Common variant of CNTNAP2 gene modulate the social performances and functional connectivity of posterior right temporoparietal junction

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Abstract
Social deficits are features of autism and highly heritable traits. A common variant in autism-related CNTNAP2 gene, rs2710102, has been linked with social performance, but the neural substrates are largely unknown. We investigated variations in social performance and functional connectivity (static and dynamic) in the subregions of right temporoparietal junction (RTPJ), a key node of brain social network, using resting-state MRI (n=399) by genotype at rs2710102 in healthy volunteers. Social performance was evaluated using the social domain of the Autism-Spectrum Quotient (AQ-social) (n=641) and fixation time on eye areas during an eye-tracking task (n=32). According to previous evidence that the A-allele is the risk allele for social dysfunction, we classified participants into GG and A-allele carriers (AA/AG) groups. The A-allele carriers showed poor social performance (high AQ-social and short fixation time on eye areas) compared with the GG carriers. In the A-allele carriers, decreased stationary functional connectivity between the orbitofrontal cortex and posterior RTPJ (pRTPJ), and decreased dynamic functional connectivity (dFC) between the medial prefrontal cortex (mPFC) and pRTPJ were observed. The fixation time at eye areas positively were correlated with the pRTPJ-mPFC dFC. These findings provided insight for genetic effect on social behavior and its potential neural substrate.

**Keywords** CNTNAP2; social performance; temporoparietal junction; medial prefrontal cortex; dynamic functional connectivity

**Introduction**
Deficits in social interaction are core features of autistic spectrum disorders, a highly heritable neurodevelopmental disorder (Ronald and Hoekstra, 2011). These social impairments typically manifest as abnormalities in social interaction and difficulties in and recognition of expression and emotion (Bauminger, 2002). For example, individuals with autism were reported less attention paid to the eyes and other core features of faces during eye-tracking studies (Pelphrey et al., 2002). Recently, genetic behavior studies suggested that social-communication abilities are heritable traits and, hence, could be modulated by genetic variations (Skuse et al., 2014; St Pourcain et al., 2014). Contactin-associated protein-like 2 (CNTNAP2) is an important gene in the human genome and has been associated with autistic spectrum disorders (Arking et al., 2008). Although the CNTNAP2 gene was initially associated with language impairments in autism (Alarcon et al., 2008), mutations in CNTNAP2 may also be involved in social dysfunction. The A allele of rs2710102, a highly circumscribed region of the CNTNAP2 gene, has been associated with social anxiety-related disorders (Stein et al., 2011), of which a key feature is difficulty with social-communication (Pickard et al., 2017). Study in children with autistic trait also suggested that the A allele of rs2710102 has also been positively associated with levels of social inhibition (Steer et al., 2010).

The neural substrates of genotype effects on social performance remain largely unexplored. Recently, several lines of evidence have suggested that modulation of the CNTNAP2 genotype affects inter-region connectivity. At the cellular level, evidence suggests that Caspr2, a protein encoded by CNTNAP2, is important for neuronal
migration and subsequent laminar organization, which indicates a crucial role for CNTNAP2 in inter-region connectivity (Strauss et al., 2006). In addition, structural and resting-state functional imaging studies have also identified impaired inter-region connectivity in individuals who are carriers of the autism risk allele of CNTNAP2 (Scott-Van Zeeland et al., 2010; Tan et al., 2010). For example, a study using resting-state imaging suggested that risk carriers of common genetic variants in CNTNAP2 are associated with having impaired functional connectivity in the medial prefrontal cortex (Scott-Van Zeeland et al., 2010), a key node for reasoning about mental states (mainly reasoning about the minds of other people), which supports successful social interaction in realistic environments (Frith and Frith, 2012).

In addition to the medial prefrontal cortex, the temporoparietal junction (TPJ) is another key neural substrate involved in reasoning about mental states (Schurz et al., 2014; Apps et al., 2015). As a supramodal association area, the TPJ, and especially the right TPJ (RTPJ), contribute to several social functions, including theory of mind, social decision making, and moral judgment (Schurz et al., 2014; Ye et al., 2015; Bitsch et al., 2018), as well as other cognitive process, such as attentional processes (Krall et al., 2016). Based on task-related functional MRI data from the BrainMap database, the RTPJ is segmented into the anterior and the posterior RTPJ (aRTPJ, pRTPJ) via the method of coactivation-based parcellation (Bzdok et al., 2013). Functionally, the anterior and posterior parts of these regions are linked to antagonistic brain networks for attentional and social processing, respectively (Bzdok et al., 2013). Consistent with this, dysfunctions in the pRTPJ during social tasks have
reported in social-related disorders, such as autism (Abu-Akel et al., 2017). Increasingly, imaging studies have also suggested impaired functional connectivity of the TPJ with other social brain regions in autism (Venkataraman et al., 2015; Igelstrom et al., 2017), although functional connectivity based on the subregions of the TPJ remains largely unknown.

Previous studies on functional connectivity have mainly focused on static functional connectivity (sFC), which is based on the assumption of spatial and temporal stationarity throughout the entire scan period. This assumption may ignore the time-varying characteristics of inter-region connections, which have been implicated by other measurements with higher temporal resolutions, such as event related potentials (Makeig et al., 2004; Onton et al., 2006). To address this issue, recent studies with resting-state fMRI developed dynamic FC (dFC) analysis to estimate the variability of inter-region synchronization (Allen et al., 2014). The credibility of the dFC derived from resting-state fMRI has been demonstrated through simultaneous EEG/fMRI studies (Britz et al., 2010; Chang et al., 2013). As previous studies suggested, inter-regions dynamic connection may reflect several cognitive function and underlie neural substrate of brain disease (Liao et al., 2018; Liu et al., 2018). Such connectivity dynamics is also closely associated with genetics (Gao et al., 2014). Of significance, it enables identification of the neurobiological features associated with normal brain development (Hutchison and Morton, 2015) and social-related disorders (Rashid et al., 2018). Hence, exploring dynamic connection may be conducive to reveal the neural substrate underlies the genetic effect on social function.

In the present study, we explored the effect of a common variant of the CNTNAP2 gene, rs2710102, on social behavior and the static and dynamic functional connectivity of RTPJ subregions. Based on the close relationship between the A allele of rs2710102 and social disorders, we first hypothesized that individuals with the A
allele of rs2710102 may present poor social performance. Social behavior was evaluated using the social sub-scales of the Autism-Spectrum Quotient (AQ) and fixation on eyes during an eye-tracking task. Human eye-to-eye contact is a primary source for social cues that play a vital role in social interaction and communication (Kendon, 1967). Gaze perception activates a social network of brain regions, including both the TPJ and medical prefrontal cortex (Carlin and Calder, 2013; von dem Hagen et al., 2014). Given that the CNTNAP2 gene potentially impacts on social-network inter-region connectivity and there are functional distinctions between the anterior and posterior RTPJ, we further assumed that a common variant of the CNTNAP2 gene, rs2710102, modulates functional connectivity (static and dynamic) differently in the anterior and posterior RTPJ. Specifically, the significant modulatory effect may be only existent for the social seed area (the posterior RTPJ), but not the attentional seed area (the anterior RTPJ).

**Materials and methods**

**Participants**

All participants were college students from Anhui Medical University. After receiving a complete description of the study, all participants provided written informed consent. The present study was approved by the Ethics Committee of Anhui Medical University. Exclusion criteria for participants included neurological or psychological diseases, alcohol or drug abuse, traumatic brain injury, or visible brain structure abnormity. Participants with a first-degree relative with a neurological or psychiatric
disorder were also excluded.

First, a total of 641 eligible participants completed the AQ, which is frequently used in measuring autistic traits and consists of social and non-social aspects as described below (Davis et al., 2017). Of these participants, rs2710102 genotype data were available for 504 participants (the sample was chosen to explore the effect of genotype social function). From the participants with available behavior (AQ) and genotype data, 447 participants completed MRI scanning. After excluding participants with poor MRI data (resulting from artifacts or excessive head motion), a total of 399 participants were included in the final analysis of functional connectivity. Of these participants, 32 participants completed the eye-tracking task.

**Autism-Spectrum Quotient (AQ)**

The AQ is increasingly used in the screening of individuals for high levels of autistic traits. It consists of 50 items, which are divided into five dimensions: communication, social skill, attention switching, imagination, and attention to detail (Baron-Cohen et al., 2001). On the basis of previous studies, there are social aspects (AQ-Social, including communication, social skills, attention switching, and imagination) and one non-social aspect (attention to detail) in the AQ (Davis et al., 2017). The AQ-social provided one index in our study to evaluate social performance. In present study, we used the Chinese version of AQ, which has good reliability (0.89) and validity (0.81) (Zhang et al., 2016). We adopted the 4-point Likert scoring system. Scores range from 1 to 4 for items showing autistic features: “definitely agree” scored 4 points, “slightly
agree” scored 3 points, “slightly disagree” scored 2 points, and “definitely disagree” scored 1 point. Some items were reverse scored.

**Eye-tracking task**

The eye-tracking task was performed using an integrated SMI Eye Tracking (SensoMotoric Instruments, Germany) to evaluate the fixation time on the interest areas of stimuli. All stimuli in the tracking task included 24 faces adapted from the Chinese Faces Affective Picture System (CFAPS). There were two male and two female faces for each of the six basic emotions, and balanced by age, sex, and emotion. Participants were instructed to look at the photographs in any manner they selected. The faces were divided into four areas of interest (AOI): the eyes, nose, mouth and non-core feature areas (the rest area of the face). The eyes-AOI can cover the eyes of each image shape covering 3% of the surface of the image (the same as the nose-AOI (1%), mouth-AOI (2%) and the non-core feature-AOI (94%)) (Supplementary materials, Figure S1). In present study, we mainly treated fixation time on eye-AOI as index for social performance, in contrast, the fixation time on non-core feature AOI was treated as index for non-social performance. The non-social performance may alter at different direction with the social performance. More information about the eye-tracking task could be found in the Supplementary materials.

**CNTNAP2 Genotyping**
Blood samples were collected to obtain DNA with standard procedures. The genotyping of all participants was determined in comparison with control DNA confirmed by sequencing in the SNP pattern. The genotype of rs2710102 is GG, GA, and AA. According to previous studies suggesting that the A allele is the risk allele for social dysfunction, we classified the genotypes of rs2710102 into GG and A carriers (AA/AG) groups. More information about the gene scanning could be found in the Supplementary materials.

**Image Data Acquisition**

Structural and functional MRI for each participant was obtained using a 3-T scanner (Discovery GE750w) at University of Science and Technology of China. During functional MRI scanning, participants were instructed to keep their eyes closed, but not to fall asleep and not specifically try to think of anything in particular. Functional images were acquired composed of 217 echo-planar imaging volumes with the following parameters: repetition time = 2,400 ms; echo time = 30 ms; flip angle = 90°; matrix size = 64 × 64, field of view = 192 × 192 mm²; slice thickness = 3 mm; 46 continuous slices (one voxel = 3 × 3 × 3 mm³). High spatial resolution T1-weighted anatomic images with 188 slices were also acquired in sagittal orientation (TR = 8.16 ms; TE = 3.18 ms; flip angle = 12; field of view = 256 × 256 mm²; slice thickness = 1 mm; and voxel size = 1 × 1 × 1 mm³).

**Functional Data Preprocessing**
Functional MRI data were preprocessed with the Data Processing Assistant for Resting-State Functional MR Imaging toolkit (Chao-Gan and Yu-Feng, 2010). For each participant, we applied the following processing steps: discarding of the first 5 volumes to achieve a steady-state, slice timing correction, realignment, spatial normalization based on the unified segmentation of structural images, nuisance regressors with 24 Friston motion parameters, white matter high signal, cerebrospinal fluid signal and global signals as regressors, filter with a temporal band-pass of 0.01-0.1 Hz and spatial smoothing (Gaussian kernel = 4 × 4 × 4 mm). Finally, motion scrubbing was conducted using the method of cubic spline to minimize the influence of the time points with high motion (defined as frame-wise displacement > 0.5), as well as one time point prior to, and two time points following each of these high motion time points.

**Static and Dynamic Functional Connectivity**

The RTPJ subregions underwent a recent data-driven characterization that revealed a subspecialization in the RTPJ using coactivation-based parcellation (Bzdok et al., 2013) (http://anima.fz-juelich.de/). Static functional connectivity (sFC) was calculated using DPARSF software. For each individual, Pearson’s correlation coefficients were computed between the mean time series of each ROI and the time series of each voxel in the remainder of the brain. To improve normality, correlation coefficients were converted to z-values using Fisher’s r-to-z transformation and results were displayed using sFC maps for each participant.
Dynamic functional connectivity (dFC) was calculated using DynamicBC software with a sliding window approach (Liao et al., 2014). In this approach, window length is an important parameter in the computation of dFC. As a previous study has suggested, the window length should optimize the balance between acquiring reliable inter-region connectivity (with longer windows) and capturing fast shifting dynamic relationships (with shorter windows) (Leonardi and Van De Ville, 2015). In present study, the window length of 50 TRs (120 s) was selected based on the recommendation of a previous resting-state dynamic analysis (Leonardi and Van De Ville, 2015; Li et al., 2018), and the window was shifted by five TRs (12s). In our data, the full-length time series was comprised of 212 TRs, so, there were 33 windows for each participant. For the time series in each window, the Pearson’s correlation coefficient of the TPJ with subregions with all other voxels was calculated and Fisher’s z-transformed, yielding a sliding-window z-value map. Then, for each participant, a set of sliding-window beta maps was used to calculate the dFC map (standard deviation in beta values at each voxel). Finally, the dFC maps were converted to z-values using Fisher’s r-to-z transformation to improve normality. Two supplementary window lengths [40 TRs (96 s) and 60 TRs (144 s)] were also chosen to validate our findings of temporal variability of the TPJ subregion connectivity.

**Statistical Analysis**

The Pearson’s $\chi^2$ test was applied to compare sex differences and two-sample $t$-tests were applied to check for differences in age, the non-social AQ aspect (attention to
detail) and social AQ aspects (AQ-social), as well as the subscales (social skills, communication, attention switching, and imagination) between the two genotype groups (AA/AG vs. GG). Voxel-wise two-sample t-tests with gender, age and mean head motion as covariates were used to quantitatively compare the differences in the sFC and dFC of the RTPJ subregions between the two genotype groups within the grey matter mask using dpabi software. All statistical maps were corrected using the Gaussian Random Field method at the threshold for voxel $P < 0.001$ and cluster $P < 0.05$. The BrainNet Viewer package was used to map the remaining regions onto cortical surfaces (Xia et al., 2013). Spearman’s correlation analyses were performed to explore the associations between the significantly different RPTJ connectivity between groups (static and dynamic) and behavioral performance within all participants or each group. Significance was determined by $P < 0.05$ (two-tailed), with no correction. In consideration of the strong impact of singular values on correlation analyses, we excluded singular data defined as greater than three standard deviations from the mean. Six participants were excluded when performing correlation analysis because of singular data for mean connectivity. Finally, there were 393 participants included in the correlation analysis for the subscales of the AQ and 32 participants for analysis of fixation time at eye-AOI and non-core feature AOI.

Results

Genotype effects on behavior performance

The genotype distribution of rs2710102 in the current study (AA = 98, AG = 240, and
GG = 166) was consistent with a previous report of variations of this gene in a healthy Chinese Han population (Ji et al., 2013). There were no significant differences in terms of sex and age between two genotype groups (AA/AG and GG group) (Supplementary materials Table S1).

There was a significant difference between genotype groups for AQ-social scores (t = 2.092, P = 0.037) (Figure 1A). Specially, this difference was mainly derived from the sub-domain of communication (t = 2.620, P = 0.009). There was no significant difference between genotype groups for the non-social AQ subscale (attention to detail) or the other AQ-social domains (social skills, attention switching, and imagination) (Supplementary materials Table S1). For the eye tracking task, the A-allele carriers of CANTNP2 rs2710102 (18 A-allele carriers and 14 GG carriers) showed shorter fixation times on the eye-AOI at trend level (t = 2.028, P = 0.054) and longer times on the non-core feature AOI (t = 2.438, P = 0.023) (Figure 1B, Supplementary materials Table S2). No significant difference was found in terms of sex, age, fixation times on the nose-AOI or mouth-AOI between genotype groups (Supplementary materials Table S2).

**Genotype Effects on the sFC of RTPJ Subregions**

Of the 504 participants included in the behavior analysis, 399 participants were included in the MRI analysis (AA/AG = 271, GG = 128). There were no significant differences between the genotype groups for gender, age, or head motion indexed by frame-wise displacement (Supplementary materials Table S3) (Jenkinson et al., 2002).
We investigated the influence of the CANTNP2 rs2710102 variation on the sFC of the anterior and posterior RTPJ for whole grey matter, respectively. We first performed a one sample \( t \)-test for the whole group, AA/AG group and GG group. Results revealed similar anterior and posterior RTPJ sFC for all three groups (Supplementary materials Figure S2). Group comparisons using two samples \( t \)-tests suggested that there was no significant difference in anterior RTPJ sFC between the AA/AG group and GG group. However, participants in AA/AG group exhibited lower sFC for the posterior RTPJ with the OFC (peak voxel MNI coordinate: \( x = -39, y = 39, z = -9; T \text{ value} = -4.20; \text{cluster size} = 16 \)) than the GG group (Figure 2).

**Genotype Effects on the dFC of RTPJ Subregions**

We conducted group-level comparisons to investigate the influence of the CANTNP2 rs2710102 variation on the dFC of anterior and posterior RTPJ. No significant difference was found for anterior RTPJ dFC between the AA/AG group and GG group. Compared with participants in the GG group, participants in the AA/AG group showed decreased dFC between posterior RTPJ and medial prefrontal cortex (mPFC) (peak voxel MNI coordinate: \( x = -3, y = 51, z = 24; T \text{ value} = -4.46; \text{cluster size} = 18 \)) than the GG group (Figure 3). The validation analysis with different sliding-window lengths also revealed decreased dFC between the posterior RTPJ and mPFC in the AA/AG group (Supplementary materials Figure S3).

**Correlation Analyses**
The correlation between the posterior RTPJ-OFC sFC and any behavior performance outcome was not significant. It was also not significant between the posterior RTPJ-mPFC dFC and any behavior performance outcome among AQ and its sub-domains among all participants or each groups. However, it is notable that dFC between the posterior RTPJ and mPFC was significantly associated with the fixation time at the eye-AOI ($r = 0.502, P = 0.003$) and the fixation time on the non-core feature AOI ($r = -0.493, P = 0.004$) (Figure 4). For the correlation within the A-allele and GG carriers respectively, posterior RTPJ-mPFC dFC was significantly associated with the eye-AOI fixation time ($r = 0.596, P = 0.025$) and the non-core feature AOI fixation time ($r = -0.572, P = 0.033$) among the GG carriers, but not the A-allele carriers.

**Discussion**

In the current study, we identified the behavioral effects of the CANTNP2 rs2710102 variation on social performance and modulatory effects on brain social-network connectivity. Specifically, the rs2710102A allele carriers had poor social function (shown by high AQ-social scores, shorter fixation times on eye areas), and diminished posterior RTPJ-OFC sFC and posterior RTPJ-mPFC dFC. The RTPJ-mPFC dFC were positively associated with social behavior.

The important role of CANTNP2 in social behavior is being increasingly implicated by research. CNTNAP2 genetic alterations have been identified in social-related disorders (mainly autistic spectrum disorders) (Bakkaloglu et al., 2008;
Rodenas-Cuadrado et al., 2014). Intriguingly, the common genetic variants in \( CNTNAP2 \), including rs2710102 investigated in the current study, are also correlated with an increased risk of social-related disorders (Alarcon et al., 2008; Steer et al., 2010; Stein et al., 2011). It is notable that the \( CNTNAP2 \) rs2710102 was traditionally frequently associated with language impairments in autism (Alarcon et al., 2008). Indeed, the G allele of rs2710102 has been deemed as a risk allele for language impairments (Vernes et al., 2008; Riva et al., 2018). Accordingly, the G allele of rs2710102 has been considered as a risk allele for autism in multiple genetic imaging studies (Scott-Van Zeeland et al., 2010; Dennis et al., 2011). However, there are also findings which support the risk role of the A allele for social-related dysfunction (Steer et al., 2010; Stein et al., 2011). For example, the A allele of rs2710102 has been positively associated with the extent of social inhibition, which it contributes to independently of the trait for autism (Steer et al., 2010). Broadly consistent with these findings, our results showed that rs2710102 A allele carriers had poor social function (demonstrated through high AQ-social scores and shorter fixation times on eye areas).

In addition to providing behavioral evidence, our results also provided imaging evidence supporting the modulatory effect of rs2710102 on brain social function. Specially, we found aberrant functional connectivity within the social network (diminished posterior RTPJ-OFC sFC and posterior RTPJ-mPFC dFC) in the A allele of rs2710102 carriers. It is well-known that the mPFC and RTPJ are regions the most associated with the inference of mental state (Schurz et al., 2014; Koster-Hale et al., 2017), which is essential to guide social behavior in real-life situations. In accord with
the idea that the eyes provide a “window to the mind,” eye-to-eye contact also activates regions implicated in the inference of mental states, including the mPFC and TPJ. Additionally, during resting-states, connectivity between the TPJ and mPFC are also linked with social cognition and behavior (Brauer et al., 2016; Van Overwalle and Marien, 2016). In contrast, the OFC is traditionally deemed to be a key node of reward networks (Wallis, 2007). Recently, the impact of motivational factors on the social function has of increasing interest (Tabibnia and Lieberman, 2007; Lin et al., 2012). Chevallier C et al. proposed a social motivation theory of autism which suggests that deficits in social cognition may be a consequence of disrupted social motivation but not the cause (Chevallier et al., 2012). Intriguingly, evidence from resting-state functional connectivity analysis also reveals that the interactions within the TPJ, mPFC, and OFC contribute to social cognition (Van Overwalle and Marien, 2016).

However, previous study based on the seed of the mPFC did not report mPFC-pRTPJ connectivity differences between the genotypes of rs2710102. Besides the difference in genotype grouping, the dynamic functional connectivity as adopted in our study may provide another potential explanation. Traditional functional connectivity assessment assumes that region coupling is stationary over time. Although convenient, this assumption may unfortunately overlook the varying nature of brain region interactions, which enable the brain to dynamically integrate and coordinate the cerebral regions responding to internal and external stimuli. Thus, the assessment of dynamic functional connectivity here provided insights into subtle and
flexible brain connectomes, which may contribute to multiple neurological and psychiatric disorders, as well as various forms of cognition. It has been demonstrated that dynamic connectomic could significantly predict cognitive performance in healthy individuals and pathological states (Liao et al., 2018; Liu et al., 2018). In the present study, we found that carriers of the risk allele for social dysfunction showed blunt variation in regional interaction (pRTPJ-mPFC). The blunt pathological states may contribute to the impairments in brain information integration and switching between cognitive processes (Liao et al., 2017; Cohen, 2018). Coincidentally, dynamic region interaction was positively associated with social performance. These findings provided novel evidence supporting the argument that dynamic interactions within the social brain network influence social performance and this effect may be modulated by genes.

It is worth noting that a relatively low effect size was observed in our study for the effect of genotype on social performance, as well as the correlation between dynamic functional connectivity and social performance. For example, the difference for AQ-social between genotype groups just achieved statistical significance at the 0.05 level in our study and we did not find significant relationship between functional connectivity and social performance with AQ. The gross assessment method (AQ-social scale) and potential ceiling effect in participants (healthy college students) may contribute to the low effect size. In addition, we also considered a p-value >0.05 (p-value = 0.054) as a “trend” for difference on FTE. This low effect size may be caused by the small sample size (n = 32). Significantly, we found a neural feature
(pRTPJ-mPFC dynamic functional connectivity) associated with this behavior. Of course, future studies with larger sample sizes and clinical samples are necessary to validate the modulatory effect of gene on the FTE and also the neural substrate.

There are several additional limitations to this study which should be considered. First, the repetition time (2,400 ms) used in present data may be not short enough to fully depict the dynamic features of brain. A multiband sequence with shorter repetition time may be a solution for use in future confirmatory research. Second, social performance in our study was measured using off-line brain signals acquisition. The relationships were obscure, although significant associations were identified. Task-based functional MRI research is needed to replicate our findings. Third, the seeds defined by population-level, not individual-level atlases likely eroded actual individual variation (Wang et al., 2015), which may lessen the correlations between pRTPJ-mPFC dynamic functional connectivity and social performance. Finally, the absence of a long scan duration reduced the reliability of measuring stationary and dynamic functional connectivity.

**Conclusion**

Our results provided novel evidences support that common variant of CNTNAP2 gene has a modulatory effect on the social performances and dynamic interaction of brain social network (pRTPJ-mPFC dynamic functional connectivity). The dynamic interaction of brain social network is associated with social performances. These findings provided insight for the genetic-brain inaction mechanism for the social
impairment in several disorders, such as autism.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and
with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Figure 1. Modulatory effect of rs2710102 on social performance. (A) Mean score in the sub-aspects of Autism-Spectrum Quotient (AQ) in two rs2710102 genotype groups. Carriers of the A allele showed poor social performance (high AQ-social score) compared to those with the GG genotype. There was no significant difference between two groups in the non-social sub-aspects (AQ-attention). (B) Fixation time percentage on different areas of interest (AOI) during eye-tracking task in two rs2710102 genotype groups. Carriers of the A allele showed shorter fixation time on eyes-AOI compared to those with the GG genotype and longer fixation time on non-core feature AOI. Error bars depict one standard error of the mean.
Figure 2. Modulatory effect of rs2710102 on the stationary functional connectivity of pRTPJ. The stationary functional connectivity pattern of pRTPJ was obtained by one-sample t-tests for rs2710102 GG homozygotes group (A) and AA/AG group (B). (C) Groups comparison revealed a decreased pRTPJ stationary connectivity with the orbital frontal cortex for the risk allele (AA/AG) compared with GG individuals. All threshold for comparisons were set as whole brain Gaussian random field (GRF) correction (voxel P < 0.001, cluster P <0.05).
Figure 3. Modulatory effect of rs2710102 on the dynamic functional connectivity of pRTPJ. (A) Groups comparison revealed a decreased pRTPJ dynamic connectivity with the medial prefrontal cortex for the risk allele (AA/AG) compared with GG individuals. Threshold for comparison was set as whole brain Gaussian random field (GRF) correction (voxel P < 0.001, cluster P < 0.05). (B) The pRTPJ-mPFC functional connectivity values were displayed for a single participant in the AA/AG group and a single participant in the GG group across the 33 sliding windows.
Figure 4. Relationship between social performance and dynamic functional connectivity of pRTPJ with medial prefrontal cortex. Individual dynamic pRTPJ-mPFC functional connectivity was positively correlated with individual fixation time on eyes-AOI (A) and negatively correlated with individual fixation time on non-core feature AOI (B).
