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Excessive Functional Coupling With Less Variability Between Salience and Default Mode Networks in Autism Spectrum Disorder

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ABSTRACT

BACKGROUND: Atypical activity in the salience network (SN) and default mode network (DMN) has been previously reported in individuals with autism spectrum disorder (ASD). However, no study to date has investigated the nature and dynamics of the interaction between these two networks in ASD.

METHODS: Here, we aimed to characterize the functional connectivity between the SN and the DMN by using resting-state functional magnetic resonance imaging data from the Autism Brain Imaging Data Exchange and comparing individuals with ASD (n = 325) to a typically developing group (n = 356). We examined static and dynamic levels of functional connectivity using the medial prefrontal cortex (mPFC) seed as a core region of the DMN.

RESULTS: We found that individuals with ASD have higher mPFC connectivity with the insula, a core region of the SN, when compared with the typical development group. Moreover, the mPFC-insula coupling showed less variability in ASD compared with the typical development group. A novel semblance-based network dynamic analysis further confirmed that the strong mPFC-insula coupling in the ASD group reduced spontaneous attentional shift for possible external elements of the environment. Indeed, we found that excessive mPFC-insula coupling was significantly associated with a tendency for reduced social responsiveness.

CONCLUSIONS: These findings suggest that the internally oriented cognition in individuals with ASD may be due to excessive coupling between the DMN and the SN.

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social and communication abilities along with restricted and repetitive patterns of behaviors and interests (1). Despite significant improvements in the diagnosis, treatment, and support programs of ASD, the neurobiological underpinnings of the core and associated symptom domains remain poorly characterized. Recent theoretical and empirical findings have highlighted that atypical activities in the default mode network (DMN) (2,3) and salience network (SN) may be contributing to the expression and severity of different aspects of ASD, including reduced social attention and motivation, as well as cognitive and behavioral inflexibility (4–6).

The DMN has been considered as the main neural network for self-referential processing (7–10). Considerable evidence shows that the DMN is typically more activated when individuals have an internal (e.g., stimulus-independent thoughts or internally oriented cognition) (11) rather than an external (i.e., an attention-demanding task) (12) focus of cognition. Thus, increased DMN activity appears to reflect stimulus-independent thought processes (13) when an individual disengages their attention from external information. Studies suggest that those with ASD show heightened neural activity in the DMN, which then results in a failure to give attention to external salient inputs, such as social or environmental cues that need to be attended to and processed (14–16).

The SN, anchored in the anterior insula and the dorsal anterior cingulate cortex, is believed to play a role in identifying environmental salient stimuli and in reconfiguring brain connectivity to process it (6). Resting-state and task-related functional magnetic resonance imaging (fMRI) studies (4,5,17) show that individuals with ASD often have atypical functionality in the SN, especially in the insula. Di Martino *et al.* (4) observed that the regional homogeneity and degree centrality of the insula region was significantly decreased in ASD, which suggests a reduced sensitivity in the SN to external stimuli (5). Importantly, a recent study used SN connectivity patterns to classify children with ASD from typically developing children and to predict the severity of the restricted and repetitive behaviors in ASD (17). These findings indicate that SN dysfunction may be an additional underlying mechanism causing individuals with ASD to be less responsive to external sensory information.

Although the critical role of the DMN and SN in ASD has been investigated extensively, the nature of the interrelationship between these networks is still unclear. It is unknown how the interaction between the regions in the SN and DMN contributes to the exaggerated internally oriented cognition and

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the reduced responsiveness to external stimuli seen in ASD. Studies examining typical development (TD) samples show that the SN has a central role in shifting network configurations, either moving from a state of deep, internally oriented cognition to one where attention is focused externally or vice versa (18–21). When there are no external inputs, the SN inhibits executive processing by functional decoupling for executive networks such as the frontal-parietal network (FPN), while also increasing its functional coupling with the DMN to maintain an internally focused state. However, when there are sensory inputs to actively process, the functional coupling between the SN and executive networks increases while the DMN is functionally decoupled from the SN. In other words, if the SN fails to disassociate from the DMN, individuals will not switch appropriately from an internally oriented cognition to a state with an external focus. The SN changes the network configuration spontaneously to monitor possible environmental changes (22,23). For example, Kucyi *et al.* (23) showed that the SN coupled and decoupled between the attention network and the DMN regardless of the experimental conditions, suggesting that moment-to-moment attentional fluctuations can also occur without external sensory inputs.

In this study, we examined the configuration dynamics between the SN and DMN in those with ASD. In particular, we hypothesized that ASD would be associated with greater functional coupling between the DMN and SN due to hyperactivity in the DMN. To test this hypothesis, we conducted a seed-based, static functional connectivity analysis at the whole-brain level with a medial prefrontal cortex (mPFC) seed. Although the DMN consists of not only mPFC but also the lateral and posterior medial parietal cortices, lateral temporal cortex, and anterior and posterior cingulate cortices (24–27), the mPFC is identified as a core region of self-relevance and social functions of the DMN (8–10,28–30). In addition, in previous studies of autism, mPFC-related alterations are the most consistent findings compared with those of any other region of the DMN (7,31–34). We expected that the ASD group would show more mPFC coupling with regions in the SN, such as the insula. We further hypothesized that the moment-by-moment neural coupling between the DMN and SN should be less variable in the ASD group, whereas there would be greater variability in connectivity changes in the TD group (22,23). To test this additional hypothesis, we performed a dynamic functional connectivity analysis to measure the variability of the connectivity between the mPFC and regions in the SN over time. Furthermore, we used a novel semblance-based network dynamic analysis (SNDA) to estimate the network switch in the neural configuration that occurs between the SN and each of the DMN and the FPN. Finally, we checked whether the observed connectivity pattern was associated with a tendency for social responsiveness (35).

METHODS AND MATERIALS

Autism Resting-State fMRI Dataset and Preprocessing

This study was carried out using resting-state fMRI data from the Autism Brain Imaging Data Exchange (4). The dataset was initially downloaded through the Mind Research Network's collaborative informatics and neuroimaging suite (36)[1]. We only included individuals with more than 100 volumes, full coverage of both T1 and echo-planar images, and without motions (framewise displacement $>$ 0.5 mm), resulting in 681 samples: 325 in the ASD group (mean age = 16.02 years, SD = 7.69, SEM = 0.430, range = 7−58 years; 12.54% female) and 356 in the TD group (mean age = 16.32 years, SD = 6.94, SEM = 0.361, range = 6−48 years; 18.01% female) (Table S1). There were no group differences in age (t_{679} = 0.283, p = .777, 95% $CI^{5000\ bootstrap}$ = −1.008 to 1.208, Cohen's d = 0.022, Bayes factor 10 [BF_{10}] = 0.089) (JASP, 0.14.1 version; https://jasp-stats.org/).

Preprocessing was performed using FSL (37), ICA-AROMA (38), and ANTs (39). Preprocessing included a 0.001 to 0.08 Hz bandpass filter, first 10 volumes cut, motion correction, 5-mm smoothing, slice-timing correction, intensity normalization, regressing out cerebrospinal fluid/white matter with individually segmented masks, independent component analysis denoising (corrected mean framewise displacement = 0.038 mm, range = 0.015–0.096 mm), and registration to standard Montreal Neurological Institute 2-mm echo-planar image brain template (40).

mPFC Seed-Based Static Functional Connectivity

Based on our hypothesis, we performed a seed-based connectivity analysis using the mPFC as the core seed region in the DMN. To this end, we extracted the mean time series of the mPFC using a previously defined mask (voxel number k = 5257; the center of gravity: x = −3, y = 49, z = 16) (Figure 1A) (41). A multiple regression analysis was performed to estimate individual functional connectivity between the mPFC and all other voxels. Then, individual-level mPFC seed connectivity maps were inputted into a nonparametric group-level analysis using the FSL *randomise* (5000 permutations) combined with threshold-free cluster enhancement correction at p = .05 (42) with two between-group designs: (ASD $>$ TD) and (ASD $<$ TD). We additionally included a mean-centered age covariate in the design matrix as a continuous nuisance regressor to attenuate age effects.

mPFC-Insula Connectivity Variability

In addition to mPFC seed analysis that identified a static mPFC connectivity with the insula on average, we evaluated how stable the functional connectivity between the mPFC and insula stayed in terms of moment-by-moment connectivity changes (Figure 1B). To quantify the stability of functional connectivity, we first examined dynamic functional connectivity (22) with mPFC and insula activity by using the tapered sliding window approach, 50-repetition time window using the Dynamic Correlation Toolbox (43) (for the region of interest mask, see the Supplement). We then calculated the mean square successive difference (MSSD) value (44) of connectivity strengths between sliding window segmented connectivity matrices as measures of moment-by-moment

[1]For downloading the dataset, we used the following set of keywords: [(Studies: ABIDE) AND (Subjects: PATIENT OR CONTROL) AND (Collection Technique: rest fMRI OR resting-state fMRI OR rest state fMRI OR Functional)].

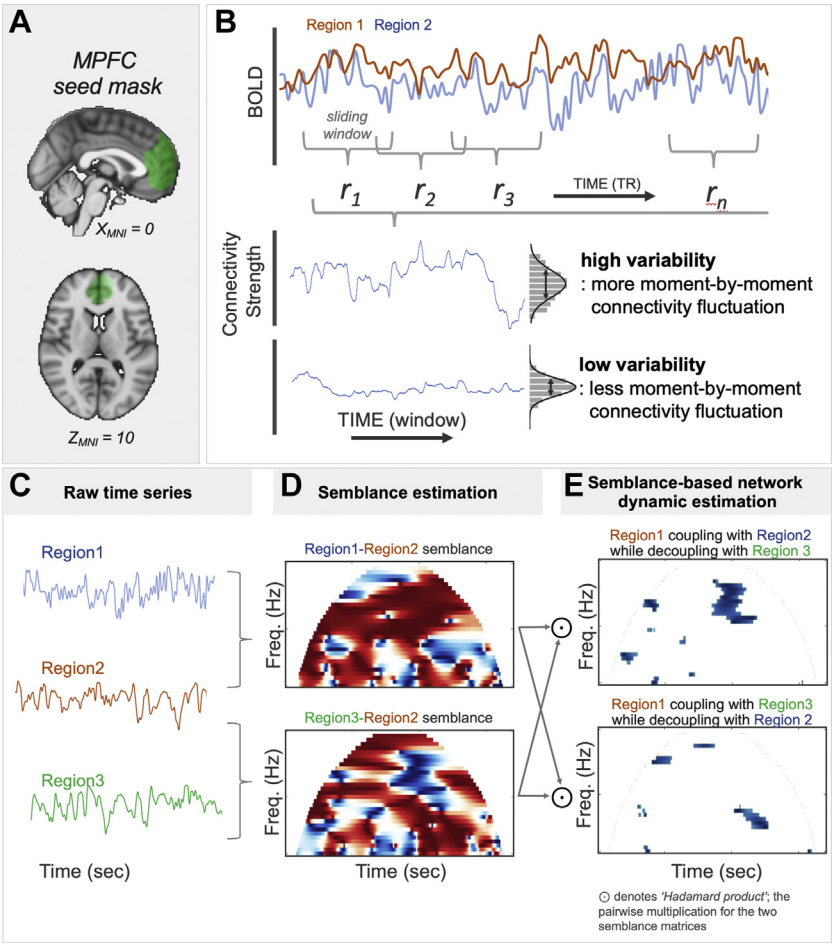

Figure 1. **(A)** Medial prefrontal cortex (MPFC) seed mask used in the seed-based static functional connectivity analysis. **(B)** Schematic figure of connectivity variability estimation. Using sliding windows, the connectivity strength value between regions was computed for each sliding window. **(C–E)** Schematic description of the semblance-based network dynamic analysis. Note that the semblance analysis **(D)** and semblance-based network dynamic analysis **(E)** are restricted in a semicircle due to filtering out the values that are contaminated by edge effects in each frequency. BOLD, blood oxygen level–dependent; Freq., frequency; MNI, Montreal Neurological Institute; TR, repetition time.

connectivity change across time, namely connectivity variability. MSSD is calculated by subtracting time point *t* from time point *t* + *1* and squaring the result. The squared values across the time are then averaged to produce an MSSD value (see equation 1).

$$\delta^2 = \sum_{i=1}^{n-1} (x_{i+1} - x_i)^2 \Big/ (n-1) \quad (1)$$

where δ^2 pertains to mPFC-insula connectivity fluctuation across time, *i* pertains to each sliding window, and *n* pertains to the number of observations for each individual. A low MSSD represents low moment-to-moment connectivity variability (i.e., high stability) between regions.

Semblance-Based Network Dynamic Analysis

To further capture the dynamic changes in connectivity based on the network switching model (6,20), we used a novel SNDA (Figure 1C). The analysis is based on a wavelet-based semblance analysis, which has been used in geoscience to compare the phase information of two different signals (45). A wavelet-based semblance analysis first transforms the two signals (e.g., A and B) into a time-by-frequency matrix (e.g., CWT_A and CWT_B) using a continuous wavelet transformation. Then, the semblance between signal A and B is calculated (see equations 2 and 3).

$$CWT_{A,B} = CWT_A \times CWT_B \quad (2)$$

$$S_{A,B} = \cos\left(\tan^{-1}\left(\Im\left(CWT_{A,B}\right)/\Re\left(CWT_{A,B}\right)\right)\right) \quad (3)$$

where $\times$ is the cross-wavelet transformation, $\Im$ is the imaginary part of $CWT_{A,B}$, and $\Re$ is the real part of $CWT_{A,B}$. $S_{A,B}$ produces a time-by-frequency matrix with values ranging from -1 to 1, where -1 indicates a π (or 180°) phase difference and 1 indicates a 0 phase difference between two signals A and B. Therefore, the method provides an interpretable measure of the phase similarity between the two signals across different frequency bands and can serve as a proxy for the degree of coupling between the two signals. The SNDA further extends the semblance analysis by taking the

Hadamard product (elementwise product) of the two semblance matrices to generate a semblance-based dynamics (SND) value (see equation 4).

$$SND_{AB,AC} = S_{A,B} \odot S_{A,C} \quad (4)$$

It offers a way to examine the phase interactions between two semblance results, where the values also range from −1 to 1. For example, suppose that there are three signals (e.g., A, B, and C) originating from three different sources. When calculating the SND from two semblances $S_{A,B}$ and $S_{A,C}$ (which is denoted as $SND_{AB,AC}$), a negative SND value indicates that one pair of signals (e.g., A and B) is coupling, while another pair of signals (e.g., A and C) is decoupling. Alternatively, a positive value indicates that both pairs of signals (e.g., A–B and A–C) are coupling at the same time.

Compared with previous methods used in measuring neural coupling (e.g., correlation coefficient), the SNDA has a couple of novel aspects. First, because it is based on a wavelet method, it measures the coupling dynamics continuously across time points and also across a predefined frequency range. Second, unlike measuring the degree of coupling between a pair of neural time series, SNDA can measure the coupling dynamics between pairs of neural series. For example, a correlation coefficient value will only provide the degree of coupling between site A and site B (i.e., if A and B are syncing, the value will be near 1, whereas if A and B are desyncing, the value will be close to −1). On the other hand, the SNDA is able to generate a single measure of whether sites A and B are coupling while sites C and D are decoupling, or whether sites A and B are decoupling while sites C and D are coupling. In other words, the SNDA is able to capture a broader pattern of dynamic change (i.e., more than one pair at the same time) compared with previous methods such as correlation coefficients. In this study, we first calculated the semblance between the insula-mPFC ($S_{I,M}$) and between the insula-FPN ($S_{I,F}$) to measure the degree of coupling for each pair. Then, we calculated the semblance-based network dynamics ($SND_{IM,IF}$) using the semblance matrices $S_{I,M}$ and $S_{I,F}$. Before taking the Hadamard product, we discarded semblance values that were above −0.7 and below 0.7 for each semblance. A cutoff value of ±0.7 roughly includes only signals that have a phase difference of less than $\pi/4$ (see Figure S1 for various criteria). The analysis was implemented using the cwt function in MATLAB 2020a (The MathWorks, Inc.) with a Morlet wavelet and frequencies ranging from 0.01 to 0.08. We excluded the area that could be contaminated by the edge effect in each frequency using the cone of influence results from the cwt function. Each cluster was estimated by using the contour function.

Social Reciprocity Assessment

To confirm that the alteration of the mPFC-insula coupling was associated with reduced social reciprocity in ASD, we conducted regression analyses between the connectivity metrics and social reciprocity scores, including the Social Responsiveness Scale (SRS) (35) and the Autism Diagnostic Observation Schedule (ADOS) (46). The SRS provides a quantitative measurement that captures an individual's characteristics of social behavior, with a higher SRS score indicating a worse performance in reciprocal social behaviors. The ADOS provides the severity of ASD features used for diagnostic measure (47). For the SRS, we combined all available individuals across groups because the measurement is not limited for a specific diagnostic purpose (n = 195; ASD = 101; TD = 94) (see Table S5 for results of each group). The ADOS is only for individuals with ASD, and thus we only included 199 ASD samples. Statistical significance was tested at α = 0.05 through bootstrapping (n = 5000) combined with the robust method (48).

RESULTS

mPFC Seed-Based Static Functional Connectivity

Whole-brain connectivity analysis of the mPFC seed between groups showed that compared with the TD group, the ASD group exhibited a significant increase in functional connectivity between the mPFC and the right anterior insula (Figure 2A). Because the anterior insula is considered to be the core region of the SN (6,20), this suggests that the mPFC, which is a core region of the DMN, is connected to the SN more strongly in the ASD group than in the TD group (Table S2 and Figure S3)[2]. The right anterior insula remained significant even when the scan site variance was controlled (see the Supplement). We also performed network region of interest analysis to confirm that the increased mPFC-insula reflected excessive connectivity between the DMN and SN and found consistent results (see the Supplement for a robustness check of SN-DMN coupling).

mPFC-Insula Connectivity Variability Over Time

Because the static functional connectivity analysis showed a stronger mPFC-insula connectivity in the ASD group than in the TD group, we next estimated functional coupling stability between the mPFC and insula. We found that the ASD group showed less variability (mean = 0.018, SD = 0.009, SEM = 0.0003) in their mPFC-insula connectivity than the TD group (mean = 0.034, SD = 0.005, SEM = 0.001) (t_{679} = 28.364, $p < .001$, 95% CI = 0.015 to 0.017, Cohen's d = 2.176, $BF_{10} > 10{,}000$) (Figure 2B). The results indicated that mPFC-insula coupling was more stable over time in the ASD group than in the TD group.

Semblance-Based Network Dynamic Analysis

Based on the network switching model, as the SN increases functional connectivity with the FPN, attentional orientation switches from internal to external, and contemporaneously, connectivity between the SN and the DMN decreases. We inferred that the stable mPFC-insula connectivity in the ASD group reflects a reduction in externally directed monitoring behavior (i.e., a reduction in monitoring one's surrounding for changes). In the TD group, though, the higher variability in the mPFC-insula connectivity can be interpreted as the SN (i.e., insula) increasing the functional connectivity with the FPN while inhibiting the DMN (i.e., mPFC) to direct attention to the external surroundings spontaneously and momentarily. From the calculated SND, we identified time × frequency clusters 1)

[2]For all uncorrected maps, see *NeuroVault:* https://neurovault.org/collections/10441/

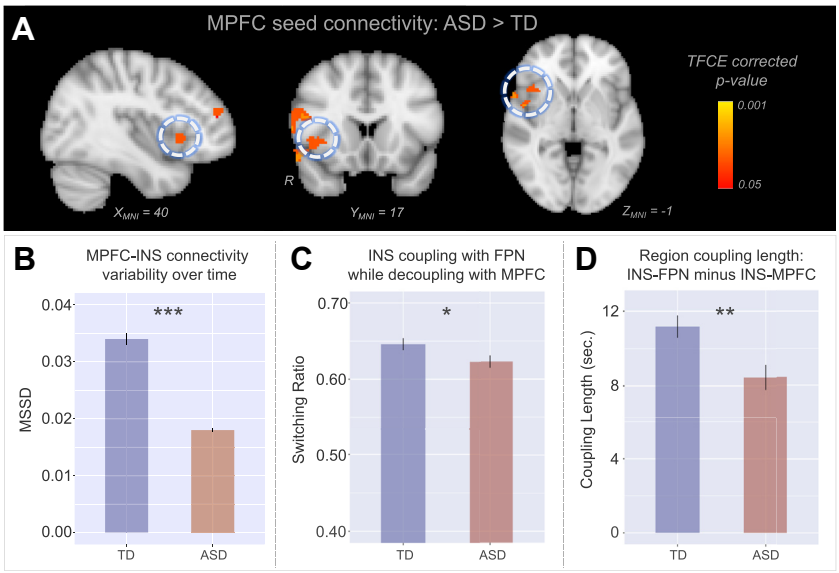

Figure 2. **(A)** Nonparametric group-level medial prefrontal cortex (MPFC) seed connectivity analysis results (5000 permutations with threshold-free cluster enhancement [TFCE] correction), showing stronger coupling with the insula (INS) in autism spectrum disorder (ASD) compared with typical development (TD). **(B)** MPFC-INS connectivity variability (mean square successive difference [MSSD]) on average, showing more stable mPFC-INS coupling over time (i.e., low MSSD) in ASD compared with TD. **(C, D)** Semblance-based network dynamic analysis results for the proportion **(C)** and duration **(D)** of frontal-parietal network (FPN) switch. Error bars denote the standard error term. ***$p < .001$, **$p < .01$, *$p < .05$ at 95% confidence interval after bootstrapping resampling ($n = 5000$). MNI, Montreal Neurological Institute.

where the insula was coupling with the FPN but decoupling with the mPFC (a switch to FPN [FPN-switch]) and 2) where the insula was coupling with the mPFC but decoupling with the FPN (a switch to mPFC [mPFC-switch]). For each participant, we counted the number of FPN-switches and mPFC-switches to measure the relative proportion of FPN-switches (i.e., FPN-switch/[FPN-switch + mPFC-switch]). We also calculated the mean duration of these time × frequency clusters and calculated the duration difference between the FPN-switch and mPFC-switch for each participant (length of FPN-switch minus length of mPFC-switch).

As shown in Figure 2C, the ASD group showed a lower proportion of FPN-switches (mean = 0.623, SD = 0.140, SEM = 0.008) than the TD group (mean = 0.646, SD = 0.141, SEM = 0.008) ($t_{679} = 2.12$, $p = .034$, 95% CI = 0.001 to 0.435, Cohen's $d = 0.163$, $BF_{10} = 0.77$), and the length difference between the FPN-switch and mPFC-switch was shorter for the ASD group (mean = 8.45 seconds, SD = 10.79, SEM = 0.598) than the TD group (mean = 11.181 seconds, SD = 12.66, SEM = 0.671) ($t_{679} = 3.01$, $p = .003$, 95% CI = 0.953 to 4.459, Cohen's $d = 0.231$, $BF_{10} = 7.06$) (Figure 2D) (see the Supplement for a robustness check on using different criteria for the analysis). Therefore, results from both the proportion and length measures implied that the ASD group had a relatively infrequent and shorter coupling between the FPN and insula than the TD group.

mPFC-Insula Connectivity Correlates of Social Behavior

The regressions analyses revealed that MSSD of mPFC-insula connectivity negatively predicted the SRS score

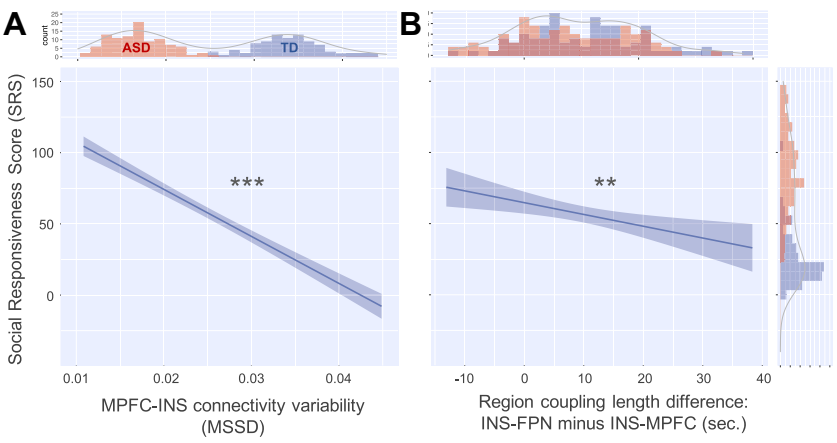

Figure 3. Results of linear regression analysis for the relationship of Social Responsiveness Scale (SRS) score with **(A)** medial prefrontal cortex (MPFC)–insula (INS) connectivity variability and **(B)** INS coupling switching length difference. The shaded area indicates the 95% confidence intervals. Asterisk denotes statistical significance at $p < .05$ level after $n = 5000$ bootstrapping resampling. ASD, autism spectrum disorder; FPN, frontal-parietal network; MSSD, mean square successive difference; TD, typical development.

(B = −3247.684, SE = 192.632, $p < .001$, 95% CI = −3628.598 to −2873.577) (Figure 3A), indicating that individuals with less change in the mPFC-insula connectivity showed reduced social responsiveness tendency. We found that the connectivity length difference of the insula switch was also significantly predictive of the SRS score (i.e., insula-FPN minus insula-mPFC; B = −0.837, SE = 0.248, $p < .01$, 95% CI = −1.292 to −0.324) (Figure 3B), that is, individuals with a higher social tendency score exhibit more frequently coupled insula connectivity with the FPN even during the resting state. To sum, these results not only indicate possible underlying neural mechanisms of the reduced social tendencies in ASD but also support the suggested circuit model regarding social behavior in general. However, we did not find such significant relationships between participants' ADOS score and their circuit variability ($p = .320$, 95% CI = -7.942×10^{-5} to 2.464×10^{-4}) and length difference ($p = .337$, 95% CI = −0.562 to 0.160).

DISCUSSION

In this study, we examined how the DMN and SN interacted in individuals. We found that the mPFC, a core DMN region, shows a stronger coupling with the insula, a core SN region, in the ASD group. We further found that the mPFC-insula coupling was stronger and more stable in the ASD group than in the TD group at the dynamic level of functional connectivity. Finally, results from the SNDA showed that the TD group had relatively frequent coupling between the FPN-insula and longer coupling durations between the FPN-insula compared with the ASD group. Importantly, we found that this reduction of configuration switches in the brain is associated with reduced social responsiveness, indicating that excessive mPFC-insula coupling may lead individuals to reduce their attention to the outside world and, consequently, social interest. Our findings are important in two ways. First, the findings are consistent with those of previous studies demonstrating the importance of the DMN and SN in the brains of those with ASD (14,17,20,49,50). It suggests that research into the mechanisms of ASD must also look beyond a single region or network. Second, by adopting the semblance-based time-frequency analysis and the SN-based network switching model (20), we have provided more detailed information on how these three intrinsic networks are synced and desynced across time, allowing this research to test the SN-based switching model more interactively.

This study extends previous findings by providing evidence that ASD exhibits limited mPFC-insula connectivity fluctuations over time, which may lead to reduced spontaneous attention shifts toward the environment. According to recent models (6), the SN inhibits DMN activity (i.e., functional decoupling) to change attentional orientation from an internal self-processing state to the external environment. Thus, the insula, as a core node of the SN, can exhibit dynamic properties to influence neural configurations spontaneously even without external stimuli being present (22,23) to continuously monitor for changes in the surrounding environment. Therefore, the stability of the mPFC-insula connections found in the ASD group can explain why individuals with ASD exhibit more internally oriented cognition and are less responsive to their external surroundings. However, this study only used intrinsic brain activity measured using the resting-state data to explore the mPFC-insula connectivity fluctuation. Although recent studies have consistently suggested that intrinsic neural activity is the backbone of the individual's psychosocial and behavioral tendencies (51), predicting task performance (52) and psychosocial behaviors (53,54), it is worth doing task-based fMRI studies in the future to examine whether this intrinsic spontaneous fluctuation in the mPFC-insula connection can lead to difficulties of attentional shifting and social cognition in ASD in the context of task-based measurement.

The strong relationship between mPFC-insula connectivity and the SRS score is worth noting. Previous clinical studies showed that the SRS can measure the degree of social deficits experienced by individuals with ASD (55–57) and attention-deficit/hyperactivity disorder (ADHD) (58) and by children from families exhibiting subthreshold autistic traits (59) or by those who have a sibling with autism or another pervasive development disorder (60). Although the SRS is mainly developed to evaluate the social characteristics of individuals with ASD, it is also used to identify individuals with limited social environment and functioning (46). For example, studies used the SRS to evaluate social characteristics of children with cardiac disease (61), in utero endocrine disrupter exposure (62), social anxiety disorders (63), an extra X chromosome (64), and other pervasive developmental disorders (60). That is, the utility of SRS is applicable to typical/subclinical populations (46,65,66). Thus, we examined the relationship between brain connectivity features and social tendencies using the SRS as a continuous variable across all samples. In this context, our findings of the relationship between circuit characteristics and social behavior may imply that the mPFC-insula circuit mechanism is a factor influencing the individuals' social-cognitive attention. Although the SRS scores across samples overlap when the distributions are plotted for each group separately, the middle range of the SRS (see the SRS score distribution in Figure 3; around 50) has relatively few samples. Thus, such a relationship between the SRS and brain features reported here requires cautious interpretation because we cannot fully eliminate the potential group effects. Finally, the results need to be referenced as an exploratory observation. Future studies may include ADHD and other clinical/subclinical populations with social or attentional deficits to explore a more comprehensive relationship between mPFC-insula connectivity and social-cognitive attention.[3]

It is still unclear what causes hyperconnectivity between the SN and the DMN in ASD. It may be due to either a limited sensitivity in detecting sensory changes or increased internally oriented cognition. If this excessive coupling is due to dysfunction of the SN, the lack of responsiveness to external stimuli observed in people with ASD could be an issue of initial sensory processing failing to prioritize external stimuli (4–6,17).

[3]As another autism diagnostic tool, we also examined the effect of the ADOS and found nonsignificant results. Nevertheless, the results were not surprising because ADOS scores were only collected for the ASD group, and the analysis was not performed along with the methods with which we examined mPFC-insula connectivity (i.e., including both groups). Moreover, there was no significant relationship found between the SRS and ADOS ($r = 0.043$).

Alternatively, it is possible that excessive coupling is due to DMN hyperactivation (14,15), which hinders the SN's ability to influence the switching of network configurations from the internally oriented mode (i.e., DMN) to the external attention mode (i.e., FPN). However, recent developmental studies provide evidence that the SN impairments may be the main cause (19). Studies found that older adults overinvest mental resources to process their external surroundings (i.e., the exact opposite case compared with ASD), suggesting that the failure of the SN in switching neural configuration from the DMN to the executive networks is the main source of older adults' increased distractibility. Similarly, studies involving children with ADHD imply that the impaired SN prioritizes the processing of external stimuli and leads children to be more prone to distraction by sensory inputs (67). Thus, it is more plausible to consider that the hyperactive DMN in ASD stems from impairments in the SN, which inhibits one from reorienting their processing focus from internal to external at the initial sensory step. However, given the nature of the resting-state blood oxygen level–dependent signal, the connectivity causality investigation is limited. Thus, a future study that includes social interactive features seems necessary.

The literature on ASD, however, reports mixed patterns of SN-related functional connectivity (6,17,68). An increased or decreased connectivity strength may depend on other factors, such as age-related effects, symptom severity, or medication status (11,17,69–71). In addition, inconsistent outcomes may result from divergent behavioral phenotypes across ASD and its comorbidities. Although atypical sensory features are common in ASD, the profiles of these vary across individuals, and sometimes within individuals, depending on the context (72). Nevertheless, an important limitation of the study is that the information in this dataset is insufficient to control or account for such divergence among symptoms. A future study with sufficient and balanced sample sizes in each demographic or phenotype group would help extend our findings.

In conclusion, these findings highlight deficits in network-wise configuration changes as a possible factor underpinning attentional impairments in ASD. The findings provide a mechanistic perspective that ASD symptoms might be associated with atypical dynamic brain configurations between independent intrinsic networks rather than, or in addition to, an atypical reactivity in a single region or network (73–75), which is a more integrated understanding of how different networks contribute to atypical behaviors in ASD. Furthermore, this study introduces a useful and novel approach not only for understanding individuals with ASD but also for furthering our understanding of the neural underpinnings of various neurodevelopmental and neuropsychiatric disorders with inattention symptoms such as ADHD (76,77).

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T-HL organized the project. Y-YC, T-HL, and HY analyzed and interpreted the data. Y-YC, JN, HY, and T-HL wrote the article. HY developed the semblance analysis method. All authors reviewed the manuscript.

Source data can be found at https://mfr.osf.io/render?url=https%3A%2F%2Fosf.io%2Fqjavk%2Fdownload.

The authors report no biomedical financial interests or potential conflicts of interest.

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