Hyperconnectivity of the Right Posterior Temporo-parietal Junction Predicts Social Difficulties in Boys with Autism Spectrum Disorder

Hsiang-Yun Chien, Hsiang-Yuan Lin, Meng-Chuan Lai, Susan Shur-Fen Gau, and Wen-Yih Isaac Tseng

The posterior right temporo-parietal junction (pRTPJ) is a key brain region representing other's mental status. Despite reports of atypical activation at pRTPJ during mentalizing in individuals with autism spectrum disorder (ASD), the intrinsic functional connectivity (iFC) of the pRTPJ remains under-investigated. We examined whether boys with ASD show altered resting-state iFC of the pRTPJ, and whether atypical iFC of the pRTPJ is associated with social deficits in ASD in a sample of 40 boys with high-functioning ASD (aged 9–17 years, mean age, 12.38 ± 2.17; mean IQ, 105.60 ± 16.06) and 42 typically developing (TD) boys (aged 9–17 years, mean age, 11.64 ± 2.71; mean IQ, 111.29 ± 13.45). Both groups received resting-state fMRI assessment after imaging data quality control for in-scanner head motion and spatial coverage. Seed-based approach was used to investigate iFC of the pRTPJ. TD and ASD boys demonstrated a resting-state pRTPJ iFC pattern comparable to the known spatial involvement of the default-mode network. Boys with ASD showed pRTPJ hyperconnectivity relative to TD boys in the right ventral occipito-temporal cortex. This atypically increased iFC in the ASD group was positively correlated with social deficits assessed by the Chinese version of the Autism Diagnostic Interview-Revised and the Social Responsive Scale. Our findings provide empirical support for functional "dysconnectivity," that is, atypical functional integration among brain regions, as an integral component of the atypical neurobiology of ASD. ***Autism Res*** *2015, 8: 427–441.* © 2015 International Society for Autism Research, Wiley Periodicals, Inc.

Keywords: autism spectrum disorder; right posterior temporo-parietal junction; resting-state fMRI; functional connectivity; ventral occipito-temporal cortex

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by difficulties in social interactions and communication. Difficulties in social reciprocity in ASD encompass several domains of social cognition and perception [Lai, Lombardo, & Baron-Cohen, 2014], including mentalizing difficulties [Frith, 2001; Senju, 2012], impaired dyadic social perception [Boucher, 2012; Pelphrey, Shultz, Hudac, & Vander Wyk, 2011], reduced social motivation [Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012], and anomalous self-referential cognition [Lombardo & Baron-Cohen, 2011]. Task-functional magnetic resonance imaging (fMRI) studies of ASD have collectively revealed anomalous activation in the so-called "social brain" regions during social-processing experiments [Dichter, 2012; Philip, Dauvermann, Whalley, Baynham, Lawrie, & Stanfield, 2012]. Moreover, emerging evidence indicates that atypical development in neural connectivity and synchrony across brain regions is associated with ASD [Minshew & Williams, 2007; Schipul, Keller, & Just, 2011; Uddin, Supekar, & Menon, 2013; Vissers, Cohen, & Geurts, 2012].

Intrinsic functional connectivity (iFC), represented by the correlation of low frequency (e.g., < 0.1 Hz) spontaneous fluctuations in neural activity measured by resting-state fMRI (rs-fMRI) blood-oxygen-level-dependent (BOLD) signal, characterizes the functional organization of the brain at a systems level [Fox & Raichle, 2007]. Previous iFC studies have demonstrated a predominance of hypoconnectivity in anterior–posterior connection [Cherkassky, Kana, Keller, & Just, 2006], interhemispheric synchronization [Anderson et al., 2011], social-affective processing circuitries [Alaerts, Woolley, Steyaert, Di Martino, Swinnen, & Wenderoth,

From the From the Department of Psychiatry, National Taiwan University Hospital, Taipei, Taiwan (H.-Y.C., H.-Y.L., M.-C.L., S.S.-F.G.); Center for Optoelectronic Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan (H.-Y.C., W.-Y.I.T.); Autism Research Centre, Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom (M.-C.L.); Department of Psychiatry, National Taiwan University College of Medicine, Taipei, Taiwan (M.-C.L., S.S.-F.G.); Graduate Institute of Brain and Mind Sciences, National Taiwan University College of Medicine, Taipei, Taiwan (S.S.-F.G., W.-Y.I.T.)
H.-Y.C. and H.-Y.L. contributed equally to this work as joint first authors.
None of the authors have declared any conflict of interest or financial interests that may arise from being named as an author on the manuscript.
Received April 07, 2014; accepted for publication November 25, 2014
Address for correspondence and reprints: Susan Shur-Fen Gau, M.D, Ph.D., Department of Psychiatry, National Taiwan University Hospital & College of Medicine, No. 7, Chung-Shan South Road, Taipei 10002, Taiwan. E-mail: gaushufe@ntu.edu.tw
Published online 28 January 2015 in Wiley Online Library (wileyonlinelibrary.com)
DOI: 10.1002/aur.1457

2014; Ebisch et al., 2011; Gotts, Simmons, Milbury, Wallace, Cox, & Martin, 2012; von dem Hagen, Stoyanova, Baron-Cohen, & Calder, 2013], and within the default-mode network (DMN) [Ebisch et al., 2011; Kennedy & Courchesne, 2008; Monk et al., 2009; von dem Hagen et al., 2013; Washington et al., 2014; Weng et al., 2010]. Some studies, however, have found a mixed pattern of over- and under-connectivity in the "theory of mind" network [Fishman, Keown, Lincoln, Pineda, & Muller, 2014] and hyperconnectivity between extrastriate cortex and frontal areas [Shen et al., 2012] in adolescents or adults with high-functioning ASD. On the other hand, children with ASD displayed hyperconnected iFC at the whole-brain level spanning across multiple functional subsystems [Di Martino et al., 2011; Lynch, Uddin, Supekar, Khouzam, Phillips, & Menon, 2013; Supekar et al., 2013; Uddin, Supekar, Lynch, 2013], while toddlers with ASD exhibited weaker interhemispheric synchronization in language areas during natural sleep [Dinstein et al., 2011]. Inconsistent findings may result from differences in developmental stages, motion artifacts, denoising methods, the chosen systems to be examined, or sample heterogeneity [Muller, Shih, Keehn, Deyoe, Leyden, & Shukla, 2011; Uddin, Supekar, & Menon, 2013]. "Dysconnectivity," that is, atypical (rather than simply decreased) integration among brain regions [Friston, 1998; Kana, Libero, & Moore, 2011], may reconcile disparate findings and provide a more general framework for understanding the neurobiology of ASD. Both hyperconnectivity and hypoconnectivity of the iFC in ASD found in the large ABIDE cohort [Di Martino et al., 2014] provide empirical support for this "dysconnectivity" hypothesis.

Irrespective of hypoconnectivity or hyperconnectivity, recent investigations have consistently shown significant association between atypical iFC and core social deficits in ASD [Alaerts et al., 2014; Gotts et al., 2012; Lynch et al., 2013; Monk et al., 2009; Nair, Treiber, Shukla, Shih, & Muller, 2013; Supekar et al., 2013; Washington et al., 2014; Weng et al., 2010], implying that the altered development of neural organization in ASD may lead to aberrancy in the functionally integrated network critical for social processing. The right temporo-parietal junction (RTPJ), an area at the conjunction of the posterior superior temporal sulcus (pSTS), inferior parietal lobule, and lateral occipital cortex, is a key structure within the "social brain network" [Pelphrey et al., 2011; Van Overwalle, 2009]. The RTPJ can be anatomically parceled into three subregions based on diffusion tractography [Mars, Sallet, Schuffelgen, Jbabdi, Toni, & Rushworth, 2012], and the posterior right temporo-parietal junction region (pRTPJ) is particularly functionally connected with areas largely overlapping with the DMN [Kubit & Jack, 2013; Mars et al., 2012]. The pRTPJ is principally involved in perspective taking [Spengler, von Cramon, & Brass, 2010] and the attribution of beliefs and intentions to others [Decety & Lamm, 2007; Kubit & Jack, 2013; Mars et al., 2012; Saxe & Kanwisher, 2003]. Unlike the selective response in neurotypical controls, pRTPJ is reported nonselectively activated during mentalizing about self and others in adults with ASD, and the reduced selectivity of pRTPJ for mentalizing is associated with social difficulties measured by the Autism Diagnostic Interview-Revised (ADI-R) [Lombardo, Chakrabarti, Bullmore, MRC Aims Consortium, & Baron-Cohen, 2011]. The pRTPJ has also been shown activated atypically in moral judgment [Koster-Hale, Saxe, Dungan, & Young, 2013] and inferring intention [Kana, Libero, Hu, Deshpande, & Colburn, 2012] in adults with ASD. Adolescents and adults with ASD display weaker synchronization between pRTPJ and supplemental motor area [Kana et al., 2012] and frontal region [Kana, Keller, Cherkassky, Minshew, & Just, 2009] during mentalizing task. Notably, Dufour et al. [2013], using different mentalizing tasks and a larger sample size, yielded inconsistent results regarding pRTPJ impairment in ASD.

Despite its important role in social cognition, pRTPJ has received insufficient attention in the resting-state functional connectivity literature in ASD. Previous studies have reported reduced iFC of RTPJ with posterior cingulate cortex (PCC) and pSTS [Fishman et al., 2014] in adolescents with ASD. With a larger sample size, the current study aimed to specifically investigate the resting-state iFC of the posterior part of RTPJ in children and adolescents with ASD. We hypothesized that boys with high-functiong ASD would have atypical pRTPJ iFC, which would be linked with the severity of reciprocal social impairment.

Methods

Participants and Procedure

The Research Ethics Committee at the National Taiwan University Hospital (NTUH) approved this study prior to implementation (ID: 20090306; ClinicalTrials.gov number, NCT00916851). The procedures and purpose of the study were explained face-to-face to the participants and their parents, who then provided written informed consent. All participants underwent the same clinical and MRI assessments.

We recruited 48 Taiwanese boys with high-functioning ASD (aged 9–17 years, full-scale intelligence quotient (IQ) above 70) consecutively from the Department of Psychiatry, NTUH, and 48 typically developing (TD) boys (aged 9–17 years) from schools in similar geographical districts to the ASD group. All boys with ASD were clinically diagnosed according to the DSM-IV-TR and ICD-10 criteria by child psychiatrists, and further

confirmed by the Chinese version of the ADI-R [Gau et al., 2010; Rutter, Le Couteur, & Lord, 2003]. The corresponding author reviewed all the medical records and the ADI-R interviews again and found all these participants met the DSM-5 diagnostic criteria for ASD [American Psychiatric Association, 2013]. The Chinese version of the ADI-R, translated into Mandarin by Gau et al. [2010], was approved by Western Psychological Services in 2007.

TD boys were recruited if they did not have any current or lifetime DSM-IV psychiatric disorder based on the Chinese version of the K-SADS-E interview [Gau, Chong, Chen, & Cheng, 2005; Orvaschel, Puig-Antich, Chambers, Tabrizi, & Johnson, 1982] with the participants and their parents. Exclusion criteria for all participants included past or current neurological or severe medical illness, lifetime diagnoses of learning disorder, substance use disorder, schizophrenia, bipolar disorder, and major depression, current severe anxiety disorders, current use of psychotropic medication except psychostimulants ($n = 5$), and a full-scale IQ less than 70. Boys with ASD who had other definite concurrent DSM-IV Axis I disorders (except for attention-deficit hyperactivity disorder) based on the K-SADS-E interview were also excluded. None of the participants took any medication for at least 1 week before and during all assessments.

Intellectual function was assessed by the Wechsler Intelligence Scale for Children – 3rd edition (WISC-III) [Wechsler, 1991]. Handedness was assessed by the Edinburgh Inventory [Oldfield, 1971]. Beside the Chinese ADI-R interview, all parents completed the Chinese version of the Social Responsiveness Scale (SRS) [Gau, Liu, Wu, Chiu, & Tsai, 2013] to assess current social deficits. The Chinese SRS, translated by Gau et al. [2013], has well-accepted psychometric properties for measuring autistic features in the Taiwanese population [Hsiao, Tseng, Huang, & Gau, 2013]. The confirmatory factor analysis revealed a four-factor structure, namely "social communication," "autism mannerism," "social awareness," and "social emotion" [Gau et al., 2013].

MRI Assessments

fMRI data acquisition. Data were obtained on a 3T scanner (Siemens Magnetom Tim Trio) with a 32-channel phased-arrayed head coil. All participants were verbally instructed to remain still with their eyes closed to complete a 6-min rs-fMRI scan. The imaging parameters were 180 echo planar imaging (EPI) volumes; TR = 2,000 ms; TE = 24 ms; flip angle = 90°; field of view (FOV) = $256 \times 256\,mm^2$; matrix size = 64×64; 34 axial slices acquired in an interleaved descending order; slice thickness = 3 mm; voxel size = $4 \times 4 \times 3\,mm^3$; imaging plane being parallel to the anterior commissure–posterior commissure (AC–PC) image plane. For spatial normalization, a high-resolution T1-weighted anatomical image was also acquired (MPRAGE; TR = 2,000 ms; TE = 2.98 ms; TI = 900 ms; flip angle = 9°; FOV = $256 \times 256\,mm^2$; matrix size = 256×256; isotropic voxel size = 1 mm).

fMRI data preprocessing. The first five EPI volumes were discarded to allow for signal equilibration. Data preprocessing was performed using Data Processing Assistant for rs-fMRI (DPARSF) [Yan & Zang, 2010], which is based on Statistical Parametric Mapping (SPM8). Image preprocessing comprised of slice timing and head motion correction. The fMRI data were then spatially normalized to the Montreal Neurological Institute (MNI) space with isotropic 3 mm voxel, via the gray matter segment obtained from structural images as follows. Individual T1-weighted image volume was coregistered to the mean fMRI volume, then segmented into gray matter, white matter (WM) and cerebrospinal fluid (CSF) using the New Segment toolbox in SPM8, with custom tissue priors generated from the Template-O-Matic toolbox using the "matched-pair" approach [Wilke, Holland, Altaye, & Gaser, 2008]. Next, we used a diffeomorphic nonlinear registration algorithm (DARTEL) [Ashburner, 2007] to create a study-specific template and to normalize segmented images to the MNI space (with modulation). Individual fMRI volumes were then spatially normalized to the MNI space using the flow fields derived from DARTEL (without modulation), to improve the accuracy of spatial normalization [Tahmasebi, Abolmaesumi, Zheng, Munhall, & Johnsrude, 2009]. Spatially normalized fMRI volumes were smoothed with an 8 mm Gaussian kernel. Linear drifts were further removed and the preprocessed EPI data was band-pass filtered (0.01–0.08 Hz).

fMRI data quality control. In–scanner head movements during rs-fMRI would produce spurious results in time series correlation [Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Satterthwaite et al., 2012; Van Dijk, Sabuncu, & Buckner, 2012]. Participants who exhibited more than 4 time points of excessive motion (>1 mm maximum frame-wise displacement), calculated by the "motion fingerprint" software [Wilke, 2012], in their resting-state scans were excluded from analyses, resulting in exclusion of three boys in the ASD group and two boys in the TD group. There was no time point exhibiting maximum framewise displacement (FD) > 1.5 mm in the EPI data of the participants included in the final analysis. Spatial coverage of normalized EPI data was inspected for each participant, and another five boys with ASD and four TD boys were excluded owing to incomplete coverage of the cerebral cortex. As a result, 40 boys with high-functioning ASD (three with concurrent ADHD) alongside 42 TD boys, with rs-fMRI data of

limited in-scanner head motion and adequate spatial coverage, were included in the final analysis.

Nuisance signal regression. Preprocessed fMRI data were further linearly regressed with nuisance covariates, including signals derived from WM, CSF, and 24-autoregressive motion parameters (six realignment motion parameters, six head motion parameters one time point before, and the 12 corresponding squared items) (Friston-24) [Friston, Williams, Howard, Frackowiak, & Turner, 1996]. To demonstrate the robustness of our findings against potential biased group differences introduced by different regression strategies [Gotts, Saad, Jo, Wallace, Cox, & Martin, 2013; Yan et al., 2013], we performed a complementary denoising regression including average global signal as an additional regressor.

Selection of seeds and functional connectivity analysis. As defined in prior work [Mars et al., 2012], the seed region of pRTPJ was chosen as a sphere around the center at the MNI coordinate 54, −55, 26, of 4 mm in radius, which has been demonstrated functionally coupled to areas associated with social cognition and the DMN. To investigate the specificity for pRTPJ, we also conducted the same analyses for the posterior part of the left TPJ (pLTPJ, generated by MarsBaR toolbox [Brett, Anton, Valabregue, & Poline, 2002] as the contralateral homologous Region of interest [ROI] of the pRPTJ, centering at −54, −55, 26). Finally, given the spatial proximity yet functional distinction between pRTPJ and pSTS, we further ensured that the pRTPJ seed did not spatially overlap with right pSTS (MNI coordinate 50, −56, 7; defined based on a meta-analysis by Van Overwalle and Baetens [2009]), as shown in Supporting Information Figure 1.

Whole-brain functional connectivity calculation was performed using the Resting-State fMRI Data Analysis Toolkit (REST) [Song et al., 2011]. The time series within the seed ROI were averaged to generate a reference time series for each participant. Pearson's correlation was calculated between the seed reference time series and the time series of each single voxel in the whole brain. The individual-level correlational maps were Fisher *z*-transformed before entering group-level analysis.

Statistical analysis. We used SAS version 9.2 (SAS Institute Inc., USA) to conduct data analyses of group comparisons in demographics and clinical measures, and connectivity-behavior correlations. Using SPM8, one-sample *t*-tests were performed on the *z*-maps of boys with ASD and TD boys, separately, to show connectivity maps for pRPTJ. Between-group comparison in connectivity of the FPCN was implemented by two-sample *t*-tests. As suggested by Yan et al. [2013], we included mean FD as a covariate in all group-level analyses to further account for motion artifacts. To explore age-related shift in connectivity as proposed by Uddin, Supekar, and Menon [2013], and the possible effects of IQ, which was not matched between groups, we additionally included age and full-scale IQ as covariates in a subsidiary analysis. Age and full-scale IQ were mean centered across all subjects before modeling.

Voxel-level analyses were restricted in the gray matter region by applying the sample-specific gray matter mask (the threshold of partial-volume-estimate > 0.15). Owing to the finite spatial coverage of the EPI scan, we excluded cerebellum in the analysis by subtracting the cerebellum ROIs derived from the Automated Anatomical Labeling template [Tzourio-Mazoyer et al., 2002] from the gray matter mask. Owing to the denoising model without global signal regression (GSReg) resulting in strong positive correlation, the threshold of the within-group iFC patterns were stringently set at a cluster-wise family-wise-error (FWE)-corrected $P < 0.05$, with a cluster-forming voxel-level threshold of $P < 10^{-10}$. The between-group statistical outcomes were FWE corrected at the cluster-level at $P < 0.05$, and using a cluster forming voxel-level threshold of $P < 0.001$.

To localize areas showing dysconnectivity, and to identify the related Brodmann areas (BA), we used xjView8 toolbox (http://www.alivelearn.net/xjview8/). Stereotaxic coordinates were reported in MNI space. The results were visualized using BrainNet Viewer [Xia, Wang, & He, 2013].

Network analysis using multiple ROIs. To further elaborate the relationships between the ROIs and the hub regions within the pRTPJ-associated network in TD and ASD boys, we defined four spherical ROIs of 4 mm in radius, derived from the pRTPJ seed, ventral medial prefrontal cortex (vmPFC), PCC, and the aberrantly connected region (from the aforementioned between-group analysis; see Results). The vmPFC and PCC ROIs were defined according to the peak coordinate in the statistical map from the within-group result in the TD group.

Time series for each of these ROIs were extracted to compute the (Pearson's) correlation matrix for all ROIs for each participant. Following Fisher's *r*-to-*z* transformation, the differences in correlation coefficients (reflecting the network structure) between each pair of ROIs were compared using independent sample *t* tests. This group comparison for the correlation coefficients was false discovery rate (FDR)-corrected for multiple comparisons at $q < 0.05$.

Functional connectivity in relation to social difficulties. To examine how abnormal iFC with pRTPJ was associated with social difficulties, we used Pearson's

Table 1. Demographic Features of the Participants

	ASD ($n = 40$)	TDC ($n = 42$)		
	Mean ± SD	Mean ± SD	t or χ^2	P
Age (range, 9–17 years)	12.38 ± 2.17	11.64 ± 2.71	$t = 1.35$	0.182
Handedness	Right = 38	Right = 38	$\chi^2 = 0.62$	0.432
Full-scale IQ	105.88 ± 15.14	114.00 ± 11.67	$t = -2.73$	0.008
Performance IQ	105.60 ± 16.06	111.29 ± 13.45	$t = -1.74$	0.086
Verbal IQ	105.75 ± 15.72	114.45 ± 10.06	$t = -3.00$	0.004
ADI-R, social	17.00 ± 7.10	—		
SRS, total scores	88.01 ± 34.62	29.97 ± 13.42	$t = 9.68$	< 0.001
Social communication and general features	37.91 ± 17.22	8.63 ± 5.18	$t = 10.06$	< 0.001
Autism mannerism	18.50 ± 8.58	4.29 ± 4.01	$t = 9.28$	<0.001
Social awareness	19.48 ± 6.04	13.03 ± 4.82	$t = 5.20$	<0.001
Social emotion	12.13 ± 5.31	3.89 ± 3.29	$t = 8.17$	<0.001
Mean of total frame-wise displacement, Jenkinson[a] (mm)	0.136 ± 0.038	0.133 ± 0.060	$t = 0.23$	0.821
Mean of total frame-wise displacement, Power[a] (mm)	0.234 ± 0.010	0.231 ± 0.016	$t = 0.13$	0.899

[a] Mean of total frame-wise displacement was calculated based on Jenkinson et al. [2002] and Power et al. [2012].

Abbreviations: ASD = autism spectrum disorder; TDC = typically developing control; ADI-R = Autism Diagnostic Interview-Revised; SRS = Social Responsiveness Scale.

correlation (r) to demonstrate brain-behavior relationships, as both the behavioral and iFC data were not significantly deviant from normal distribution. Aberrant functional connectivity values were calculated for seed-ROIs pairs, and were transformed to z values. ROIs were defined as a sphere of 4 mm in radius around the peak coordinates within clusters showing significant between-group differences in our main analysis (i.e., without GSReg). Behavioral social deficits were indexed by the total scores of "Qualitative Abnormalities in Reciprocal Social interaction" on the Chinese ADI-R for past behaviors, together with the Chinese SRS (total and subdomain raw scores) reflecting current status. FDR correction [Benjamini & Hochberg, 2000] was performed to correct for multiple comparisons, with significance set at $q < 0.05$, and q between 0.05 and 0.1 as trend-level significant.

Results

Demographic and Clinical Characteristics

Compared to TD boys, boys with high-functioning ASD had lower full-scale and verbal IQs, and higher total scores and subscores of the Chinese SRS. There were no significant group differences in age, handedness and performance IQ. The extent of average FD, based on the measures proposed by either Jenkinson, Bannister, Brady, and Smith [2002] or Power et al. [2012], during rs-fMRI scan was well matched between groups (Table 1 and Supporting Information Fig. 2).

Right Posterior temporo-parietal Junction was Hyperconnected to Right Ventral Occipito-temporal Cortex in ASD

TD boys demonstrated pRTPJ iFC with bilateral mPFC, PCC, middle temporal lobe, and contralateral posterior TPJ (Fig. 1), comparable to the known spatial involvement of the DMN [Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010]. Boys with ASD also demonstrated a similar iFC pattern of pRTPJ with the DMN, except for additional involvement of the right ventral occipito-temporal cortex (VOTC).

As shown in Table 2 and Figure 1, boys with ASD, relative to TD boys, had pRTPJ hyperconnectivity with the right VOTC involving the lingual gyrus (LG), fusiform gyrus (FG), and middle occipital gyrus (MOG), each with a group-difference peak. The pRTPJ iFC patterns in both groups and between-group difference were mostly unchanged in the subsidiary analysis including age and full-scale IQ as additional covariates (Supporting Information Fig. 3). There was no significant correlation between age and pRTPJ-right VOTC connectivity (Supporting Information Fig. 4). Similar patterns of group difference were shown after GSReg (Supporting Information Table 1 and Fig. 5). There were no significant group differences in iFC of the pLTPJ in either direction (Supporting Information Fig. 6).

The Network Structure of pRTPJ Intrinsic Connectivity

In the correlation matrix of the hubs within the pRTPJ-associated network, we found that the VOTC was only significantly hyperconnected with the pRTPJ, but not with the other components of the network, in boys with ASD relative to TD boys (Table 3 and Fig. 2).

Correlations between Aberrant iFC of pRTPJ and Social Impairment

Higher scores in both the ADI-R and the Chinese SRS is indicative of poorer social function. There were significantly positive correlations between the pRTPJ-right MOG connectivity and total SRS scores ($r = 0.35$,

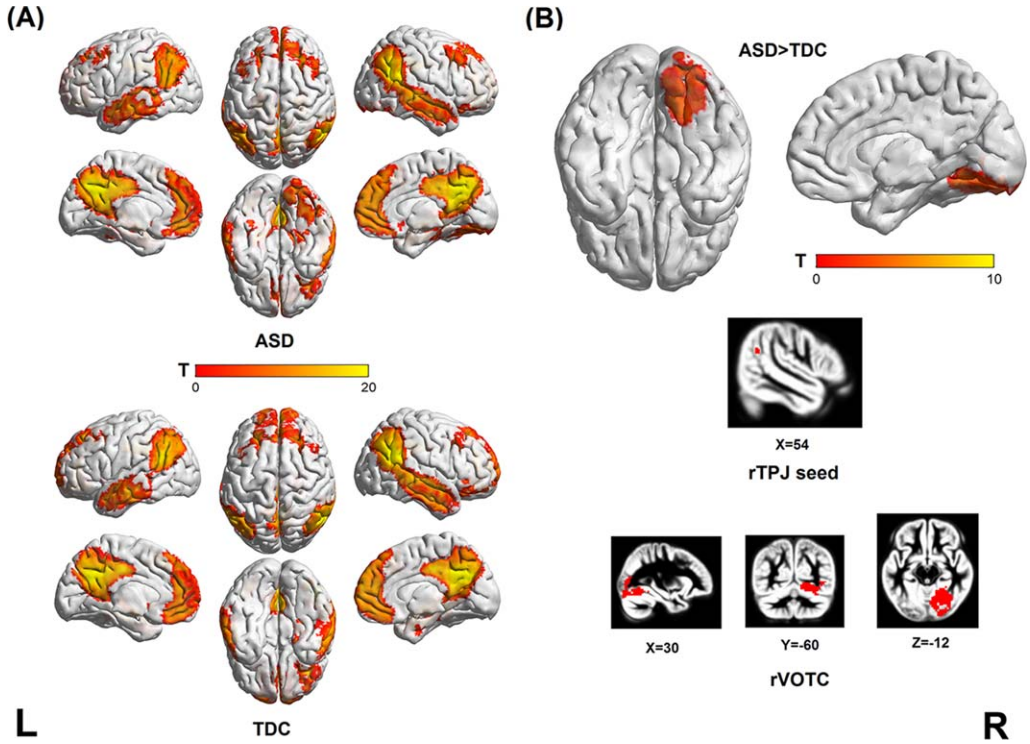

Figure 1. Resting-state functional connectivity of the right posterior temporo-parietal junction (pRTPJ), without global signal regression during the calculation of BOLD signal correlation. (A) At the whole-brain level, the pRTPJ displays within-group functional connectivity maps in both the autism spectrum disorder (ASD) and typically developing control (TDC) groups, respectively (thresholded at cluster-wise FWE-corrected $P < 0.05$, with a cluster-forming voxel-level threshold of $P < 10^{-10}$). Functional connectivity map based on pRTPJ shows patterns comparable to DMN in both the TDC and ASD groups. (B) Hyperconnectivity between the pRTPJ and right VOTC is demonstrated in the ASD group compared to the TDC group. Coordinates are given in the MNI space. Functional connectivity maps and group-differences are superimposed on the Ch2 brain surface in BrainNet Viewer and the custom study-specific template. Abbreviations: TDC: typically developing control; T: t value; L: left; R: right.

Table 2. Brain Regions with Altered pRTPJ Connectivity in ASD

Regions	Peak coordinate (MNI)			Cluster size (no. of voxels)	B.A.
	x	*y*	*z*		
ASD > TDC Right lingual gyrus	15	−60	−9	388[a]	19
Right middle occipital gyrus	36	−75	3		
Right fusiform gyrus	30	−60	−12		

[a] One cluster with 3 separate peaks.

Abbreviations: pRTPJ = right posterior temporo-parietal junction; ASD = autism spectrum disorder; TDC = typically developing control; No. = number; MNI = Montreal Neurological Institute; B.A. = Brodmann area.

Table 3. FDR *q* Values of Between-group Comparisons for Each Pair of the Anatomical Hubs of the Default Network and Right VOTC

ROI	PCC	vmPFC	rVOTC[a]
pRTPJ	0.127	0.768	0.00026*
PCC		0.061[b]	0.163
vmPFC			0.768

*significantly stronger functional connectivity in the ASD group than the typically developing group ($q < 0.05$, FDR corrected).

[a] This is the ROI involving lingual gyrus, middle occipital gyrus, and fusiform gyrus.

[b] Marginally weaker functional connectivity in the ASD group than the typically developing group.

Abbreviations: ROI = Region of interest; pRTPJ = right posterior temporo-parietal junction; PCC = posterior cingulate cortex; vmPFC = ventral medial prefrontal cortex; rVOTC = right ventral occipito-temporal cortex.

$q = 0.044$), and the "social communication" ($r = 0.38$, $q = 0.044$), the "social emotion" ($r = 0.36$, $q = 0.044$) and the "autism mannerism" ($r = 0.36$, $q = 0.044$) subscores. pRTPJ connectivity with other two subregions showed trends of positive correlations with the same SRS scores ($r = 0.24$–0.30, $q = 0.075$–0.083). There was also a significantly positive correlation between social reciprocity deficits on the ADI-R and pRTPJ-right FG connectivity ($r = 0.35$, $q = 0.044$). In the TD group, in contrast, no significant correlations were found between iFC and social functioning indexed by the SRS. The group differences in correlation patterns; however,

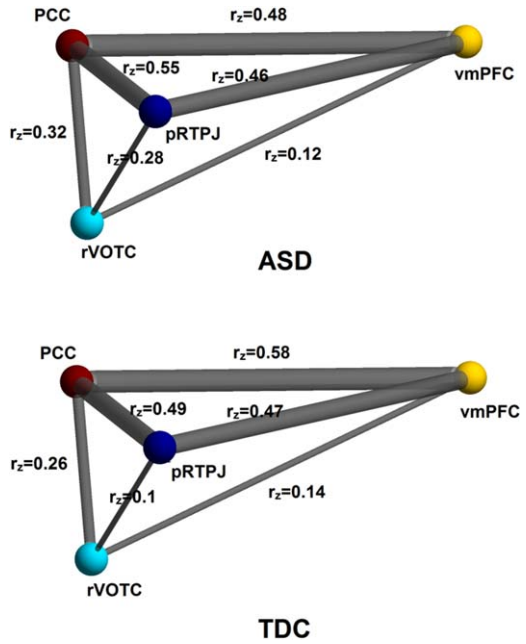

Figure 2. Network analysis of 4 ROIs within the functional connectivity map of the pRTPJ. These ROIs are 4mm in radius and centered on the MNI coordinates derived from the significant clusters of the within-group functional connectivity map of pRTPJ in the typically developing control group. The network is visualized using BrainNet Viewer. The thickness indicates strength of connection, that is, the stronger the ROI connectivity is, the thicker the line is. Abbreviations: TDC: typically developing control; vmPFC: ventral medial prefrontal cortex; r_z: *z*-transformed correlational value.

did not reach statistical significance when using a multiple regression model with iFC as the dependent variable and group, SRS, and group-by-SRS interaction as regressors, to test the effect of group-by-SRS interaction on iFC (Table 4, Fig. 3, and Supporting Information Figs. 7 and 8).

Discussion

In this study, we found that pRTPJ showed adult-like resting-state connectivity with brain regions associated with the DMN in both TD and ASD boys. However, boys with ASD showed hyperconnectivity between the pRTPJ and VOTC compared to TD boys, which was associated with the severity of their social deficits. Our findings provide empirical support for "dysconnectivity" as a neurobiological characteristic associated with ASD, which is further associated with social deficits, an essential feature of ASD.

iFC of pRTPJ and the Relation to DMN

The pRTPJ has been reported distinctively engaged in mentalizing [Decety & Lamm, 2007; Kubit & Jack, 2013], and functionally coupled with the dorsal medial prefrontal subsystem of the DMN [Andrews-Hanna et al., 2010] in mediating introspection about mental status [Andrews-Hanna, 2012]. Our findings that the posterior parts of bilateral TPJ were temporally synchronized with PCC, mPFC, and middle temporal lobe, spatially comparable to the DMN in adulthood in both groups [Andrews-Hanna et al., 2010], suggest that specific functional connection of the TPJ [Mars et al., 2012] could also be observed in late childhood, even in those with ASD. This supports the concept that functional brain organization is by and large conserved throughout the developmental process [Supekar, Musen, & Menon, 2009; Uddin, Supekar, Ryali, & Menon, 2011].

Hyperconnectivity between the pRTPJ and VOTC in ASD

The hyperconnected cluster with the pRTPJ in ASD, when compared with TD, involves several regions in the right VOTC, including the right LG, right MOG, and right FG. Multiple regions of VOTC have been reported as key nodes of the visual recognition network responding to a range of visual stimuli [Price & Devlin, 2011]. Specifically, the LG is implicated in deriving biological forms from motion information in TD individuals [Materna, Dicke, & Thier, 2008; Pelphrey, Morris, & McCarthy, 2005; Servos, Osu, Santi, & Kawato, 2002]. The MOG acts together with LG in processing biological motion information [Dayan, Casile, Levit-Binnun, Giese, Hendler, & Flash, 2007; Pelphrey, Morris, Michelich, Allison, & McCarthy, 2005], and joins forces with the posterior part of the FG for scenes/objects recognition [de Haan & Cowey, 2011; Saygin, Osher, Koldewyn, Reynolds, Gabrieli, & Saxe, 2012; Sewards, 2011]. Regarding FG, notably, the spatial extent of the aberrant cluster we found spans from the right mid-FG posteriorly to the MOG. This area is posterior-medial to, and may be functionally distinct from, the fusiform face area [Caspers, Zilles, Eickhoff, Schleicher, Mohlberg, & Amunts, 2013; Dalton et al., 2005; Kanwisher & Yovel, 2006; Saygin et al., 2012], which has been reported atypical in mediating facial processing and attribution of social meaning in individuals with ASD [Dichter, 2012]. This midposterior part of the FG is necessary for physical aspects of facial perception [Kanwisher & Yovel, 2006; Peelen & Downing, 2005], processing geometric information of actions [Dayan et al., 2007] and implicit emotional processing [Sabatinelli et al., 2011], and may demonstrate an activation pattern with gradient of increasing object selectivity and decreasing face selectivity from the mid-FG to the MOG [Caspers et al., 2013; Weiner & Grill-Spector, 2010]. Acting coordinately, the posterior-FG influences the MOG, then to the LG during processing biological

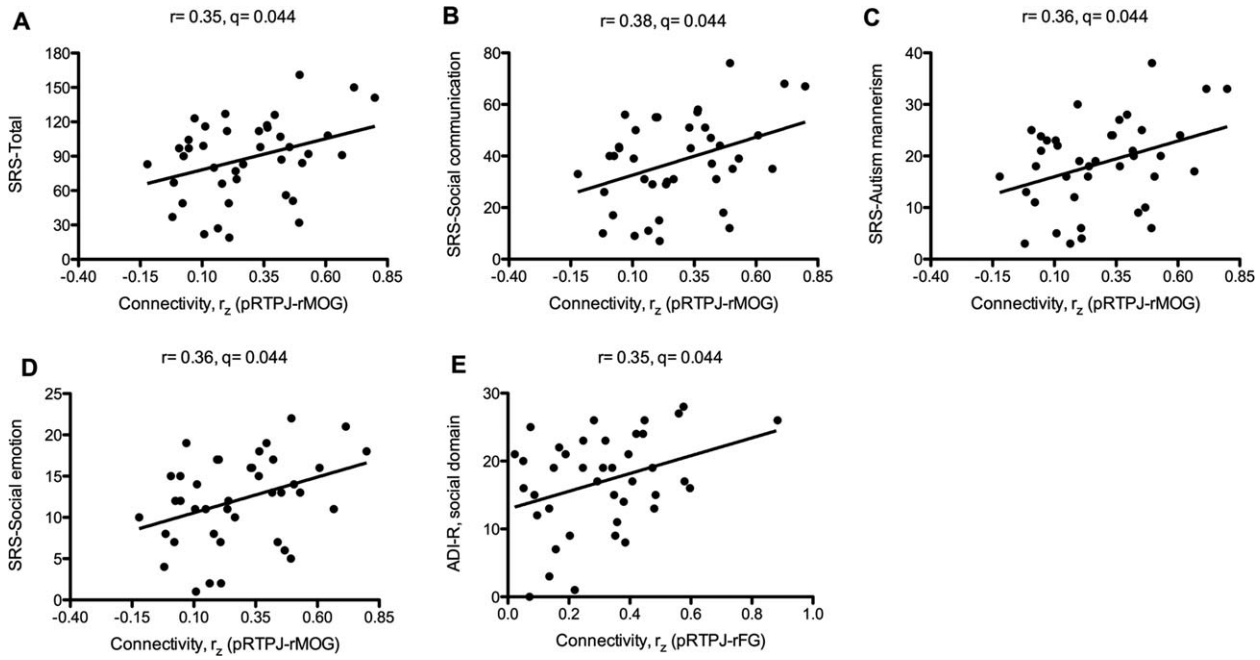

Figure 3. Exploratory correlations between aberrant connectivity and degree of social deficits in boys with ASD. Scatter plots show the associations between the iFC (r_z: *z*-transformed correlational value) between the pRTPJ and right middle occipital gyrus (rMOG) and (A) the Chinese version of SRS total scores, (B) the SRS "communication" subscores, (C) the SRS "autism mannerism" subscores, and (D) the SRS "social emotion" subscores. (E) Scatter plot shows the association between the pRTPJ-right fusiform gyrus (rFG) iFC and the Chinese version of ADI-R social scores. Other scatter plots for trend-level correlations between atypical iFC and autistic symptom measures are provided in Supporting Information Figures 4 and 5.

motion information [McKay, Simmons, McAleer, Marjoram, Piggot, & Pollick, 2012]. Taken together, the atypically connected right VOTC cluster observed in this study may be implicated in nonfacial visual processing. Meta-analyses based on activation likelihood estimation have revealed under-activation of the mid-FG yet over-activation of the posterior-FG during social tasks in ASD [Di Martino, Ross, Uddin, Sklar, Castellanos, & Milham, 2009; Lombardo, Baron-Cohen, Belmonte, & Chakrabarti, 2011]. Individuals with ASD also display enhanced task-related activity for a broad range of visual functioning in the low-level visual cortices overlapping with the aberrant connected cluster found here [Samson, Mottron, Soulieres, & Zeffiro, 2012]. Some studies [Ecker et al., 2012; Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2006] suggest that neuroanatomical abnormalities in the occipito-temporal cortices might partially contribute to social impairment in ASD. However, it remains unclear how interactions between lower-level sensory-perceptual processing cortices and regions mediating higher-level cognition contribute to the development of ASD. Our study, therefore, shed new light on the role of brain regions involving in non-face visual processing and its aberrant connection to the mentalizing network in ASD.

In terms of connectivity, there have been reports that the VOTC is functionally coupled with the task-positive network [Grady et al., 2010; Kennedy & Courchesne, 2008], and has functional connections with the pSTS during both rest and task conditions [McKay et al., 2012; Shih, Keehn, Oram, Leyden, Keown, & Muller, 2011; Turk-Browne, Norman-Haignere, & McCarthy, 2010]. The pSTS is implicated in representing and identifying biological motion [Hein & Knight, 2008], perceiving intentions [Vander Wyk, Hudac, Carter, Sobel, & Pelphrey, 2009], and facial processing [Hein & Knight, 2008]. Interactions between the VOTC and the pSTS may be essential for integrating information from faces and actions with the social/physical contexts to facilitate the understanding of intention. These external social cues may be processed from the VOTC to pSTS, then relayed to the anatomically adjacent pRTPJ, which is a critical junction area where different types of social information are assembled and integrated [Kubit & Jack, 2013] (as illustrated in Supporting Information Fig. 1). The integration of these lower-level processes contributes to higher-level mentalizing, for which rTPJ is directly involved [Saxe & Kanwisher, 2003]. Therefore, our findings of increased connectivity between the VOTC and pRTPJ in boys with ASD may reflect interference to the integration of incoming sensory information important for social cognition, resulting in social difficulties in ASD.

Table 4. Correlations between Autistic Social Difficulties and iFC for the Two Groups

	pRTPJ-rLingual		pRTPJ-rMOG		pRTPJ-rFG	
	r	*q*	*r*	*q*	*R*	*q*
Autism spectrum disorder						
ADI-R, social	0.05	0.343	0.15	0.195	0.35	0.044*
SRS, total scores	0.25	0.083[a]	0.35	0.044*	0.27	0.075[a]
Social communication	0.29	0.075[a]	0.38	0.044*	0.30	0.075[a]
Autism mannerism	0.25	0.083[a]	0.36	0.044*	0.27	0.076[a]
Social awareness	0.05	0.343	0.08	0.304	0.16	0.189
Social emotion	0.24	0.083[a]	0.36	0.044*	0.27	0.076[a]
Typically Developing Controls						
SRS, total scores	−0.02	1	−0.11	1	−0.08	1
Social communication	0.13	1	−0.03	1	0.09	1
Autism mannerism	0.04	1	−0.04	1	−0.003	1
Social awareness	−0.24	0.895	−0.22	0.895	−0.33	0.69
Social emotion	0.03	1	−0.03	1	0.00	1

*Significant correlation between social difficulties and functional connectivity ($q < 0.05$, FDR corrected).

[a] Marginally significant correlation between social difficulties and functional connectivity.

Abbreviations: ADI-R = Autism Diagnostic Interview-Revised; SRS = Social Responsiveness Scale; pRTPJ = right posterior temporo-parietal junction; rLingual = right lingual gyrus; rMOG = right middle occipital gyrus; rFG = right fusiform gyrus.

Our findings of the hyperconnectivity between pRTPJ and right VOTC is in contrast to the prediction from an overall underconnectivity in ASD [Just, Keller, Malave, Kana, & Varma, 2012], but rather pointing to a more general "dysconnectivity" account. Empirical evidence in support of the underconnectivity theory primarily comes from several iFC and task-evoked fMRI studies in adolescents and adults [Just et al., 2012; Muller et al., 2011; Vissers et al., 2012]. Nonetheless, emerging literature now reports a mixed pattern of under- and over-connectivity in individuals with ASD [Di Martino et al., 2014; Fishman et al., 2014]. It remains unclear whether intrinsic hyperconnectivity in ASD can be explained in terms of developmental shift [Uddin, Supekar, & Menon, 2013], compensatory strategies [Kana et al., 2011], or differences in methodological approaches [Nair, Keown, Datko, Shih, Keehn, & Müller, 2014]. Considering the moderate sample size and the lack of pubertal stage assessment, we did not stratify our sample (aged 9–17 years) based on any arbitrary age cut-off. We did not find age-related linear shift in connectivity either, probably owing to the relatively restricted age range. These null findings should not be taken as evidence for a lack of effect from chronological age and pubertal stage on iFC, given the limited sample size and data variances. Future studies with larger sample and a wider age range may be more sensitive in picking up these effects, in which case findings should be characterized in association with chronological age and/or pubertal stage of the participants.

Our data indicate that ASD boys with greater social difficulties displayed greater pRTPJ-right VOTC hyperconnectivity, suggesting that aberrant iFC may underlie social deficits in ASD. Beyond our expectation, brain hyperconnectivity was also related to the "autism mannerism" subscores on the Chinese SRS [Gau et al., 2013]. A speculation is that hyperconnectivity might restrain adaptable resource allocation, resulting in mental inflexibility and insistence for sameness. Alternatively, this finding may be explained by the fact that some behaviors related to social-communication domain in the original SRS [Constantino & Gruber, 2005], for example, "turn-taking interactions," "starting social interactions," are now categorized in the "autism mannerism" subdomain by factor analysis in the Chinese SRS [Gau et al., 2013]. This specification would indicate that the "autism mannerism" subscores, though named so, still indexes inflexibility of social reciprocity to a certain extent.

Interestingly, we did not observe significant association between the connection aberrancy and "social awareness" scores of the Chinese SRS. In terms of psychological constructs, "social awareness" involves multiple components, including perception, self-other recognition, interpretation, and memory [Wegner & Giuliano, 1983]. Lumping together heterogeneous behaviors within the "social awareness" domain might restraint the identification of specific brain-behavior correlation patterns. The moderate sample size may also hinder the detection of small-effect correlations. Another reason for this lack of detectable correlation may be of psychometric reasons. The Chinese ADI-R is an investigator-based semistructured interview scale for parents of individuals with ASD to assess their children's core autistic features [Gau et al., 2010; Rutter et al., 2003], whereas the Chinese SRS is a parent-report questionnaire about the extent of autistic-like traits of the child [Gau et al., 2013]. In light of this, the noted moderate correlation between SRS and ADI-R [Bolte, Westerwald, Holtmann, Freitag, & Poustka, 2011; Constantino et al., 2003] echoes the observed differences in the associations of atypical iFC with the severity of social difficulties indexed by different scales. Nonetheless, we observed the same directionality of brain-behavioral associations across the ADI-R and SRS scores, substantiating the validity of the findings. Notably, although an optimized FDR approach was used to control for type I error, we should acknowledge the caveat to interpret the trend-level associations. Future study with a larger sample size and better indices for social cognition will be helpful.

In this study, only the pRTPJ seed displayed atypical iFC in the ASD group. Notably, the atypically

connected VOTC was found in the right hemisphere. Some studies [Kanwisher, McDermott, & Chun, 1997; Peelen & Downing, 2005; Pelphrey, Morris, & McCarthy, 2005] suggest a right lateralized system of occipital-temporal regions engaged in the sensory processing of socially relevant information, while regions involved in social communication, including PCC and mPFC, are left-lateralized [Gotts, Jo, Wallace, Saad, Cox, & Martin, 2013]. This suggests the quintessence in integration of bilateral hemispheric activity for complex social cognition. However, we did not identify significant group differences in iFC of the posterior TPJ on the left hemisphere, even though pLTPJ has been suggested to play a role in social-communication [Ciaramidaro et al., 2007; Saxe & Kanwisher, 2003]. A formal examination of group differences in the laterality of iFC is, however, beyond the scope of this study. Better-powered datasets are needed to formally examine hemispheric differences in iFC of TPJ, to further test for atypical asymmetry of neural networks in ASD [Cardinale, Shih, Fishman, Ford, & Muller, 2013].

Methodological Considerations

To prevent potential bias in the observed group differences introduced by GSReg [Gotts, Saad et al., 2013; Saad et al., 2012], regression model without GSReg was opted as the main denoising method. However, this strategy might risk inadequately accounting for confounds from motion artifacts [Power, Mitra, Laumann, Snyder, Schlaggar, & Petersen, 2014; Yan et al., 2013]. We, therefore, additionally examined the potential effect of GSReg, and the results endorse robustness of the main findings.

We applied several strategies to address the concerns about in-scanner head motion impacts on iFC. These include stringent motion inclusion criteria, matching the ASD and control groups on average FD, nuisance regression against Friston-24 parameters at an individual level, together with individual mean FD included as a covariate in the group-level analysis [Yan et al., 2013]. The combination of these strategies is expected to minimize the impacts of head-motion on iFC studies.

To avoid exhausting visual stimulation, the participants were asked to keep their eyes closed throughout rs-fMRI image acquisition. Prior studies focusing on the impact of eye-open/closed states on iFC differences reported that functional connectivity maps of DMN [Yan et al., 2009] and all major neural networks [Patriat et al., 2013] appear to be similar across eye-open/closed conditions. BOLD signal intensity [Feige, Scheffler, Esposito, Di Salle, Hennig, & Seifritz, 2005] and test–retest reliability [Patriat et al., 2013] of the visual network are higher for eye-open when compared to eye-closed conditions. However, these works were done with TD participants, and it is unknown if the effects of eye-opening vs. closed are dependent on the presence of neuropsychiatric conditions. Future studies should focus on the impacts of eye-open/closed conditions in relation to current findings in an ASD population, given that there is still a lack of consensus in this aspect in acquiring rs-fMRI data.

Limitations

Several limitations should be acknowledged. First, as the participants are of average or above-average IQ and are biologically male, it is, thus, unknown whether the current findings could be generalized to other subgroups on the spectrum, given the heterogeneity in ASD [Lai, Lombardo, Chakrabarti, & Baron-Cohen, 2013]. Second, the study is cross-sectional and correlational, thus cannot address etiological and developmental effects. Third, three participants with co-occurring ASD and ADHD were not excluded in the current study, rendering possible confounding comorbidity effects. However, a high co-occurring rate of ADHD in ASD has been reported [Taurines, Schwenck, Westerwald, Sachse, Siniatchkin, & Freitag, 2012], and partly common causal factors are likely shared by the two conditions [Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011]. Future works investigating individuals with ASD with/without ADHD will help address the issue. Lastly, given the moderate-sized sample of this study, the findings await to be replicated in independent datasets in the future.

Our data provide new evidence that intrinsic hyperconnectivity between the pRTPJ and the right VOTC was associated with social deficits in boys with high-functioning ASD. Considering that pRTPJ is a key structure for human social cognition, and that the right VOTC is essential for processing socially related visual information, we speculate that atypical pRTPJ-right VOTC connection may hinder effective integration of socially relevant perceptual information, contributing to social difficulties in ASD. Our findings provide empirical support for understanding the neurobiology of ASD in the framework of "dysconnectivity", rather than uniformly under-connected neural networks.

Acknowledgments

This work was supported by the National Science Council of Taiwan (NSC97-3112-B-002-009, NSC98-3112-B-002-004, NSC 99-2627-B-002-016, NSC 100-2627-B-002-013), the National Health Research Institute (NHRI-EX98-9407PC, NHRI-EX100-0008PI), National Taiwan University (AIM for Top University Excellent Research Project: 10R81918-03, 101R892103), National Taiwan University Hospital (NTUH101-S1910) and in part by the Department

of Medical Imaging and 3T MRI Lab in National Taiwan University Hospital. We are grateful for all participants and their parents for taking part in the study. We thank Dr. Michael Lombardo for valuable discussions during the preparation of the manuscript. Dr. Meng-Chuan Lai is supported by the William Binks Autism Neuroscience Fellowship, the European Autism Interventions - A Multicentre Study for Developing New Medications (EU-AIMS), and Wolfson College, Cambridge.

References

Alaerts, K., Woolley, D.G., Steyaert, J., Di Martino, A., Swinnen, S.P., & Wenderoth, N. (2014). Underconnectivity of the superior temporal sulcus predicts emotion recognition deficits in autism. Social Cognitive and Affective Neuroscience, 9, 1589–1600.

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC: American Psychiatric Association.

Anderson, J.S., Druzgal, T.J., Froehlich, A., DuBray, M.B., Lange, N., Alexander, A.L., et al. (2011). Decreased interhemispheric functional connectivity in autism. Cerebral Cortex, 21, 1134–1146.

Andrews-Hanna, J.R. (2012). The brain's default network and its adaptive role in internal mentation. Neuroscientist, 18, 251–270.

Andrews-Hanna, J.R., Reidler, J.S., Sepulcre, J., Poulin, R., & Buckner, R.L. (2010). Functional-anatomic fractionation of the brain's default network. Neuron, 65, 550–562.

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. NeuroImage, 38, 95–113.

Benjamini, Y., & Hochberg, Y. (2000). On the adaptive control of the false discovery rate in multiple testing with independent statistics. Journal of Educational and Behavioral Statistics, 25, 60–83.

Bolte, S., Westerwald, E., Holtmann, M., Freitag, C., & Poustka, F. (2011). Autistic traits and autism spectrum disorders: The clinical validity of two measures presuming a continuum of social communication skills. Journal of Autism and Developmental Disorders, 41, 66–72.

Boucher, J. (2012). Putting theory of mind in its place: Psychological explanations of the socio-emotional-communicative impairments in autistic spectrum disorder. Autism, 16, 226–246.

Brett, M., Anton, J.-L., Valabregue, R., & Poline, J.-B. (2002). Region of interest analysis using the MarsBar toolbox for SPM 99. NeuroImage, 16, S497.

Cardinale, R.C., Shih, P., Fishman, I., Ford, L.M., & Muller, R.A. (2013). Pervasive rightward asymmetry shifts of functional networks in autism spectrum disorder. JAMA Psychiatry, 70, 975–982.

Caspers, J., Zilles, K., Eickhoff, S.B., Schleicher, A., Mohlberg, H., & Amunts, K. (2013). Cytoarchitectonical analysis and probabilistic mapping of two extrastriate areas of the human posterior fusiform gyrus. Brain Structure and Function, 218, 511–526.

Cherkassky, V.L., Kana, R.K., Keller, T.A., & Just, M.A. (2006). Functional connectivity in a baseline resting-state network in autism. Neuroreport, 17, 1687–1690.

Chevallier, C., Kohls, G., Troiani, V., Brodkin, E.S., & Schultz, R.T. (2012). The social motivation theory of autism. Trends in Cognitive Sciences, 16, 231–239.

Ciaramidaro, A., Adenzato, M., Enrici, I., Erk, S., Pia, L., Bara, B.G., et al. (2007). The intentional network: How the brain reads varieties of intentions. Neuropsychologia, 45, 3105–3113.

Constantino, J.N., Davis, S.A., Todd, R.D., Schindler, M.K., Gross, M.M., Brophy, S.L., et al. (2003). Validation of a brief quantitative measure of autistic traits: Comparison of the social responsiveness scale with the autism diagnostic interview-revised. Journal of Autism and Developmental Disorders, 33, 427–433.

Constantino, J.N., & Gruber, C.P. (2005). Social Responsiveness Scale (SRS). Los Angeles: Western Psychological Services.

Dalton, K.M., Nacewicz, B.M., Johnstone, T., Schaefer, H.S., Gernsbacher, M.A., Goldsmith, H.H., et al. (2005). Gaze fixation and the neural circuitry of face processing in autism. Nature Neuroscience, 8, 519–526.

Dayan, E., Casile, A., Levit-Binnun, N., Giese, M.A., Hendler, T., & Flash, T. (2007). Neural representations of kinematic laws of motion: Evidence for action-perception coupling. Proceedings of the National Academy of Sciences of the United States of America, 104, 20582–20587.

de Haan, E.H., & Cowey, A. (2011). On the usefulness of 'what' and 'where' pathways in vision. Trends in Cognitive Sciences, 15, 460–466.

Decety, J., & Lamm, C. (2007). The role of the right temporoparietal junction in social interaction: How low-level computational processes contribute to meta-cognition. Neuroscientist, 13, 580–593.

Di Martino, A., Kelly, C., Grzadzinski, R., Zuo, X.N., Mennes, M., Mairena, M.A., et al. (2011). Aberrant striatal functional connectivity in children with autism. Biological Psychiatry, 69, 847–856.

Di Martino, A., Ross, K., Uddin, L.Q., Sklar, A.B., Castellanos, F.X., & Milham, M.P. (2009). Functional brain correlates of social and nonsocial processes in autism spectrum disorders: An activation likelihood estimation meta-analysis. Biological Psychiatry, 65, 63–74.

Di Martino, A., Yan, C.G., Li, Q., Denio, E., Castellanos, F.X., Alaerts, K., et al. (2014). The autism brain imaging data exchange: Towards a large-scale evaluation of the intrinsic brain architecture in autism. Molecular Psychiatry, 19, 659–667.

Dichter, G.S. (2012). Functional magnetic resonance imaging of autism spectrum disorders. Dialogues in Clinical Neuroscience, 14, 319–351.

Dinstein, I., Pierce, K., Eyler, L., Solso, S., Malach, R., Behrmann, M., et al. (2011). Disrupted neural synchronization in toddlers with autism. Neuron, 70, 1218–1225.

Dufour, N., Redcay, E., Young, L., Mavros, P.L., Moran, J.M., Triantafyllou, C., et al. (2013). Similar brain activation during false belief tasks in a large sample of adults with and without autism. PloS One, 8, e75468.

Ebisch, S.J., Gallese, V., Willems, R.M., Mantini, D., Groen, W.B., Romani, G.L., et al. (2011). Altered intrinsic

functional connectivity of anterior and posterior insula regions in high-functioning participants with autism spectrum disorder. Human Brain Mapping, 32, 1013–1028.

Ecker, C., Suckling, J., Deoni, S.C., Lombardo, M.V., Bullmore, E.T., Baron-Cohen, S., et al. (2012). Brain anatomy and its relationship to behavior in adults with autism spectrum disorder: A multicenter magnetic resonance imaging study. Archives of General Psychiatry, 69, 195–209.

Feige, B., Scheffler, K., Esposito, F., Di Salle, F., Hennig, J., & Seifritz, E. (2005). Cortical and subcortical correlates of electroencephalographic alpha rhythm modulation. Journal of Neurophysiology, 93, 2864–2872.

Fishman, I., Keown, C.L., Lincoln, A.J., Pineda, J.A., & Muller, R.A. (2014). Atypical cross talk between mentalizing and mirror neuron networks in autism spectrum disorder. JAMA Psychiatry, 71, 751–760.

Fox, M.D., & Raichle, M.E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nature Reviews: Neuroscience, 8, 700–711.

Friston, K.J. (1998). The disconnection hypothesis. Schizophrenia Research, 30, 115–125.

Friston, K.J., Williams, S., Howard, R., Frackowiak, R.S., & Turner, R. (1996). Movement-related effects in fMRI time-series. Magnetic Resonance in Medicine, 35, 346–355.

Frith, U. (2001). Mind blindness and the brain in autism. Neuron, 32, 969–979.

Gau, S.S., Chong, M.Y., Chen, T.H., & Cheng, A.T. (2005). A 3-year panel study of mental disorders among adolescents in Taiwan. American Journal of Psychiatry, 162, 1344–1350.

Gau, S.S.F., Chou, M.C., Lee, J.C., Wong, C.C., Chou, W.J., Chen, M.F., et al. (2010). Behavioral problems and parenting style among Taiwanese children with autism and their siblings. Psychiatry and Clinical Neurosciences, 64, 70–78.

Gau, S.S.-F., Liu, L.-T., Wu, Y.-Y., Chiu, Y.-N., & Tsai, W.-C. (2013). Psychometric properties of the Chinese version of the social responsiveness scale. Research in Autism Spectrum Disorders, 7, 349–360.

Gotts, S.J., Jo, H.J., Wallace, G.L., Saad, Z.S., Cox, R.W., & Martin, A. (2013). Two distinct forms of functional lateralization in the human brain. Proceedings of the National Academy of Sciences of the United States of America, 110, E3435–E3444.

Gotts, S.J., Saad, Z.S., Jo, H.J., Wallace, G.L., Cox, R.W., & Martin, A. (2013). The perils of global signal regression for group comparisons: A case study of Autism Spectrum Disorders. Frontiers in Human Neuroscience, 7, 356.

Gotts, S.J., Simmons, W.K., Milbury, L.A., Wallace, G.L., Cox, R.W., & Martin, A. (2012). Fractionation of social brain circuits in autism spectrum disorders. Brain, 135, 2711–2725.

Grady, C.L., Protzner, A.B., Kovacevic, N., Strother, S.C., Afshin-Pour, B., Wojtowicz, M., et al. (2010). A multivariate analysis of age-related differences in default mode and task-positive networks across multiple cognitive domains. Cerebral Cortex, 20, 1432–1447.

Hadjikhani, N., Joseph, R.M., Snyder, J., & Tager-Flusberg, H. (2006). Anatomical differences in the mirror neuron system and social cognition network in autism. Cerebral Cortex, 16, 1276–1282.

Hein, G., & Knight, R.T. (2008). Superior temporal sulcus--It's my area: Or is it? Journal of Cognitive Neuroscience, 20, 2125–2136.

Hsiao, M.N., Tseng, W.L., Huang, H.Y., & Gau, S.S. (2013). Effects of autistic traits on social and school adjustment in children and adolescents: The moderating roles of age and gender. Research in Developmental Disabilities, 34, 254–265.

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. NeuroImage, 17, 825–841.

Just, M.A., Keller, T.A., Malave, V.L., Kana, R.K., & Varma, S. (2012). Autism as a neural systems disorder: A theory of frontal-posterior underconnectivity. Neuroscience & Biobehavioral Reviews, 36, 1292–1313.

Kana, R.K., Keller, T.A., Cherkassky, V.L., Minshew, N.J., & Just, M.A. (2009). Atypical frontal-posterior synchronization of Theory of Mind regions in autism during mental state attribution. Social Neuroscience, 4, 135–152.

Kana, R.K., Libero, L.E., Hu, C.P., Deshpande, H.D., & Colburn, J.S. (2012). Functional brain networks and white matter underlying theory-of-mind in autism. Social Cognitive and Affective Neuroscience, 9, 98–105.

Kana, R.K., Libero, L.E., & Moore, M.S. (2011). Disrupted cortical connectivity theory as an explanatory model for autism spectrum disorders. Physics of Life Reviews, 8, 410–437.

Kanwisher, N., McDermott, J., & Chun, M.M. (1997). The fusiform face area: A module in human extrastriate cortex specialized for face perception. Journal of Neuroscience, 17, 4302–4311.

Kanwisher, N., & Yovel, G. (2006). The fusiform face area: A cortical region specialized for the perception of faces. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 361, 2109–2128.

Kennedy, D.P., & Courchesne, E. (2008). The intrinsic functional organization of the brain is altered in autism. NeuroImage, 39, 1877–1885.

Koster-Hale, J., Saxe, R., Dungan, J., & Young, L.L. (2013). Decoding moral judgments from neural representations of intentions. Proceedings of the National Academy of Sciences of the United States of America, 110, 5648–5653.

Kubit, B., & Jack, A.I. (2013). Rethinking the role of the rTPJ in attention and social cognition in light of the opposing domains hypothesis: Findings from an ALE-based meta-analysis and resting-state functional connectivity. Frontiers in Human Neuroscience, 7, 323.

Lai, M.C., Lombardo, M.V., & Baron-Cohen, S. (2014). Autism. Lancet, 383, 896–910.

Lai, M.C., Lombardo, M.V., Chakrabarti, B., & Baron-Cohen, S. (2013). Subgrouping the autism "spectrum": Reflections on DSM-5. PLoS Biology, 11, e1001544.

Lombardo, M.V., & Baron-Cohen, S. (2011). The role of the self in mindblindness in autism. Consciousness and Cognition, 20, 130–140.

Lombardo, M.V., Baron-Cohen, S., Belmonte, M.K., & Chakrabarti, B. (2011). Neural endophenotypes of social behavior in autism spectrum conditions. In J. Decety & J.T. Cacioppo (Eds.), The oxford handbook of social neuroscience (pp. 830–847). New York: Oxford University Press.

Lombardo, M.V., Chakrabarti, B., Bullmore, E.T., MRC Aims Consortium, & Baron-Cohen, S. (2011b). Specialization of right temporo-parietal junction for mentalizing and its relation to social impairments in autism. NeuroImage, 56, 1832–1838.

Lynch, C.J., Uddin, L.Q., Supekar, K., Khouzam, A., Phillips, J., & Menon, V. (2013). Default mode network in childhood autism: Posteromedial cortex heterogeneity and relationship with social deficits. Biological Psychiatry, 74, 212–219.

Mars, R.B., Sallet, J., Schuffelgen, U., Jbabdi, S., Toni, I., & Rushworth, M.F. (2012). Connectivity-based subdivisions of the human right "temporoparietal junction area": Evidence for different areas participating in different cortical networks. Cerebral Cortex, 22, 1894–1903.

Materna, S., Dicke, P.W., & Thier, P. (2008). The posterior superior temporal sulcus is involved in social communication not specific for the eyes. Neuropsychologia, 46, 2759–2765.

McKay, L.S., Simmons, D.R., McAleer, P., Marjoram, D., Piggot, J., & Pollick, F.E. (2012). Do distinct atypical cortical networks process biological motion information in adults with Autism Spectrum Disorders? NeuroImage, 59, 1524–1533.

Minshew, N.J., & Williams, D.L. (2007). The new neurobiology of autism: Cortex, connectivity, and neuronal organization. Archives of Neurology, 64, 945–950.

Monk, C.S., Peltier, S.J., Wiggins, J.L., Weng, S.J., Carrasco, M., Risi, S., et al. (2009). Abnormalities of intrinsic functional connectivity in autism spectrum disorders. NeuroImage, 47, 764–772.

Muller, R.A., Shih, P., Keehn, B., Deyoe, J.R., Leyden, K.M., & Shukla, D.K. (2011). Underconnected, but how? A survey of functional connectivity MRI studies in autism spectrum disorders. Cerebral Cortex, 21, 2233–2243.

Nair, A., Keown, C.L., Datko, M., Shih, P., Keehn, B., & Müller, R.A. (2014). Impact of methodological variables on functional connectivity findings in autism spectrum disorders. Human Brain Mapping, 35, 4035–4048.

Nair, A., Treiber, J.M., Shukla, D.K., Shih, P., & Muller, R.A. (2013). Impaired thalamocortical connectivity in autism spectrum disorder: A study of functional and anatomical connectivity. Brain, 136, 1942–1955.

Oldfield, R.C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia, 9, 97–113.

Orvaschel, H., Puig-Antich, J., Chambers, W., Tabrizi, M.A., & Johnson, R. (1982). Retrospective assessment of prepubertal major depression with the Kiddie-SADS-E. Journal of the American Academy of Child Psychiatry, 21, 392–397.

Patriat, R., Molloy, E.K., Meier, T.B., Kirk, G.R., Nair, V.A., Meyerand, M.E., et al. (2013). The effect of resting condition on resting-state fMRI reliability and consistency: A comparison between resting with eyes open, closed, and fixated. NeuroImage, 78, 463–473.

Peelen, M.V., & Downing, P.E. (2005). Selectivity for the human body in the fusiform gyrus. Journal of Neurophysiology, 93, 603–608.

Pelphrey, K.A., Morris, J.P., & McCarthy, G. (2005a). Neural basis of eye gaze processing deficits in autism. Brain, 128, 1038–1048.

Pelphrey, K.A., Morris, J.P., Michelich, C.R., Allison, T., & McCarthy, G. (2005b). Functional anatomy of biological motion perception in posterior temporal cortex: An FMRI study of eye, mouth and hand movements. Cerebral Cortex, 15, 1866–1876.

Pelphrey, K.A., Shultz, S., Hudac, C.M., & Vander Wyk, B.C. (2011). Research review: Constraining heterogeneity: The social brain and its development in autism spectrum disorder. Journal of Child Psychology and Psychiatry, 52, 631–644.

Philip, R.C., Dauvermann, M.R., Whalley, H.C., Baynham, K., Lawrie, S.M., & Stanfield, A.C. (2012). A systematic review and meta-analysis of the fMRI investigation of autism spectrum disorders. Neuroscience & Biobehavioral Reviews, 36, 901–942.

Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., & Petersen, S.E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. NeuroImage, 59, 2142–2154.

Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., & Petersen, S.E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. NeuroImage, 84, 320–341.

Price, C.J., & Devlin, J.T. (2011). The interactive account of ventral occipitotemporal contributions to reading. Trends in Cognitive Sciences, 15, 246–253.

Rommelse, N.N., Geurts, H.M., Franke, B., Buitelaar, J.K., & Hartman, C.A. (2011). A review on cognitive and brain endophenotypes that may be common in autism spectrum disorder and attention-deficit/hyperactivity disorder and facilitate the search for pleiotropic genes. Neuroscience & Biobehavioral Reviews, 35, 1363–1396.

Rutter, M., Le Couteur, A., & Lord, C. (2003). Autism diagnostic interview-revised. Los Angeles, CA: Western Psychological Services.

Saad, Z.S., Gotts, S.J., Murphy, K., Chen, G., Jo, H.J., Martin, A., et al. (2012). Trouble at rest: How correlation patterns and group differences become distorted after global signal regression. Brain Connect, 2, 25–32.

Sabatinelli, D., Fortune, E.E., Li, Q., Siddiqui, A., Krafft, C., Oliver, W.T., et al. (2011). Emotional perception: Meta-analyses of face and natural scene processing. NeuroImage, 54, 2524–2533.

Samson, F., Mottron, L., Soulieres, I., & Zeffiro, T.A. (2012). Enhanced visual functioning in autism: An ALE meta-analysis. Human Brain Mapping, 33, 1553–1581.

Satterthwaite, T.D., Wolf, D.H., Loughead, J., Ruparel, K., Elliott, M.A., Hakonarson, H., et al. (2012). Impact of in-scanner head motion on multiple measures of functional connectivity: Relevance for studies of neurodevelopment in youth. NeuroImage, 60, 623–632.

Saxe, R., & Kanwisher, N. (2003). People thinking about thinking people. The role of the temporo-parietal junction in "theory of mind." NeuroImage, 19, 1835–1842.

Saygin, Z.M., Osher, D.E., Koldewyn, K., Reynolds, G., Gabrieli, J.D., & Saxe, R.R. (2012). Anatomical connectivity patterns predict face selectivity in the fusiform gyrus. Nature Neuroscience, 15, 321–327.

Schipul, S.E., Keller, T.A., & Just, M.A. (2011). Inter-regional brain communication and its disturbance in autism. Frontiers in Systems Neuroscience, 5, 10.

Senju, A. (2012). Spontaneous theory of mind and its absence in autism spectrum disorders. Neuroscientist, 18, 108–113.

Servos, P., Osu, R., Santi, A., & Kawato, M. (2002). The neural substrates of biological motion perception: An fMRI study. Cerebral Cortex, 12, 772–782.

Sewards, T.V. (2011). Neural structures and mechanisms involved in scene recognition: A review and interpretation. Neuropsychologia, 49, 277–298.

Shen, M.D., Shih, P., Ottl, B., Keehn, B., Leyden, K.M., Gaffrey, M.S., et al. (2012). Atypical lexicosemantic function of extrastriate cortex in autism spectrum disorder: Evidence from functional and effective connectivity. NeuroImage, 62, 1780–1791.

Shih, P., Keehn, B., Oram, J.K., Leyden, K.M., Keown, C.L., & Muller, R.A. (2011). Functional differentiation of posterior superior temporal sulcus in autism: A functional connectivity magnetic resonance imaging study. Biological Psychiatry, 70, 270–277.

Song, X.W., Dong, Z.Y., Long, X.Y., Li, S.F., Zuo, X.N., Zhu, C.Z., et al. (2011). REST: A toolkit for resting-state functional magnetic resonance imaging data processing. PloS One, 6, e25031.

Spengler, S., von Cramon, D.Y., & Brass, M. (2010). Resisting motor mimicry: Control of imitation involves processes central to social cognition in patients with frontal and temporo-parietal lesions. Social Neuroscience, 5, 401–416.

Supekar, K., Musen, M., & Menon, V. (2009). Development of large-scale functional brain networks in children. PLoS Biology, 7, e1000157.

Supekar, K., Uddin, L.Q., Khouzam, A., Phillips, J., Gaillard, W.D., Kenworthy, L.E., et al. (2013). Brain hyperconnectivity in children with autism and its links to social deficits. Cell Reports, 5, 738–747.

Tahmasebi, A.M., Abolmaesumi, P., Zheng, Z.Z., Munhall, K.G., & Johnsrude, I.S. (2009). Reducing inter-subject anatomical variation: Effect of normalization method on sensitivity of functional magnetic resonance imaging data analysis in auditory cortex and the superior temporal region. NeuroImage, 47, 1522–1531.

Taurines, R., Schwenck, C., Westerwald, E., Sachse, M., Siniatchkin, M., & Freitag, C. (2012). ADHD and autism: Differential diagnosis or overlapping traits? A selective review. ADHD Attention Deficit and Hyperactivity Disorders, 4, 115–139.

Turk-Browne, N.B., Norman-Haignere, S.V., & McCarthy, G. (2010). Face-specific resting functional connectivity between the fusiform gyrus and posterior superior temporal sulcus. Frontiers in Human Neuroscience, 4, 176.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage, 15, 273–289.

Uddin, L.Q., Supekar, K., Lynch, C.J., Khouzam, A., Phillips, J., Feinstein, C., et al. (2013a). Salience network-based classification and prediction of symptom severity in children with autism. JAMA Psychiatry, 70, 869–879.

Uddin, L.Q., Supekar, K., & Menon, V. (2013b). Reconceptualizing functional brain connectivity in autism from a developmental perspective. Frontiers in Human Neuroscience, 7, 458.

Uddin, L.Q., Supekar, K.S., Ryali, S., & Menon, V. (2011). Dynamic reconfiguration of structural and functional connectivity across core neurocognitive brain networks with development. Journal of Neuroscience, 31, 18578–18589.

Van Dijk, K.R., Sabuncu, M.R., & Buckner, R.L. (2012). The influence of head motion on intrinsic functional connectivity MRI. NeuroImage, 59, 431–438.

Van Overwalle, F. (2009). Social cognition and the brain: A meta-analysis. Human Brain Mapping, 30, 829–858.

Van Overwalle, F., & Baetens, K. (2009). Understanding others' actions and goals by mirror and mentalizing systems: A meta-analysis. NeuroImage, 48, 564–584.

Vander Wyk, B.C., Hudac, C.M., Carter, E.J., Sobel, D.M., & Pelphrey, K.A. (2009). Action understanding in the superior temporal sulcus region. Psychological Science, 20, 771–777.

Vissers, M.E., Cohen, M.X., & Geurts, H.M. (2012). Brain connectivity and high functioning autism: A promising path of research that needs refined models, methodological convergence, and stronger behavioral links. Neuroscience & Biobehavioral Reviews, 36, 604–625.

von dem Hagen, E.A., Stoyanova, R.S., Baron-Cohen, S., & Calder, A.J. (2013). Reduced functional connectivity within and between 'social' resting state networks in autism spectrum conditions. Social Cognitive and Affective Neuroscience, 8, 694–701.

Washington, S.D., Gordon, E.M., Brar, J., Warburton, S., Sawyer, A.T., Wolfe, A., et al. (2014). Dysmaturation of the default mode network in autism. Human Brain Mapping, 35, 1284–1296.

Wechsler, D. (1991). WISC-III: Wechsler intelligence scale for children. TX: Psychological Corporation San Antonio.

Wegner, D.M., & Giuliano, T. (1983). Social awareness in story comprehension. Social Cognition, 2, 1–17.

Weiner, K.S., & Grill-Spector, K. (2010). Sparsely-distributed organization of face and limb activations in human ventral temporal cortex. NeuroImage, 52, 1559–1573.

Weng, S.J., Wiggins, J.L., Peltier, S.J., Carrasco, M., Risi, S., Lord, C., et al. (2010). Alterations of resting state functional connectivity in the default network in adolescents with autism spectrum disorders. Brain Research, 1313, 202–214.

Wilke, M. (2012). An alternative approach towards assessing and accounting for individual motion in fMRI timeseries. NeuroImage, 59, 2062–2072.

Wilke, M., Holland, S.K., Altaye, M., & Gaser, C. (2008). Template-O-Matic: A toolbox for creating customized pediatric templates. NeuroImage, 41, 903–913.

Xia, M., Wang, J., & He, Y. (2013). BrainNet Viewer: A network visualization tool for human brain connectomics. PloS One, 8, e68910.

Yan, C., Liu, D., He, Y., Zou, Q., Zhu, C., Zuo, X., et al. (2009). Spontaneous brain activity in the default mode network is sensitive to different resting-state conditions with limited cognitive load. PloS One, 4, e5743.

Yan, C.G., Cheung, B., Kelly, C., Colcombe, S., Craddock, R.C., Di Martino, A., et al. (2013). A comprehensive assessment of

regional variation in the impact of head micromovements on functional connectomics. NeuroImage, 76, 183–201.
Yan, C.G., & Zang, Y.F. (2010). DPARSF: A MATLAB Toolbox for "Pipeline" Data Analysis of Resting-State fMRI. Frontiers in Systems Neuroscience, 4, 13.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.