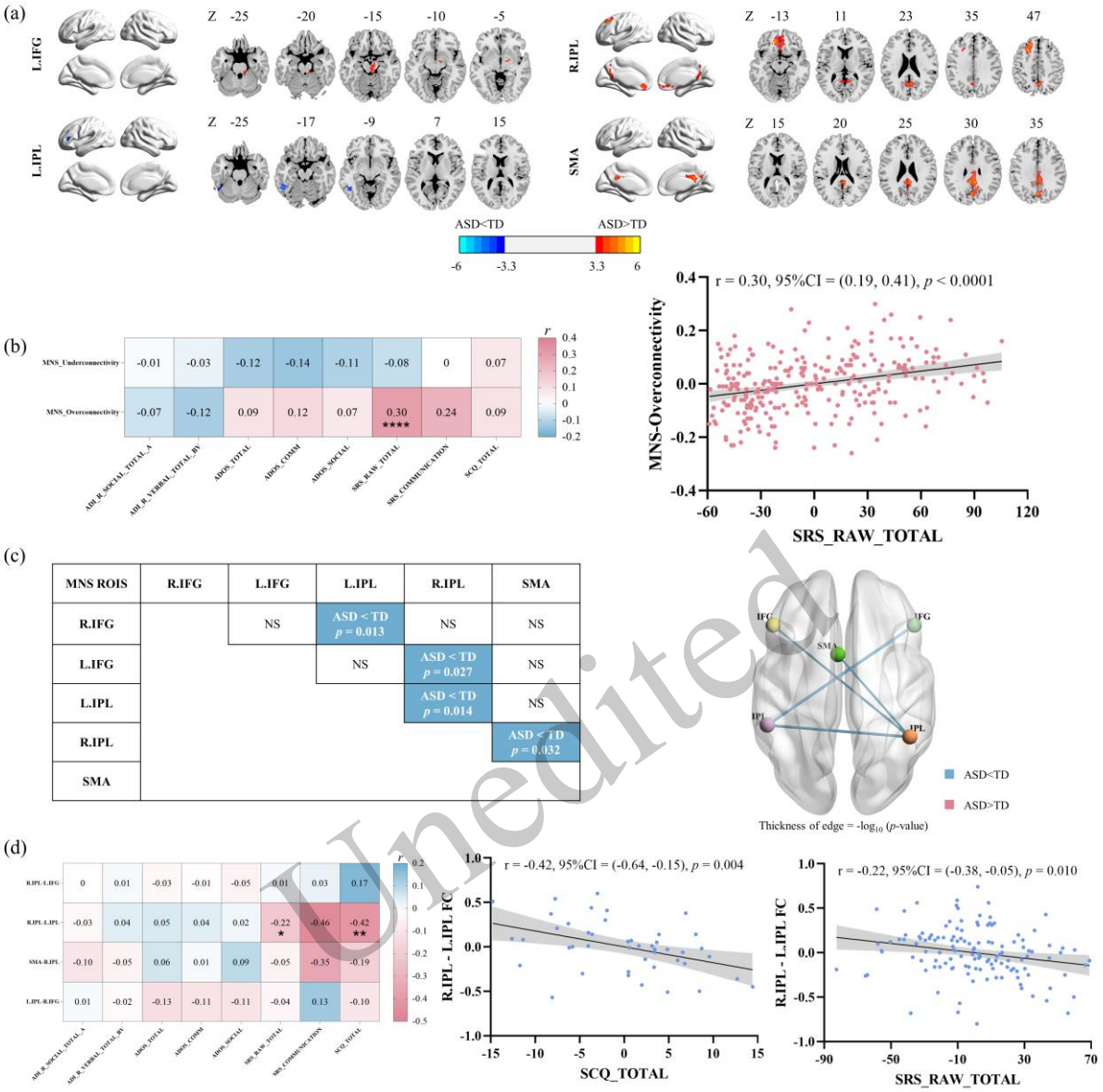

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Fig. 4 Aberrant functional connectivity and its relationship with clinical symptom scores for the MNS network. (a) Between-group differences of the whole-brain seed-based FC maps of the MNS. Surface and axial maps depict significant group differences between the ASD and TD groups for each seed in the MNS. Red to yellow and dark- to light-blue represent stronger and weaker FC in the ASD group relative to the TD group, respectively (Gaussian random field theory correction with voxel-wise $p < 0.001$ and cluster-wise $p < 0.05$). (b) Partial Pearson's correlation results between voxel-wise FC indices and clinical symptom scores (with asterisks indicating significant results surviving Bonferroni correction with significance threshold at $p < 0.00625$ (0.05/8)). The pink scatterplots show the relationship between the overconnectivity indices (average peak FC for all significantly overconnected clusters within the MNS network) and social symptoms. The dark grey shadings indicate 95% confidence intervals. (c) The table summarizes the two-sample *t*-test results of ROI-wise FC within the MNS network ($p < 0.05$, uncorrected). White cells represent non-significant FC, blue cells represent autism-related hypoconnectivity (ASD < TD). The brain net visualizes significant group differences for ROI-wise FC within the MNS network ($p < 0.05$, uncorrected). The thickness of the edge indicates $-\log_{10}$ (*p*-value). The glass brains were generated using BrainNet Viewer (http://www.nitrc.org/projects/bnv/). (d) Partial Pearson's correlation results between ROI-wise FC indices and clinical symptom scores (with asterisks indicating significant results surviving FDR correction). The scatterplots show the relationship between the aberrant ROI-wise FCs and social symptoms. The dark grey shadings indicate 95% confidence intervals. SCQ, Social Communication Questionnaire; ADOS, Autism Diagnostic Observation Schedule; SRS, Social Responsiveness Scale; IPL, inferior parietal lobules. L: left hemisphere; R: right hemisphere.

Table 2 Regions exhibiting group differences (ASD vs TD) in whole-brain voxel-wise FC.

ROI	Cluster Size(#Voxels)	Cluster Region(s)	Peak *t*	Peak MNI		
				x	y	z
ToM						
PC	996	ACC_pre_L	-6.20	-9	39	-6
	793	Calcarine_L	-5.94	-6	-45	6
	234	Frontal_Inf_Tri_R	5.60	48	48	-3
	215	Frontal_Inf_Tri_L	4.97	-48	48	9
	155	Frontal_Inf_Oper_R	4.67	36	6	30
	81	Frontal_Sup_2_L	-4.30	-21	33	45
	77	Temporal_Pole_Sup_R	4.79	51	15	-12
	76	Occipital_Mid_L	-5.08	-39	-75	36
	76	Frontal_Sup_2_L	-4.68	-21	60	6
R.TPJ	466	Calcarine_L	-5.70	-12	-63	18
	230	Frontal_Sup_Medial_L	-5.13	-9	42	18
	71	Frontal_Sup_2_L	-4.64	-24	60	15
L.TPJ	46	SN_pr_L	4.54	-12	-18	-12
mPFC	140	Frontal_Inf_Tri_R	4.18	48	27	27
	95	Cuneus_L	-4.37	-12	-63	24
	80	Frontal_Med_Orb_R	-4.73	3	63	-9
	75	Frontal_Sup_Medial_L	-4.49	-6	54	15
MNS						
R.IFG		None				
L.IFG	63	SN_pr_R	4.27	6	-30	-18
L.IPL	100	Temporal_Inf_L	-4.95	-51	-51	-18
	62	Frontal_Inf_Tri_L	-4.75	-45	36	12
R.IPL	241	Precuneus_L	4.56	-9	-54	18
	209	Frontal_Med_Orb_L	4.90	-15	39	-15
	193	Frontal_Mid_2_L	5.31	-24	21	45
SMA	233	Cingulate_Post_R	4.91	6	-42	30
	93	Precuneus_L	5.10	0	-69	33

Statistical significance level is corrected for multiple comparisons using Gaussian random field theory correction with voxel-wise $p < 0.001$ and cluster-wise $p < 0.05$. The peak coordinate is defined in Montreal Neurological Institute (MNI) space. ASD, autism spectrum disorder; FC, functional connectivity; TD, typically developing; ToM, theory of mind; MNS, mirror neuron system.

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3.4 Aberrant functional connectivity between ToM and MNS in ASD

Two-sample *t*-tests revealed a dominant overconnectivity pattern between ToM and MNS networks (Fig. 5a). Specifically, compared with the TD group, increased FC was found between the PC and right IFG, and the bilateral IPL and SMA, and decreased FC was found between the mPFC and left IFG in the ASD group. However, the ROI-wise FC failed to survive multiple comparisons. Moreover, the FC between the PC and left IPL was negatively related to social communication from the subscale in the ADOS ($r = -0.21$, $p = 0.004$) and ADOS TOTAL scores ($r = -0.18$, $p = 0.009$, FDR corrected; Fig. 5c). Within-group results of the ROI-wise FC between ToM and MNS seeds are presented in Fig. S4 in the Supplemental Information ($p < 0.05$, uncorrected).

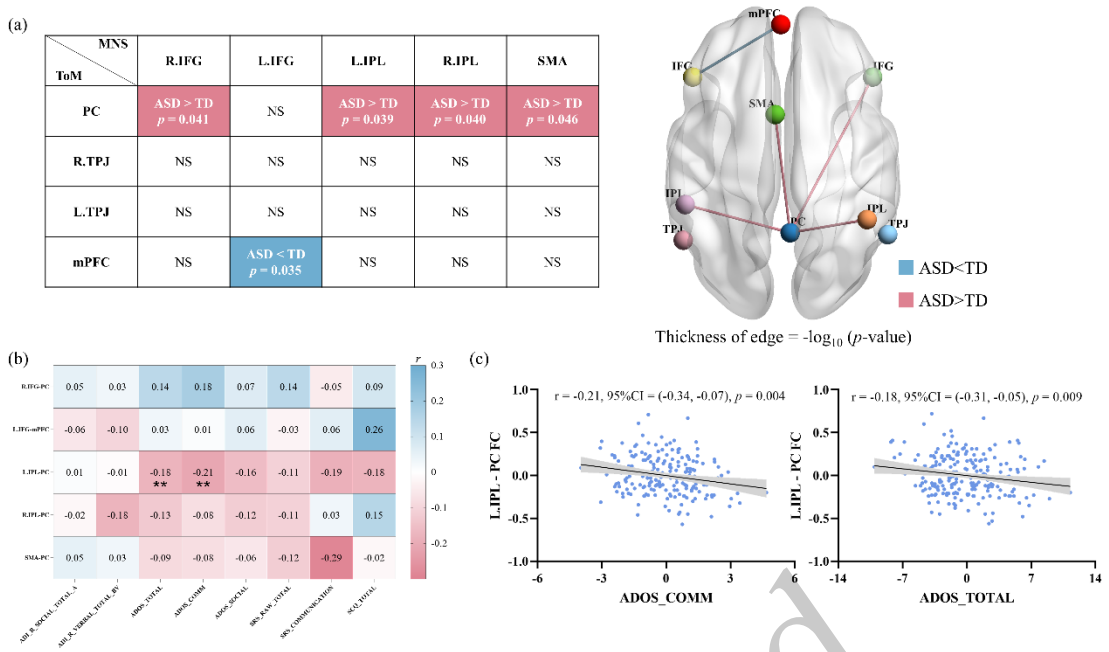

Fig. 5 Aberrant between-network functional connectivity and their correlations with clinical symptoms.
(a) The table summarizes the two-sample *t*-test results of ROI-wise FC between ToM and MNS networks ($p < 0.05$, uncorrected). White cells represent non-significant FC, blue cells represent autism-related hypoconnectivity (ASD < TD), and pink cells represent autism-related hyperconnectivity (ASD > TD). The brain net visualizes significant group differences for ROI-wise FC between ToM and MNS networks. The blue edges represent the FC that is significantly weaker in ASD relative to TD. The pink edges reflect the FC that is significantly stronger in ASD relative to TD. The thickness of the edge indicates $-\log_{10}$ (*p*-value). The glass brains were generated using BrainNet Viewer (http://www.nitrc.org/projects/bnv/). (b) Partial Pearson's correlation results between ROI-wise FC indices and clinical symptom scores (with asterisks indicating significant results surviving FDR correction). (c) The scatterplots show the relationship between the aberrant ROI-wise FCs and social symptoms. The dark grey shadings indicate 95% confidence intervals. IPL, inferior parietal lobules; PC, precuneus.

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4 Discussion

This study investigated both the abnormal patterns of the seed-based whole-brain FC and within- and between-network FC of ToM and MNS in ASD using RS-fMRI data from a large-scale multi-site dataset, i.e., ABIDE I. The seed-based whole-brain FC analysis revealed both hypo- and hyper-connectivity in ASD, which sheds light on their associations with ASD symptomatology. Correlation analyses revealed that severe social symptoms were significantly predicted by the increases in ToM-Overconnectivity and MNS-Overconnectivity, and by the decreases in ToM-Underconnectivity. For the within- and between-network analysis, we observed atypically decreased FC between the bilateral IPL within the MNS and increased FC between the PC and left IPL, which were related to social deficit severity in ASD. Our results provide a comprehensive understanding of the neurophysiological mechanisms underlying the social cognitive difficulties in ASD.

4.1 Aberrant functional connectivity of ToM in ASD

Our findings demonstrated mixed patterns of both over- and under-connectivity between the ToM and the whole brain, which have also been observed in other studies (Di Martino, et al., 2014; Yerys, et al., 2015; Martínez et al., 2020; Guo et al., 2022; Ilioska, et al., 2023). Fishman et al. found mixed reports of hypo- and hyper-connectivity between ToM seeds and the whole brain, which is consistent with our results (Fishman, et al., 2014). The correlation analysis showed that ToM-Underconnectivity was negatively related to the ADOS total

score, SRS total score, SCQ total score, ADOS communication score, and ADOS social score in ASD. Higher scores indicate more severe social deficits. In individuals with autism, the FC between ToM seeds and the whole brain was significantly below the level of TD controls. Further, the lower connectivity between ToM and the whole brain tends to appear with more severe autism social deficits. Positive correlations were found between symptom severity (measured by ADOS total score, ADOS communication score, SRS total score, and SCQ total score) and ToM-Overconnectivity. The relationships between overconnectivity and symptom severity indicate disease-related change tendency in ASD. However, Fishman et al. detected positive correlations between ADI-R social and communication scores and ToM-Overconnectivity and ToM-Underconnectivity, which were not found in our study (Fishman, et al., 2014).

According to the division of the human cerebral cortex by Yeo et al. (Yeo et al., 2011), we found that, in ASD, ToM had reduced FC with both the default mode network (DMN), including the ACC, SFG, and mPFC, and the salience network, including the calcarine sulcus, MOG, and cuneus. The anterior–posterior DMN connections, such as SFG-PC and ACC-PC, were noticeably decreased in ASD compared to TD controls. Our findings were consistent with the previously observed tendency for reduced FC in the DMN in ASD (Just et al., 2012), such as between the ACC/mPFC and the PCC/ PC (Cherkassky et al., 2006; Washington and Vanmeter, 2015), and between the right IPL and right SFG (Wiggins et al., 2011). Washington et al. found correlations between ACC/mPFC-PCC connectivity and SRS Autistic Mannerism scores, and showed an increase in symptom severity coinciding with decreased FC (Washington, et al., 2014). Assaf et al. (Assaf, et al., 2010) investigated the role of the altered FC of default-mode sub-networks in ASD and found that, compared to controls, ASD patients showed decreased FC between the PC and mPFC/ACC—DMN core areas—which agreed with our study. Furthermore, FC magnitude in these regions was negatively correlated with the severity of patients' social and communication deficits as measured by the ADOS and the SRS, which is consistent with our correlation analysis results. For all these correlations, decreased FC was associated with more severe symptoms. Similarly, Cherkassky et al. (Cherkassky, et al., 2006) reported decreased FC between the ACC and PC in ASD patients using a formal DMN connectivity analysis after combining data from different cognitive tasks. Weng et al. (Weng, et al., 2010) examined FC between a PCC seed and other areas of the default network and found that poorer social functioning was associated with weaker connectivity between the PCC and SFG. An increasing number of studies have suggested that the failure to integrate the functions of the anterior-most node (ACC/mPFC) and posterior-most node (PCC/PC) may potentially manifest in social difficulties in ASD (Cherkassky, et al., 2006; Washington, et al., 2014; Doyle-Thomas et al., 2015). Therefore, anterior and posterior underconnectivity may be the biological mechanism underlying the impaired social function in ASD (Just, et al., 2012; Yoon et al., 2022).

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4.2 Aberrant functional connectivity of MNS in ASD

Through a voxel-wise analysis, we found that the MNS and other voxels in the whole brain exhibited a mixed pattern of both hypo- and hyper-connectivity in ASD, and we found that MNS-Overconnectivity was positively correlated with SRS total score. However, our results were inconsistent with Fishman's results, where direct group comparisons revealed no significant between-group differences in FC for any of the MNS seeds (Fishman, et al., 2014). Obviously, different seeds and coordinates may affect the results (Smith et al., 2011; Balsters et al., 2016). Fishman and colleagues selected six regions within the MNS, including the anterior intraparietal sulcus, posterior superior temporal sulcus, and PMC. These selections were based on a meta-analysis of over 200 fMRI studies conducted in 2009 (Van Overwalle and Baetens, 2009). However, these ROIs were derived from TD participants, potentially overlooking crucial nodes of the MNS in ASD and thus possibly misrepresenting the network. Recent studies have indicated that the SMA, IPL, and IFG more accurately reflect abnormalities in action observation in ASD (Yang and Hofmann, 2016; Chan and Han, 2020). We have synthesized the results of published meta-analyses (Schurz, et al., 2014; Yang and Hofmann, 2016; Chan and Han, 2020), reviews (Müller and Fishman, 2018), and recent fMRI studies (Cole, et al., 2019) to provide seeds that more comprehensively depict the characteristics of ToM and the MNS. According to the

division of the cerebral cortex by Yeo et al. (Yeo, et al., 2011), we found that the MNS had increased FC with the DMN in ASD, such as PC, PCC, and SFG. The voxel-wise analysis of the MNS repeated the results of our ROI-wise analysis, which showed increased FC between ToM and the MNS.

Compared to TD controls, individuals with ASD generally displayed decreased FC within the MNS network, particularly involving the bilateral IPL. Our findings are consistent with previous studies reporting reduced FC within the MNS in ASD (Alaerts et al., 2014; Fishman, et al., 2014; Alaerts et al., 2015; Fishman, et al., 2015). RS-fMRI studies have revealed decreased FC between the bilateral IPL (Washington, et al., 2014; Li, et al., 2019) and its negative association with the social subscore of the ADOS (Washington, et al., 2014) in ASD. Additionally, previous studies have also demonstrated decreased FC in the other ROIs (i.e., bilateral IFG) of the MNS in ASD individuals relative to their TD counterparts, with the connectivity strength being negatively associated with the severity of communication impairments, as measured by the ADOS (Dinstein et al., 2011). In conclusion, numerous studies have consistently observed that hypoconnectivity in the MNS stands out as a significant feature of ASD. It is worth noting that, although there are differences in statistical strength (*t*-value size), the results of the ROI-wise analysis are consistent with those of the voxel-wise analysis (Table S3).

4.3 Aberrant functional connectivity between ToM and MNS in ASD

The aberrant FC highlights a significant prevalence of increased FC between ToM and the MNS in ASD. Firstly, we identified hyperconnectivity between the PC and SMA in ASD, a finding consistent with Lynch et al.'s research (Lynch et al., 2013). Previous studies have suggested that both the PC and SMA are associated with sensorimotor functions (Margulies et al., 2009), and the PC is involved in higher-order reasoning processes (Van Veluw and Chance, 2014). Therefore, the observed PC-SMA overconnectivity may explain the reported challenges in comprehending and executing chained action sequences in ASD. Secondly, our results demonstrated hyperconnectivity between the PC and bilateral IPL in ASD. Consistent with our results, Delbruck et al. (Delbruck, et al., 2019), who likewise harnessed the ABIDE dataset, documented similar hyperconnectivity patterns linking the PC/PCC with the right IPL within the cohort of ASD patients. The PC collaborates with the IPL on tasks involving both self and non-self spatial information processing, as well as abstract mental imagery tasks (Cavanna and Trimble, 2006). Disruptions in this collaboration, specifically the aberrant FC between the PC and right IPL, could potentially explain the atypical performance of individuals with ASD on ToM tasks. Correlation analysis also demonstrated that FC between the left IPL and PC was negatively correlated with ADOS communication scores.

Normative developmental trajectories witness a concomitant increase in the integration (via reinforced intra-network connections) and segregation (via weakened inter-network connections) of functional brain networks (i.e., ToM and MNS) (Rudie et al., 2012; Fishman, et al., 2014; Hong, et al., 2019; Todorova, et al., 2019; Martínez, et al., 2020; Schurz et al., 2020). We can reasonably speculate that the hyperconnectivity between the ToM and MNS networks in ASD may result from a lesser degree of functional isolation between the two essential social brain subnetworks that manifest impairments in ASD. That is to say, the observed atypical ToM–MNS overconnectivity in the context of ASD likely reflects an underdeveloped or aberrant maturation of the two neural networks crucial for the comprehension of others.

4.4 Limitations

The present study has some limitations. First, using open-access datasets like ABIDE involves certain restrictions including scanning protocols, equipment, and potential changes in data quality due to data collection variations across multiple sites. Despite preprocessing and multi-site effects correction efforts, potential data quality differences and confounding factors from multi-site collection still affect result reliability. Second, parent-report measures like the SRS and SCQ have inherent limitations in comprehensively capturing distinct nuances of social abilities, particularly sensory processing, which may have introduced subjective biases and measurement errors in terms of measuring autism symptoms. Third, it is important to acknowledge that FC

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measurements, while informative, do not provide a causal understanding of the observed anomalies. Future studies using longitudinal design or experimental manipulation will help elucidate the causal relationship between FC changes and behavioral indicators of ASD.

5 Conclusion

In summary, we identified both over- and under-connectivity between ToM and the whole brain, and overconnectivity between the MNS and the whole brain, which were correlated with social dysfunction in ASD. Additionally, we observed atypically increased segregation within the MNS and integration between ToM and the MNS, which are associated with social deficits in ASD. These findings may provide deep insights into the pathophysiological basis underlying social deficits in ASD and contribute to the development of more effective interventions for ASD.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

Qiu-Rong Zhang wrote the manuscript and contributed to data analysis. Chen Yang analyzed the data and prepared the figures and tables. Xing-Ke Wang, Wen-Qiang Dong, and Sheng-Zhi Ma contributed to data curation and revised the manuscript. Li-Xia Yuan offered suggestions, designed the research, and revised the manuscript. All authors have read and approved the final manuscript, and therefore, take responsibility for the integrity of the study.

Compliance with ethics guidelines

Qiu-Rong Zhang, Chen Yang, Xing-Ke Wang, Wen-Qiang Dong, Sheng-Zhi Ma, and Li-Xia Yuan declare that they have no conflict of interest. Our study processed and analyzed data from a well-known public dataset (ABIDE) independently collected across more than 24 sites. It is clearly stated on the official website (http://fcon_1000.projects.nitrc.org/indi/abide/) that all data collected from each site were based on studies approved by the local Institutional Review Boards (IRB) and written informed consent/assent were obtained for all participants.

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