Atypical Cross Talk Between Mentalizing and Mirror Neuron Networks in Autism Spectrum Disorder

Inna Fishman, PhD; Christopher L. Keown, MS; Alan J. Lincoln, PhD; Jaime A. Pineda, PhD; Ralph-Axel Müller, PhD

IMPORTANCE Converging evidence indicates that brain abnormalities in autism spectrum disorder (ASD) involve atypical network connectivity, but it is unclear whether altered connectivity is especially prominent in brain networks that participate in social cognition.

OBJECTIVE To investigate whether adolescents with ASD show altered functional connectivity in 2 brain networks putatively impaired in ASD and involved in social processing, theory of mind (ToM) and mirror neuron system (MNS).

DESIGN, SETTING, AND PARTICIPANTS Cross-sectional study using resting-state functional magnetic resonance imaging involving 25 adolescents with ASD between the ages of 11 and 18 years and 25 typically developing adolescents matched for age, handedness, and nonverbal IQ.

MAIN OUTCOMES AND MEASURES Statistical parametric maps testing the degree of whole-brain functional connectivity and social functioning measures.

RESULTS Relative to typically developing controls, participants with ASD showed a mixed pattern of both over- and underconnectivity in the ToM network, which was associated with greater social impairment. Increased connectivity in the ASD group was detected primarily between the regions of the MNS and ToM, and was correlated with sociocommunicative measures, suggesting that excessive ToM-MNS cross talk might be associated with social impairment. In a secondary analysis comparing a subset of the 15 participants with ASD with the most severe symptomology and a tightly matched subset of 15 typically developing controls, participants with ASD showed exclusive overconnectivity effects in both ToM and MNS networks, which were also associated with greater social dysfunction.

CONCLUSIONS AND RELEVANCE Adolescents with ASD showed atypically increased functional connectivity involving the mentalizing and mirror neuron systems, largely reflecting greater cross talk between the 2. This finding is consistent with emerging evidence of reduced network segregation in ASD and challenges the prevailing theory of general long-distance underconnectivity in ASD. This excess ToM-MNS connectivity may reflect immature or aberrant developmental processes in 2 brain networks involved in understanding of others, a domain of impairment in ASD. Further, robust links with sociocommunicative symptoms of ASD implicate atypically increased ToM-MNS connectivity in social deficits observed in ASD.

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Humans are an inherently social species. Our survival and success depend on our ability to navigate and thrive in complex social situations. This core ability is commonly impaired in autism spectrum disorder (ASD), a neurodevelopmental disorder affecting as many as 1 in 88 children. Despite the highly heterogeneous symptom manifestation, impairments in social functioning, including diminished social responsiveness, difficulty relating to others, and recognizing others’ emotions and intentions, are defining features of ASD. These social deficits are considered the most universal and specific characteristics of ASD, both defining and distinguishing it from other developmental disorders. Yet, the neural mechanisms underlying social impairments remain largely undetermined, despite attracting a great deal of research.

Currently, 2 debatably related prominent theories account for social dysfunction in ASD, theory of mind (ToM) and the mirror neuron system (MNS). The ToM, also known as the mentalizing system, refers to the ability to infer contents of other people’s minds, including their beliefs and intentions. This ability to attribute mental states, to or mentalize, is impaired, or at least delayed in ASD, giving rise to the mind-blindness theory of autism. The MNS refers to the brain mirror mechanisms that allow us to understand meaning of the actions and emotions of others by internally simulating and replicating them (as inferred from the original discovery in macaques of neurons firing during both action execution and observation). Evidence showing that imitation, a behavioral correlate of the MNS, is impaired in ASD has given rise to the dominant theory that atypical MNS functioning may be a key to understanding the nature of social deficits in ASD (although see the article by Dinstein and colleagues for alternative views).

Even though both ToM and the MNS are involved in understanding others, a meta-analysis of more than 200 functional magnetic resonance imaging task-based activation studies confirmed that, functionally and anatomically, they are 2 distinct systems. While the MNS is an action-understanding system, activated only in the presence of biological motion (eg, when moving body parts such as hands or face are observed), ToM is recruited during a more abstract processing of others’ intentionality, in the absence of any biological motion. Although it is understood that judging others in the real world likely involves both ToM and MNS, the functional distinction between them determined by this meta-analysis has been adapted here. Anatomically, the meta-analysis identified ToM with a frontal-posterior network of brain regions, including the medial prefrontal cortex (mPFC), bilateral temporal-parietal junction (TPJ), and posterior cingulate cortex (PCC)/precuneus, while the human MNS engaged the anterior intraparietal sulcus (aIPS), also referred to as the rostral inferior parietal lobule (IPL), premotor cortex (PMc) also referred to as the caudal inferior frontal gyrus (IFG), and posterior superior temporal sulcus (pSTS).

While neuroimaging and electrophysiological evidence suggests that ASD is associated with localized abnormalities in certain ToM and MNS brain areas, it is also becoming increasingly evident that ASD is characterized by abnormal connectivity throughout the brain, presumed to stem from altered neurodevelopmental trajectories. Wide-spread abnormalities in interregional connections in ASD have been predominantly demonstrated with functional connectivity magnetic resonance imaging (fcMRI), assessing functional coordination between spatially distributed brain regions. Functional connectivity (FC), inferred from interregional cross-correlations of the blood oxygen level-dependent (BOLD) signal, can be detected even at rest, in the absence of an overt cognitive task. Importantly, those patterns correspond to brain networks recruited during specific cognitive or mental processes and are, therefore, thought to reflect intrinsically organized functional networks formed by a long history of frequent coactivation associated with functional specialization. Moreover, resting-state FC patterns are largely consistent with anatomical connectivity and appear robust and highly reliable across individuals.

The present study investigated whether adolescents with ASD show altered FC in the MNS and ToM, 2 brain networks putatively impaired in ASD and involved in social processing, by using resting-state fcMRI to assess interregional BOLD correlations in these networks. Our aims were 2-fold: to examine the extent of functional specialization, as deduced from the FC, of the ToM and MNS networks in adolescents with ASD (eg, whether the 2 networks are functionally segregated) and to relate FC of these networks involved in understanding others to variation on clinical measures of social impairment. It was hypothesized that individuals with ASD would exhibit aberrant connectivity within and between these networks, compared with matched typically developing (TD) controls, and that those participants with greatest social impairments within the ASD group would show the most atypical connectivity patterns.

Methods

Participants

Thirty adolescents with ASD and 26 TD adolescents, between 11 and 18 years of age, were enrolled in the study. After excluding 5 participants with ASD because of excessive head motion (> 15% of time points) and 1 TD adolescent because of hardware malfunction, the final sample included 25 participants with ASD and 25 TD participants matched for age, handedness, and nonverbal IQ (Table 1). The ASD diagnoses were established using the Autism Diagnostic Interview-Revised (ADI-R), the Autism Diagnostic Observation Schedule (ADOS), and expert clinical judgment (by one of us, A.J.L.) according to DSM-IV criteria. History of autism-related medical conditions (eg, epilepsy, Fragile X syndrome, tuberous sclerosis) served as an exclusionary criterion. Inclusion in the TD group required absence of personal or family history of autism and of personal history of any other neurological or psychiatric conditions. All participants had verbal and nonverbal IQ scores greater than 70, as assessed by the Wechsler Abbreviated Scale of Intelligence. In addition to the ADI- and ADOS-derived indices of social behavior available only for participants with ASD, social functioning was also assessed in all participants using the Social Responsiveness Scale (SRS), an informant-based rating scale measuring social impairments characteristic of ASD; it was ad-
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Original Investigation Research

Effect of full width at half maximum of 6 mm. The resulting images were spatially smoothed with an isotropic Gaussian filter to an effective full width at half maximum of 6 mm. The resulting images were then bandpass filtered at 0.008 ≤ f < 0.08 Hz to isolate frequencies at which intrinsic network-specific BOLD correlations predominate.

Magnetic Resonance Imaging Data Acquisition

Imaging data were acquired on a 3-T scanner with an 8-channel head coil (MR750; GE). High-resolution anatomical images were obtained using a standard T1-weighted fast spoiled gradient recalled echo (SPGR) sequence (repetition time = 11.08 milliseconds; echo time = 4.3 milliseconds; flip angle = 45°; field of view = 256 mm × 256 mm; slice thickness = 1.5 mm; and 1 mm³ resolution). Functional T2*-weighted echo-planar images were acquired in one 6-minute, 10-second resting-state scan consisting of 185 whole-brain volumes (repetition time = 2000 milliseconds; echo time = 30 milliseconds; flip angle = 90°; field of view = 220 mm × 64 mm matrix; 3.4-mm³ in-plane resolution; 3.4-mm slice thickness; and 42 axial slices covering the whole brain). Throughout the scan, participants were instructed to keep their eyes on a white fixation cross displayed in the center of a screen.

Functional Magnetic Resonance Imaging Data Preprocessing

Images were processed primarily using Analysis of Functional NeuroImages (AFNI). The first 5 frames were discarded to remove signal equilibration effects, resulting in 180 total whole-brain volumes. Functional data were slice-time and motion-corrected by realigning to the first time point, field-map corrected to remove distortions resulting from magnetic field inhomogeneity, coregistered to the anatomical image using a single transformation matrix, resampled to 3.0-mm isotropic voxels, standardized to the N27 Talairach template, and spatially smoothed with an isotropic Gaussian filter to an effective full width at half maximum of 6 mm. The resulting images were then bandpass filtered at 0.008 ≤ f < 0.08 Hz to isolate frequencies at which intrinsic network-specific BOLD correlations predominate.

To minimize the confounding effects of head motion on BOLD correlations, 6 scan-to-scan rigid-body motion parameters (3 rotations, 3 translations) estimated from realignment of functional volumes were modeled as nuisance variables and removed with regression, along with the mean white matter and ventricular signals extracted from the masks derived from the Freesurfer automated segmentation of anatomical images into tissue compartments and reduced by 1 voxel in all directions (all regressors bandpass filtered at 0.008 ≤ f < 0.08 Hz). Time points with excessive head motion (head displacement > 1.5 mm, computed as the root sum of square of displacement between any two time points) and their immediately preceding and following time points were censored from further analyses; blocks of time with fewer than 10 usable consecutive images were also excluded. Based on this criterion, the mean percentage of data censored from all 50 participants was less than 1%. Percentage of censored data did not differ between groups (mean: ASD, 0.71%; TD, 0.67%; t1,48 = 0.06, P = .95). Finally, the root mean square of displacement (RMSD) across the entire time series, calculated for each participant, did not differ between the groups (mean: ASD, 0.133; TD, 0.125; t1,48 = 0.28, P = .82), and was not significantly correlated with age (P = .13) or full-scale IQ (P = .16).

Table 1. Participant Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) [Range]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>ASD (n = 25)</td>
<td>TD (n = 25)</td>
</tr>
<tr>
<td>Handedness, R/L</td>
<td>23/3</td>
<td>3/3</td>
</tr>
<tr>
<td>Age, y</td>
<td>11.8 (1.5)</td>
<td>14.4 (1.5)</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>111 (15) [83-145]</td>
<td>106 (10) [67-126]</td>
</tr>
<tr>
<td>Nonverbal IQ</td>
<td>111 (15) [70-140]</td>
<td>108 (11) [86-129]</td>
</tr>
<tr>
<td>Full-scale IQ</td>
<td>113 (15) [81-141]</td>
<td>108 (10) [88-128]</td>
</tr>
<tr>
<td>ADOS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communication</td>
<td>2.9 (1.4) [0-6]</td>
<td>NA</td>
</tr>
<tr>
<td>Social interaction</td>
<td>7.6 (1.2) [1-13]</td>
<td>NA</td>
</tr>
<tr>
<td>Repetitive behavior</td>
<td>2.0 (1.4) [0-5]</td>
<td>NA</td>
</tr>
<tr>
<td>ADI-R score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social interaction</td>
<td>16.5 (6.2) [6-25]</td>
<td>NA</td>
</tr>
<tr>
<td>Communication</td>
<td>12.6 (6.2) [2-25]</td>
<td>NA</td>
</tr>
<tr>
<td>Repetitive behavior</td>
<td>6.0 (2.3) [3-11]</td>
<td>NA</td>
</tr>
<tr>
<td>SRS, total score</td>
<td>78.5 (9.8) [58-94]</td>
<td>41.5 (5.1) [35-52]</td>
</tr>
</tbody>
</table>

Abbreviations: ADI-R, Autism Diagnostic Interview–Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; NA, not available; SRS, Social Responsiveness Scale; TD, typically developing.

Four of 25 participants with ASD met either the ADOS or the ADI-R cutoff while meeting the clinical diagnostic criteria determined by expert clinical judgment (21 of 25 participants met both ADOS and ADI-R cutoffs). Twelve ASD participants presented with comorbid psychiatric conditions, including attention-deficit/hyperactivity disorder (5), obsessive compulsive disorder (2), depression (3), and anxiety (4), with 2 of 12 participants with ASD diagnosed with more than 1 comorbid condition. Ten participants with ASD were reported to be taking psychotropic medications, as detailed in eAppendix 1 and eTable 1 in Supplement.

Twelve ASD participants presented with comorbid psychiatric conditions, including attention-deficit/hyperactivity disorder (5), obsessive compulsive disorder (2), depression (3), and anxiety (4), with 2 of 12 participants with ASD diagnosed with more than 1 comorbid condition. Ten participants with ASD were reported to be taking psychotropic medications, as detailed in eAppendix 1 and eTable 1 in Supplement.
fcMRI Analyses

Following functional magnetic resonance imaging preprocessing and removal of nuisance variables, the average BOLD time course was extracted from each seed and correlated with the time courses of all voxels across the brain (whole-brain voxelwise correlations), for every participant. The resulting cor-

Figure 1. Within-Group Functional Connectivity Maps for Mirror Neuron System (MNS) (Top Panel) and Theory of Mind (ToM) (Bottom Panel) Seeds

Results of the within-group (autism spectrum disorder [ASD], typically developing [TD]; P < .05, corrected) analyses obtained for each MNS and ToM seed (top and bottom panels, respectively) are presented in a conjunction view. Seed regions of interest are presented on the axial slices on the left (red dots reflect the actual size of the spherical regions of interest). Inflated maps were generated using Surface Mapping with Analysis of Functional Neuroimages (SUMA, http://afni.nimh.nih.gov/afni/suma). L indicates left; laIPS, left anterior intraparietal sulcus (Talairach coordinates −40, −40, 45); lpSTS, left posterior superior temporal sulcus (−50, −55, 10); lPMC, left premotor cortex (−40, 5, 40); lTPJ, left temporal-parietal junction (−50, −55, 25); mPFC, medial prefrontal cortex (0, 50, 20); PC, precuneus; PCC, posterior cingulate cortex (0, −60, 40); R, right; raIPS, right anterior intraparietal sulcus (40, −40, 45); rpSTS, right posterior superior temporal sulcus (50, −55, 10); rPMC, right premotor cortex (40, 5, 40); and rTPJ, right temporal-parietal junction (50, −55, 25).
relation coefficients were converted to normally distributed z values (using Fisher r-to-z transformation) and entered into 1- and 2-independent sample(t) tests to examine within- and between-group FC effects. All statistical maps were corrected for multiple comparisons with a cluster size-corrected threshold of P < .05, using Monte Carlo simulation.55

Summary Connectivity Scores and Correlations With Clinical Measures
To examine relationships between social impairment and FC, within- and between-network connectivity indices were computed by averaging z scores for all within- and between-network region of interest (ROI) pairs, respectively. To minimize multiple comparisons (and associated type I error), 4 a priori selected social-functioning measures were chosen for the correlational analyses with connectivity indices within the ASD cohort, including 3 diagnostic scores (2 ADI-R sociocommunicative components including ADI-R Social and ADI-R Communication, and the ADOS Communication + Social [CS] total score) and 1 parental report sociability score (SRS-Total). The relationship between FC and these 4 measures were examined using Spearman correlations because of the skewed distributions of the clinical measures. Because neither connectivity indices nor social measures were significantly correlated with age (all r's < 0.22, all P's > .56), age was excluded from any further analyses.

Results
Whole-Brain Connectivity
Results from the whole-brain within-group FC analyses performed for each of the 10 seeds are summarized in Figure 1 (see eTable 2 and 3 in Supplement for detailed descriptions, including peak coordinates). Direct group comparisons (corrected P < .05) revealed no significant between-group differences in FC for any of the MNS seeds but several significant clusters of differential connectivity for the ToM network, including underconnectivity (TD > ASD) of the bilateral TPJ with the bilateral superior temporal gyri and PCC/precuneus, and overconnectivity (ASD > TD) of the mPFC with the superior parietal lobule (SPL) and middle temporal gyrus, and of PCC/precuneus with the middle frontal gyrus (MFG) and IFG (Figure 2A and Table 2).

Summary Connectivity Indices and Their Relationship to Clinical Measures
Given this mixed pattern of both weaker and stronger BOLD correlations in the ToM, its connectivity was summarized with 2 separate indices calculated by averaging z scores for significantly underconnected and overconnected clusters, respectively. Because no significant clusters emerged in a direct between-group comparison of the MNS, its mean connectivity was computed by averaging z scores for all MNS ROI pairs. Finally, mean ToM-MNS between-network connectivity was estimated by averaging z scores for all between-network ROI pairs. A correlational matrix of 4 connectivity indices multiplied by 4 social measures yielded a Bonferroni-adjusted P < .05/16 = .003. Significant correlations were detected between ASD social symptoms and the extent of ToM overconnectivity (Table 3); namely, the mean z score for ToM overconnected clusters was correlated with ADI-R Social and ADI-R Communication scores (r = 0.45, P < .05 and r = 0.51, P < .01, respectively), although neither survived Bonferroni correction for multiple comparisons. While no significant FC group differences were detected for the MNS network, its average connectivity was positively correlated with ADI-R Social scores (r = 0.50, P = .01, uncorrected) such that greater MNS connectivity was associated with increases in social symptoms of ASD. Further, the ToM-MNS between-network connectivity was significantly correlated with ADI-R Social scores (r = 0.58, P = .003), indicating that greater ToM-MNS cross talk (atypically increased connectivity and reduced segregation between networks) was associated with more severe social impairment. Importantly, the relationship between abnormal ToM-MNS cross talk and greater social impairment in ASD does not generalize to other between-network patterns of connectivity, as detailed in eAppendix 2 and eTable 5 in Supplement, providing support to the notion that social dysfunction in ASD is specifically associated with inadequate segregation between 2 social networks, ToM and MNS.

Post hoc Analysis: Replication and Robustness of Findings in ASD Subset With Most Severe Symptoms
Based on these positive relationships between symptom severity and MNS and ToM-MNS FC, a post hoc FC analysis was performed in a subset of participants with ASD (n = 15) with the highest level of social symptoms as defined by ADOS-CS scores 10 or greater (see eFigure in Supplement for within-group connectivity maps). Direct group comparison of this ASD subsample and 15 TD participants optimally matched on age, motion, and IQ (eTable 4 in Supplement) corroborated earlier results of increased connectivity (ASD > TD) of the mPFC and PCC regions of ToM but also revealed increased, rather than weaker, connectivity (ASD > TD) of the right TPJ region of ToM (Figure 2B, Table 4). Notably, this analysis yielded a significant between-group difference in the MNS network, which was absent in the direct comparison of total samples, with greater connectivity (ASD > TD) between the right aIPS and left superior frontal gyrus and PCC (Figure 2B, Table 4). Finally, consistent with analyses for the entire cohort, positive correlation was detected between greater ToM-MNS between-network connectivity and ADI-Social scores (r = 0.56, P = .04; Figure 2B, right panel), although it did not survive Bonferroni correction for multiple comparisons.

Discussion
We used resting-state fMRI to investigate FC in 2 brain networks crucial for social processing (ToM and MNS) in adolescents with ASD, relative to TD controls. In contrast to previous findings of predominantly reduced connectivity in ASD detected at rest in other functional networks,56-58 a mixed pattern of both overconnectivity and underconnectivity was observed in the ToM network. Namely, relative to TD partici-
pants, adolescents with ASD showed enhanced connectivity between mPFC and the SPL, precuneus and right posterior middle temporal gyrus, as well as between PCC/precuneus and the right middle and inferior frontal gyri. On the other hand, the ASD group showed weaker connectivity between the bilateral TPJ and PCC and superior temporal gyrus, including pSTS.

An unexpected finding was the lack of significant between-group differences in the MNS FC. However, when directly comparing a subset of the participants with ASD with the most severe sociocommunicative symptoms and a matched TD subsample, overconnectivity was detected between the rIPS region of the MNS and PCC, as well as between rIPS and the left superior frontal gyrus. This secondary analysis involving only the participants with ASD with the greatest symptom severity also revealed overconnectivity in 3 ToM seeds, namely between the rTPJ and the left MFG, mPFC and the bilateral superior and MFG, and PCC and the right MFG and left IFG. Remarkably, no underconnectivity effects were observed for this more homogeneous ASD subsample; instead, increased connectivity was detected for both MNS and ToM networks. These findings appear inconsistent with the theory of generally reduced long-distance connectivity in ASD or the more specific hypothesis of frontoparietal underconnectivity.

Critically, close examination of the regional specificity of these findings, observed both in the entire sample and in the

Figure 2. Regions Exhibiting Group Differences (Autism Spectrum Disorder [ASD] vs Typically Developing [TD]) in Functional Connectivity (FC) and the Relationship Between FC and Clinical Severity in the ASD Group

A. Clusters of significantly different FC (P < .05, corrected) in participants with ASD relative to the TD participants are illustrated for the theory of mind (ToM) seeds. The scatterplot on the right shows the relationship between the ToM–mirror neuron system (MNS) overconnectivity (average z scores for all between-network region of interest pairs) and social symptomatology measured by the Autism Diagnostic Interview–Revised (ADI-R) Social scores (Spearman r = 0.58, P = .003). B, Clusters of significantly different FC (P < .05, corrected) in the subset of 15 participants with ASD and Autism Diagnostic Observation Schedule (ADOS) Communication + Social (CS) of 10 or greater and 15 matched TD participants. All depicted ToM and MNS seeds yielded overconnected clusters (ASD > TD). The scatterplot on the right shows the relationship between the ToM–MNS overconnectivity (average z scores for all between-network region of interest pairs) and social symptoms measured by the ADI-R Social scores (Spearman r = 0.56, P = .04). Increasing ADI-Social values indicate greater social impairment. rTPJ indicates right temporal-parietal junction; L, left; mPFC, medial prefrontal cortex; PC, precuneus; PCC, posterior cingulate cortex; rIPS, right anterior intraparietal sulcus, R, right; and rTPJ, right temporal-parietal junction.
subset of participants with greatest symptom severity, revealed that atypical connectivity in ASD occurred between the regions of the MNS and ToM. For instance, in the analysis of the entire sample, the bilateral TPJ region of ToM showed reduced connectivity with the superior temporal gyrus, which included the pSTS region of the MNS. Similarly, clusters found to be overconnected with precuneus—a ToM seed-contained IFG, a canonical MNS region. Likewise, in the secondary subset analysis, clusters that emerged as significantly overconnected in both MNS and ToM networks also contained regions from the other network (Table 4); for instance, the rIPS seed of the MNS was overconnected (ASD > TD) with the PCC region of ToM. This pattern of atypical ToM-MNS cross talk suggests that the 2 social brain systems putatively impaired in ASD8,33-35 are less functionally segregated from one another in adolescents with ASD. This is in contrast with typical development, during which functional brain networks become simultaneously more integrated (within-network connections strengthen) and segregated (between-network connections weaken).36,60,61 Thus, the excess ToM-MNS connectivity observed in ASD may reflect immature or aberrant development.

Table 2. Regions Exhibiting Group Differences (ASD vs TD) in FC, Separately for MNS and ToM Seedsa

<table>
<thead>
<tr>
<th>Seed</th>
<th>Peak Location</th>
<th>Talairach Coordinates</th>
<th>Cluster Volume, μL</th>
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</tr>
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<tbody>
<tr>
<td>MNS</td>
<td>lIPS None</td>
<td>x: -50 y: -28 z: 12</td>
<td>918</td>
<td>4.64</td>
</tr>
<tr>
<td></td>
<td>rIPS None</td>
<td>x: 20 y: -34 z: 26</td>
<td>918</td>
<td>3.75</td>
</tr>
<tr>
<td></td>
<td>IPMC None</td>
<td>x: -56 y: -26 z: 12</td>
<td>2808</td>
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<tr>
<td></td>
<td>rPMC None</td>
<td>x: 2 y: -44 z: 50</td>
<td>2322</td>
<td>4.46</td>
</tr>
<tr>
<td></td>
<td>lSTS None</td>
<td>x: 46 y: -20 z: 14</td>
<td>1485</td>
<td>4.47</td>
</tr>
<tr>
<td>ToM</td>
<td>rTPJ L, superior temporal gyrus/pSTS</td>
<td>x: -14 y: -62 z: 50</td>
<td>1755</td>
<td>-4.82</td>
</tr>
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<td></td>
<td>rTPJ R, middle temporal gyrus</td>
<td>x: 46 y: -50 z: 20</td>
<td>810</td>
<td>-4.33</td>
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<tr>
<td></td>
<td>rPCC None</td>
<td>x: 38 y: 26 z: 38</td>
<td>999</td>
<td>-5.17</td>
</tr>
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</table>

Table 3. Correlations Between Connectivity Indices and Social Symptoms Measures in Participants With Autism Spectrum Disordera

<table>
<thead>
<tr>
<th>Variable</th>
<th>ADOS-CS</th>
<th>ADI-R Social</th>
<th>ADI-R Communication</th>
<th>SRS Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ToM overconnectivity (PCC, mPFC)</td>
<td>-0.29</td>
<td>0.45b</td>
<td>0.51c</td>
<td>-0.04</td>
</tr>
<tr>
<td>ToM underconnectivity (bilateral TPJ)</td>
<td>-0.14</td>
<td>0.22</td>
<td>0.05</td>
<td>-0.42</td>
</tr>
<tr>
<td>MNS connectivity</td>
<td>-0.10</td>
<td>0.56b</td>
<td>0.47b</td>
<td>-0.26</td>
</tr>
<tr>
<td>ToM-MNS between-network connectivity</td>
<td>-0.07</td>
<td>0.58c</td>
<td>0.37d</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Abbreviations: ADI-R, Autism Diagnostic Interview–Revised; ADOS-CS, Autism Diagnostic Observation Schedule Communication + Social; MNS, mirror neuron system; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; SRS, Social Responsiveness Scale; ToM, theory of mind; TPJ, temporal-parietal junction.

a All correlation coefficients are calculated with Spearman rank correlations for n = 25.

b P < .05 (uncorrected).

c P < .01 (uncorrected).

d P < .003 (Bonferroni corrected, P < .05).

The detection of ToM overconnectivity in ASD is particularly noteworthy given the findings indicating reduced activity in the ToM and MNS networks plays a role in autistic symptomatology.

Overconnectivity was most pronounced in a subsample of 15 participants with ASD with the highest symptom severity. As one possibility, cross talk between ToM and MNS, which largely accounted for the overconnectivity effects, might reflect a compensatory mechanism involving strengthening of the atypical connections secondary to social deficits. Specifically, the dynamic nature and complexity of social stimuli and social interactions may be overtaxing for inefficient neural networks in ASD; as a result, overconnectivity may be a consequence of an overuse of aberrant social circuits. The observed links between ToM-MNS cross-network connectivity and sociocommunicative symptom severity may support this interpretation. At the very least, these findings suggest that connectivity of and between the ToM and MNS networks plays a role in autistic symptomatology.
There were several key findings in the study. Firstly, there was evidence of reduced specialization of mentalizing brain regions in autism, as demonstrated by activation for tasks that do not pertain to ToM. This suggests that the ToM network is considered crucial for understanding the social impairments observed in ASD.

Secondly, the study observed a greater ToM connectivity in ASD, which might be in line with the idea that social dysfunction is associated with heightened activity associated with reduced efficiency and behavioral impairment in this domain.

The findings also suggest links between ToM and MNS connectivity and ASD socio-communication impairment. While the study observed reduced connectivity between the networks, this pattern of findings could suggest that at least some of the atypical ToM and MNS connectivity observed here may reflect neural abnormalities possibly contributing to the early emergence of the disorder.

The conclusions of the study are that the current results demonstrate atypical connectivity of and between ToM and MNS networks in adolescents with ASD, predominantly reflected in overconnectivity. Moreover, the extent of atypical connectivity was correlated with greater social dysfunction, suggesting that abnormal neural connections involving the mentalizing and mirror neuron systems are related to the social impairments observed in ASD.
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REFERENCES


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