OPEN

Molecular Psychiatry (2018) 23, 1659–1665

www.nature.com/mp

ORIGINAL ARTICLE

Alterations in resting state connectivity along the autism trait continuum: a twin study

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Autism spectrum disorder (ASD) has been found to be associated with alterations in resting state (RS) functional connectivity, including areas forming the default mode network (DMN) and salience network (SN). However, insufficient control for confounding genetic and environmental influences and other methodological issues limit the generalizability of previous findings. Moreover, it has been hypothesized that ASD might be marked by early hyper-connectivity followed by later hypo-connectivity. To date, only a few studies have explicitly tested age-related influences on RS connectivity alterations in ASD. Using a within-twin pair design ($N = 150$ twins; 8–23 years), we examined altered RS connectivity between core regions of the DMN and SN in relation to autistic trait severity and age in a sample of monozygotic (MZ) and dizygotic (DZ) twins showing typical development, ASD or other neurodevelopmental conditions. Connectivity between core regions of the SN was stronger in twins with higher autistic traits compared to their co-twins. This effect was significant both in the total sample and in MZ twins alone, highlighting the effect of non-shared environmental factors on the link between SN-connectivity and autistic traits. While this link was strongest in children, we did not identify differences between age groups for the SN. In contrast, connectivity between core hubs of the DMN was negatively correlated with autistic traits in adolescents and showed a similar trend in adults but not in children. The results support hypotheses of age-dependent altered RS connectivity in ASD, making altered SN and DMN connectivity promising candidate biomarkers for ASD.

Molecular Psychiatry (2018) **23,** 1659–1665; doi:10.1038/mp.2017.160; published online 1 August 2017

INTRODUCTION

Altered patterns of brain connectivity have been suggested as a key neurobiological correlate of the behavioral characteristics of autism spectrum disorder (ASD). However, as findings are inconsistent, the precise brain connectivity characteristics of ASD remain unclear. A large number of resting-state (RS) functional magnetic resonance imaging (MRI) brain connectivity studies have shown a complex pattern of both hypo- and hyper-connectivity in ASD.[1–3] Notably, a large multi-site classification study including ASD and typically developing individuals ($N = 252$, 6–36 years) showed that of the top 100 biomarkers of brain connectivity achieving together 90.8% accuracy, 45% were related to hyper-connectivity and the remaining 55% to hypo-connectivity.[4] It is likely that the observed inconsistencies in classical brain connectivity investigations are limited by methodological issues, such as insufficient control for head motion or the inclusion of global signal regression which can modulate or even invert the direction of functional connectivity differences.[5–7] Moreover, gender has recently been shown to modulate the direction of connectivity differences in ASD.[8] In contrast, another study found default mode network (DMN) hypo-connectivity in both genders.[9] Finally, another source of bias that has been largely overlooked is the impact of age-related changes on functional connectivity.[10] However, it has been pointed out that patterns of hyper-connectivity are more commonly reported in younger individuals with ASD and a recent model suggests early hyper-connectivity followed by later hypo-connectivity.[10]

Several lines of experimental evidence suggest RS connectivity in the DMN and the salience network (SN) to be of paramount significance (see Supplementary Table 1). The DMN is presumed to be involved in self-referential processing and its central nodes are located in the posterior cingulate cortex (PCC) and the ventro-medial prefrontal cortex (vmPFC).[11] The SN, which has its central hubs in the anterior insula (AI) and the anterior cingulate cortex (ACC), has been suggested to be crucial for the identification of salient stimuli.[12] Reduced DMN RS connectivity has been observed across age-groups in individuals with ASD, both within the DMN[13–16] and between the DMN and other regions.[17–20] In contrast, some studies have reported increased DMN RS connectivity.[13,20–22] Reduced SN RS connectivity has been found in children, adolescents and adults with ASD, affecting connectivity within the SN as well as connectivity between SN key nodes and sensory, prefrontal, and emotion processing regions.[19,22–27] Moreover, increased connectivity within the SN and between the insula and striatal/retrosplenial regions has been reported in children with ASD.[13,21,28] Age effects on connectivity involving both DMN and SN core regions have also been demonstrated.[20,24]

Taken together, there is strong experimental support for altered brain connectivity of the SN and the DMN in ASD. Further, twin and family studies indicate that both genetic and environmental

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Received 13 January 2017; revised 16 May 2017; accepted 19 June 2017; published online 1 August 2017

Table 1. Twin sample characteristics

	All pairs	*MZ pairs*	*DZ pairs*	*Children*	*Adolescents*	*Adults*
Total no. of pairs	75	46	29	22	31	22
Gender, m/f	42 / 33	28 / 18	14 / 15	13 / 9	17 / 14	12 / 10
Age mean (s.d.)	16.16 (3.34)	16.95 (3.09)	16.61 (3.85)	12.12 (1.54)	16.16 (1.21)	20.12 (1.83)
IQ mean (s.d.)	97.95 (15.27)	98.43 (16.27)	97.19 (13.62)	98.70 (13.28)	100.50 (16.05)	93.97 (15.36)
ASD discordant	17	6	11	8	4	5
ASD concordant	6	6	0	2	3	1
Mean autistic traits (s.d.)	39.96 (28.90)	35.47 (29.00)	47.09 (28.19)	48.41 (32.11)	35.47 (24.56)	37.84 (30.05)
Mean within-pair difference in autistic traits (s.d.)	21.63 (25.65)	14.37 (19.46)	33.14 (39.12)	26.00 (28.36)	14.81 (20.00)	26.86 (28.74)

Abbreviations: ASD, autism spectrum disorder; DZ, dizygotic; f, female; IQ, intelligence quotient; m, male; MZ, monozygotic. Sample characteristics of the included pairs are listed for both the entire sample and sub-samples of interest: zygosity-group-specific and age-group-specific characteristics.

factors, as well as their interplay, influence ASD etiology.[29–32] Age and gender bias, in combination with limited control over genetic and environmental confounders, are likely to have contributed to earlier mixed findings of RS connectivity in ASD. To this end, discordant monozygotic (MZ) twin pair designs provide excellent methodological control over genetic as well as shared environmental factors, including age, gender and other possible confounding variables such as family background and parental age. So far, only few studies have applied this design in ASD research.[33] To the best of our knowledge, the present study is the first to test the relationship between autistic traits and RS connectivity of DMN and SN using a discordant twin pair design. While a part of our twin sample is discordant for ASD diagnosis, the focus in the present study is on quantitative discordancy for autistic traits. The latter is in line with the RDoC (Research Domain Criteria, NIH) recommendations and the current views of ASD forming the extreme end of a continuum of behaviors. By including both MZ ($n = 46$ pairs) and DZ twin pairs ($n = 29$ pairs), we aimed to distinguish between genetic and environmental contributions to alterations in RS functional MRI brain connectivity. In the light of recent evidence of potential age-effects on brain connectivity differences in ASD, we further tested for differences between age-groups in our sample. Thus, the main target for the present twin study was to investigate putative differences in intrinsic functional brain connectivity with emphasis on the functional integrity of the DMN and SN networks along the continuum of autistic traits.

MATERIALS AND METHODS

Participants

We included MZ and DZ twin pairs (8–23 years), predominantly sampled from a population-based twin cohort (The Child and Adolescent Twin Study in Sweden),[34] prioritizing pairs being screened positively for ASD trait discordance according to the Autism—Tics, attention deficit hyperactive disorder (ADHD) and other Comorbidities Inventory.[35,36] The twins were discordant or concordant for ASD or other neurodevelopmental disorders or typically developing, and were assessed within the Roots of Autism and ADHD Twin Study Sweden (RATSS).[37] From the entire sample collected until August 2016 ($N = 240$ individuals), we included 150 twins (75 complete same-sex pairs of which 42 were male) in the analysis that fulfilled the inclusion criteria specified in the Supplementary Text. Of the included individuals, 29 fulfilled diagnostic criteria for ASD (17 discordant pairs of which 11 were male and six concordant pairs of which three were male), 18 further individuals fulfilled criteria for other neurodevelopmental disorders, and 16 further for other psychiatric disorders. The study was approved by the local Stockholm Ethics Board and informed consent was obtained from all participants. Twin sample characteristics are summarized in Table 1.

Behavioral and diagnostic assessment

Twins were assessed by a team of experienced clinicians, and clinical diagnoses endorsed by results from standardized tools; the Autism Diagnostic Interview—Revised (ADI-R)[38] the Autism Diagnostic Observation Schedule-2 (ADOS-2),[39] the Kiddie Schedule for Affective Disorders and Schizophrenia—Present and Lifetime Version (K-SADS-PL)[40] or the Diagnostic Interview for ADHD in Adults (DIVA 2.0).[41] Autistic traits were measured by parent, close family member or spouse report on the Social Responsiveness Scale-2 (SRS-2)[42] using total raw scores as recommended for research settings (see Supplementary Text).[42] General intelligence quotient (IQ) was assessed with the Wechsler Intelligence Scales for Children or Adults, 4th Edition (WISC-IV; WAIS-IV).[43,44]

Image acquisition and preprocessing

To familiarize the participants with the MRI scanning procedure, subjects completed a 5–7 min pre-scanning training session in a mock scanner. The following ~50 min MRI session in a 3 Tesla MR750 GE-scanner included a 5 min T1-weighted Spoiled Gradient Echo anatomical scan (176 slices, TR = 8.2 s, FOV = 240 mm) and a 10 min RS T2*-weighted Echo Planar Imaging Scan (45 slices, TR = 3 s, 205 volumes, FOV = 288 mm, matrix size = 96x96). During the RS scan, a white cross on black background was presented. Participants were instructed to look at the cross throughout the RS functional MRI run. Functional images were pre-processed in AFNI,[45] following its standard pipeline (afni_proc.py, http://bit.ly/2iujuuH), and a recommendation[46] to combine several methods for noise reduction (please see the Supplementary Text for a detailed description).

Selection of regions of interest

All analyses were hypotheses-driven and performed on predefined regions of interest (ROIs). On the basis of our aim to investigate SN and DMN brain connectivity, we extracted functional MRI signal intensity time courses from four ROIs (radius 10 mm) encompassing core hubs within the DMN (PCC [−6, −44,34] and vmPFC [−2, 38, −12]) and the SN (right AI = rAI [39, 23, −4] and ACC [6, 24, 32]). The selection of coordinates was based on the peaks of activity yielded by a previous Independent Component Analysis study conducted in typically developed children and adults.[47]

Statistical analyses

Correlation coefficients (Pearson's r) between ROI signal time courses were calculated as measures of both within- (PCC-vmPFC; rAI-ACC) and between-network connectivity (PCC-rAI, PCC-ACC, vmPFC-ACC, vmPFC-rAI) for all subjects. Although our primary hypothesis was focused on within-network connectivity, we included between-network connectivity for completeness. Correlation coefficients were Fischer-transformed in order to reduce distribution skewness. All statistical analyses were performed in R using the Generalized Estimating Equation framework[48] (see Supplementary Text). In this model, the Fischer-transformed correlation coefficients served as outcome variables. Autistic traits were the main predictor and mean head motion (see Supplementary Text) across all image volumes was included as covariate. In order to control for potential IQ effects, we repeated the analyses adding IQ as a covariate. The relationship between within-network connectivity estimates and autistic traits was further tested in the MZ- and DZ- sub-cohorts. A χ^2-test was run in order to determine whether the sub-cohort-specific estimates differed significantly from each other. To test the clinical relevance of our findings beyond trait autism, additional regressions were conducted on a sub-sample of twin pairs discordant or concordant for ASD (23 pairs) using the

same framework where within-network connectivity estimates were predicted by clinical ASD diagnosis instead of autistic traits while including head motion and IQ as covariates (see Supplementary Text).

Similar to within-network connectivity, the between-network connectivity estimates were tested for within-pair correlations between connectivity strength and autistic traits using conditional linear regression models with head motion and IQ as covariates. The Bonferroni corrected alpha-level was set to 0.025 for the main analysis of the two within-network connections and to 0.008 when additionally including the four between-network connections in order to adjust for multiple comparisons. *P*-values exceeding the applied alpha-level are explicitly described as trends not surviving correction.

Because previous reports indicated that age strongly impacts on connectivity differences in ASD, we added age group as a grouping variable to each conditional linear regression model. As suggested previously,[10] we stratified our cohort into three age groups: children (8-13 years; 22 pairs), adolescents (14-17 years; 31 pairs) and adults (18-24 years; 22 pairs). Age-group-specific estimates were tested across all groups for differences using χ^2-tests and followed up with *post-hoc* χ^2-tests for pairs of age-groups if significant. We tested for differences between age- and zygosity-groups in the behavioral predictor variables (autistic traits, IQ, head motion) as well as mean within-pair differences in these measures using two-sample *t*-tests and sex-ratio using χ^2-tests.

RESULTS

Comparison of demographic variables between groups

Results are summarized in Supplementary Table 2. While the children and adult groups did not differ from each other in autistic traits, the adolescent group had fewer traits compared to the child-group. In addition, children had higher mean head motion estimates compared to both adolescents and adults. Importantly, there were no age group differences in within-pair differences for any of the variables. Zygosity-groups differed in autistic traits with DZ pairs showing higher mean values and larger intra-pair differences. There were no group differences in sex-ratio.

Within-network connectivity in relation to autistic traits and ASD

Across the whole sample, conditional linear regression of within-DMN connectivity between the PCC and vmPFC showed no significant within-pair relationship with autistic traits or head motion. Adding IQ as a covariate did not change these results. Within-pair estimates from MZ vs DZ sub-cohorts were not different from each other. Connectivity between rAI and ACC within the SN was greater in twins with higher autistic traits compared to their co-twins while head motion did not show a within-pair correlation. Adding IQ as a covariate did not change these results. The comparison of within-pair estimates from MZ and DZ sub-cohorts revealed that they were not different from each other. However, the effect was only significant in the MZ sub-cohort. Similarly to autistic traits, ASD diagnosis was positively associated with rAI-ACC connectivity but not PCC-vmPFC connectivity within the sub-sample of ASD-discordant and ASD-concordant twin pairs (see Supplementary Table 3). Exploratory whole-brain analyses (see Supplementary Text and Supplementary Fig. 3) indicated that the finding of positive within-pair correlation between autistic traits and rAI-ACC connectivity was not restricted to the ROI-to-ROI approach, but could be observed in the whole brain with a lenient threshold of uncorrected $P > 0.01$.

Age-group-specific results

When adding age group as factor to the conditional linear regression, autistic traits were negatively correlated with PCC-vmPFC connectivity in adolescents while a similar negative correlation in adults did not survive Bonferroni correction and no correlation was seen in children. In contrast, rAI-ACC connectivity was positively correlated in children and nonsignificant in the other two age-groups. Comparing age-group-specific estimates of each model revealed a difference between age groups for PCC-vmPFC connectivity but not for the rAI-ACC connectivity. *Post-hoc* χ^2-tests indicated that adolescents and adults were not different from each other regarding the association between PCC-vmPFC connectivity and autistic traits while children were different from both, adolescents and adults. Intra-pair differences in PCC-vmPFC and rAI-ACC connectivity are plotted as a function of intra-pair differences in autistic traits for each age group in Supplementary Fig. 2. Whole-sample and group-specific (age and zygosity) results are summarized in

Table 2. Within-twin pair results of PCC-vmPFC and rAI-ACC connectivity

	PCC-vmPFC connectivity (DMN)				*rAI-ACC connectivity (SN)*			
	Estimate (β)	P-*value*	*s.e.*	*Z-value*	*Estimate (β)*	P-*value*	*s.e.*	Z-*value*
Whole sample								
Autistic traits	−0.0006	0.422	0.001	−0.804	**0.0026**	**0.006***	**0.001**	**2.773**
Head motion	−1.0605	0.136	0.711	−1.493	−0.8089	0.171	0.591	−1.368
IQ	−0.0022	0.298	0.002	−1.040	0.0005	0.818	0.002	0.231
Split by zygosity group								
Autisitc traits (MZ)	−0.0004	0.842	0.0018	−0.199	**0.0045**	**0.005***	**0.0016**	**2.784**
Autistic traits (DZ)	−0.0008	0.331	0.0008	−0.972	0.0019	0.055	0.0010	1.915
Head motion	−1.0733	0.132	0.7133	−1.505	−0.8860	0.136	0.0020	−1.490
IQ	−0.0021	0.336	0.0022	−0.961	0.0012	0.593	0.0022	0.535
Split by age group								
Autistic traits (children)	0.0015	0.154	0.001	1.426	**0.0040**	**0.022***	**0.002**	**2.287**
Autistic traits (adolescents)	**−0.0022**	**0.025***	**0.001**	**−2.244**	0.0027	0.071	0.002	1.807
Autistic traits (adults)	−0.0020	0.040	0.001	−2.056	0.0013	0.223	0.001	1.219
IQ (across age-groups)	−0.0027	0.124	0.002	−1.537	0.0002	0.940	0.002	0.075
Head motion (across age-groups)	−1.3420	0.073	0.748	−1.793	−0.9665	0.128	0.635	−1.523

Abbreviations: ACC, anterior cingulate cortex; DMN, default mode network; DZ, dizygotic; IQ, intelligence quotient; MZ, monozygotic; PCC, posterior cingulate cortex; rAI, right anterior insula; SN, salience network; vmPFC, ventromedial prefrontal cortex. Within-pair estimates for the two within-network connections: first for the whole sample, then including the factors 'zygosity' or 'age group', respectively. Head motion (ENorm) = normalized Euclidean distance of the six rigid-body motion parameters between neighboring image volumes across all volumes across the entire scan. *P*-values are uncorrected and Bonferroni corrected alpha level was set to $P < 0.025$, bold with *, associations surviving Bonferroni correction at this level.

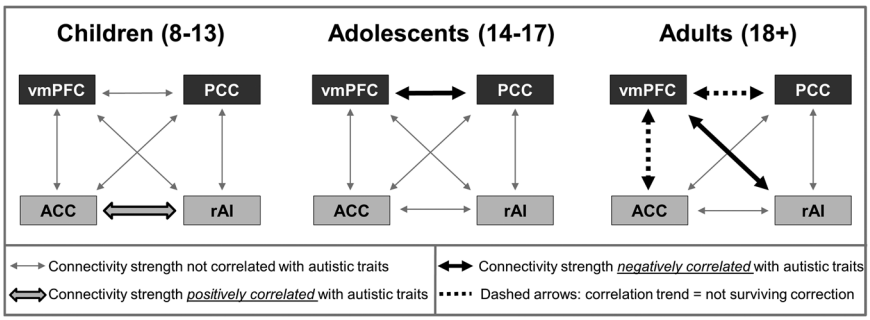

Figure 1. Overview of the age-group specific results of within-twin pair connectivity between each pair of ROIs within DMN (dark gray) and SN (light gray) regions, as a function of autistic traits. A positive correlation between rAI-ACC connectivity (light gray bold arrow) was only significant in children while negative within-pair correlations (black arrows) between autistic traits and connectivity within the DMN and between DMN and SN were only seen in the older sub-groups. Dashed bold arrows indicate associations with $P < 0.05$ uncorrected but not surviving Bonferroni correction. ACC, anterior cingulate cortex; DMN, default mode network; SN, salience network.

Table 2, clinical sub-sample results in Supplementary Table 3 and age- and zygosity-group comparisons in Supplementary Table 4.

Between-network connectivity in relation to autistic traits

Across the whole sample, none of the between-network connections showed a within-pair correlation, neither with autistic traits nor IQ. Head motion was positively correlated with connectivity in two of the models (rAI-PCC and ACC-PCC) but did not survive Bonferroni correction (see Supplementary Table 5). Age-group-specific estimates were different from each other for rAI-vmPFC and vmPFC-ACC connectivity, respectively (see Supplementary Table 4). Post-hoc tests indicated that for both of these connectivity estimates only children and adults differed from each other. A negative within-pair correlation between autistic traits and rAI-vmPFC connectivity was seen in adults but not the other age groups. For the vmPFC-ACC connectivity, only adults showed a negative association with autistic traits but this effect did not survive correction. Age-group-specific results are shown in Figure 1.

DISCUSSION

Our results show that altered RS connectivity forms a correlate of continuously distributed autistic traits. They are in line with earlier results of population-based studies on adolescents and adults, indicating that RS connectivity correlates with both autistic traits[49–52] and ASD symptom severity scores in clinical samples.[14,53,54] However, our results extend the latter findings as they show the relationship within twin pairs, where most genetic and environmental confounders are controlled for. Indeed, twins with higher autistic traits showed increased within-SN connectivity compared to their co-twins. This association remained significant in a sub-sample of MZ twins. Since MZ twins are genetically identical, with the exception of putative post-twinning *de novo* mutations, differences in phenotypes seen in MZ twin pairs can be attributed to non-shared environmental factors. Our results therefore indicate that environmental factors are important modulators of functional connectivity correlates of ASD.

While our results are consistent with previous reports of increased connectivity of SN key nodes in children with ASD[13,21,28] they are inconsistent with observations of decreased connectivity of SN regions.[19,22–24,26,27] The latter findings originated predominantly from adult samples or samples spanning large age ranges. When stratifying our sample by age, the positive correlation between autistic traits and within-SN connectivity was strongest in children, consistent with the observation that hyper-connectivity in ASD is more commonly reported in younger individuals.[10,55] However, age-groups did not differ significantly from each other regarding this relationship in our sample. The SN has been hypothesized to be decisive for identifying salient stimuli, building a central interface between bottom-up sensory information processing, attention guidance, emotion processing, motor function and cognition.[12] It has been suggested that alterations in social cognition that are characteristic of ASD might be related to alterations in the SN since these functions depend on the perception of what is salient.[56] In line with this notion, a meta-analysis found consistently reduced activation of the insula in ASD compared to typically developing individuals during social processing.[57] Altered salience processing might further be related to sensory issues such as sensory hyper- or hypo-sensitivity[56] as well as enhanced attention to detail characteristic of ASD.[58,59]

In contrast to the findings in the SN, within-DMN connectivity was significantly different between age-groups with a negative correlation in adolescents and a similar trend in adults, but not in children. A possible interpretation of these findings could be that autistic trait related connectivity changes in the DMN emerge later in development, maybe as a result of relatively late DMN maturation.[60] Since neither IQ nor gender (see Supplementary Table 2) differed between groups, differences between age-groups are unlikely to be driven by these factors. It needs to be pointed out that the adolescent group showed lower mean autistic traits compared to the child group. Consequently, age group comparisons need to be interpreted with caution. However, autistic traits were not different between children and adults while these groups were most different regarding the relationship between within-DMN connectivity and autistic traits. Moreover, within-pair differences in the behavioral variables did not differ between age-groups. Reduced connectivity of DMN-hubs has commonly been reported in individuals with ASD at different ages.[13–20,22] The DMN has been shown to be recruited during tasks requiring self-referential imagination and therefore been suggested to have a key role in self-relevant mentalizing.[61] This hypothesis is consistent with the DMN's overlap with networks essential for social cognition.[61] Reduced DMN connectivity in individuals with ASD and high autistic traits might therefore be related to social cognition difficulties in ASD. Consistent with this hypothesis, reduced connectivity of DMN hubs has been found to correlate with severity of social impairment in children[13] and with communication deficits in adults with ASD.[15]

DMN and SN are interconnected and it has been suggested that the SN performs dynamic switching between DMN and the so called Central-Executive Network (CEN)—a network that is believed to be critical for keeping information active in working memory as well as decision-making in the context of goal directed behavior.[12,62] When testing connectivity between the hubs of DMN and SN, we found a negative within-pair correlation between autistic traits and connectivity between rAI and vmPFC only in adults. If the SN indeed modulates DMN activity, a reduced RS

connectivity between these networks in adults with higher autistic traits could indicate that this modulatory function is weaker. In line with this notion, it has been hypothesized that the DMN might be under-active in ASD owing to dysfunctional regulatory mechanisms depending on other networks.[11]

Current developmental models of ASD suggest early hyper-connectivity followed by decreased connectivity in adulthood.[10,55,63,64] In the light of the marked effects of puberty on brain maturation in concert with the observation of an age-related discontinuity of connectivity findings in ASD that coincides with this period, puberty has been suggested as critical period regarding the manifestation of connectivity alterations associated with ASD.[10] Our age-group-specific results (see Figure 1) fit these hypotheses. However they indicate that age-effects on the relationship between autistic traits and connectivity might be network-specific.

Our findings differ from those of a recent study comparing DMN and SN RS connectivity between individuals with and without ASD in different age groups.[64] They report decreased within-DMN and increased DMN to SN connectivity in children, decreased DMN to SN connectivity in adolescents and no differences to controls in adults with ASD. However, our results are in line with a study which reported that connectivity between DMN key nodes increased less with age in individuals with ASD compared to typically developing—a result possibly explaining hypo-connectivity within this network in adulthood.[65]

Limitations

Given that specific ROI-based hypotheses were tested in the current study, we cannot exclude the possibility of overlooking differences. To investigate the accuracy of the chosen ROIs as compared to other brain regions, we ran an exploratory whole-brain analysis (see Supplementary Text) using the same statistical model as in the ROI-to-ROI approach but with voxel-wise connectivity estimates from seed correlations of the PCC and the rAI, respectively, as outcome variables. Since we used a lenient threshold (uncorrected $P < 0.01$, minimum cluster size = 50 voxels) the results need to be interpreted with caution. They indicate that additional regions might play a role in the within-pair relationship between autistic traits and DMN as well as SN-connectivity (Supplementary Fig. 3). However, the direction of the association with autistic was consistent with the results from the ROI-to-ROI analyses (decreased DMN connectivity and increased SN connectivity in twins with higher autistic traits) and a cluster overlapping with the ACC ROI was found for the rAI seed correlation.

Exact ROI placement has been shown to influence RS connectivity at least quantitatively.[66] Since higher inter-subject spatial variance of cortical areas has been reported in ASD, ROI placement could potentially bias results of altered connectivity in ASD.[67] However, spatial variance might be less of an issue in twin studies, given that brain structural aspects such as area-specific brain volumes are strongly heritable.[68] Further, analyzing what is commonly referred to as 'static' RS connectivity, that is, temporal correlations across the entire scan, this study is not taking the dynamic alterations in RS connectivity into account that have recently been demonstrated to be informative in general[62,69] and specifically informative in ASD.[70] Testing differences of dynamic RS connectivity patterns in relation to autistic traits in twins would therefore be an interesting avenue for future research. Moreover, including not only the DMN and SN but also the CEN could yield additional important insights, given the dynamic interaction between these networks.[12] Finally, while our age-specific analyses provide insights to age-related impact on the relationship between RS connectivity and autistic traits and ASD, only longitudinal studies enable to fully understand those developmental changes.

CONCLUSION

Although applying maximum of control over potential confounding factors, our results confirm the hypotheses of altered DMN and SN connectivity being correlated with autistic traits while underlining the relevance of environmental and developmental influences.

CONFLICT OF INTEREST

SB discloses that he has in the last 5 years acted as an author, consultant or lecturer for Shire, Medice, Roche, Eli Lilly, Prima Psychiatry, GLGroup, System Analytic, Kompetento, Expo Medica and Prophase. He receives royalties for text books and diagnostic tools from Huber/Hogrefe, Kohlhammer and UTB. The remaining authors declare no conflict of interest.

ACKNOWLEDGMENTS

We thank all participants of the Roots of Autism and ADHD Twin Study Sweden project as well as our colleagues Annelies van't Westeinde, Charlotte Willfors, Lynnea Myers, Elin Vahlgren, Eric Zander, Kerstin Andersson, Steve Berggren, Torkel Carlsson, Christina Coco, Martin Hammar, Johanna Ingvarsson, Johan Isaksson, Elzbieta Kostrzewa, Anna Lövgren, Anna Råde and Kristiina Tammimies for their contributions. The study was funded by the Swedish Research Council, Vinnova, Formas, FORTE, the Swedish Brain foundation (Hjärnfonden), Stockholm Brain Institute, Autism and Asperger Association Stockholm, Queen Silvia Jubilee Fund, Solstickan Foundation, PRIMA Child and Adult Psychiatry, the Pediatric Research Foundation at Astrid Lindgren Children's Hospital, Sällskapet Barnavård, the Swedish Foundation for Strategic Research, Jerring Foundation, the Swedish Order of Freemasons, Kempe-Carlgrenska Foundation, Sunnderdahls Handikappsfond, The Jeansson Foundation, the Innovative Medicines Initiative Joint Undertaking (grant agreement number 115300), which comprises financial contribution from the European Union's Seventh Framework Programme (FP7 /2007–2013) and in-kind contributions from companies belonging to the European Federation of Pharmaceutical Industries and Associations (EU-AIMS).

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)