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The social brain in female autism: a structural imaging study of twins

Élodie Cauvet,[1,†] Annelies van't Westeinde,[1,†] Roberto Toro,[2,3,4] Ralf Kuja-Halkola,[5] Janina Neufeld,[1] Katell Mevel,[6] and Sven Bölte[1,7,8]

[1]Department of Women's and Children's Health, Karolinska Institutet, Stockholm Health Care Services, Stockholm 11330, Sweden, [2]Department of Neuroscience, Human Genetics and Cognitive Functions, Institut Pasteur, Paris 75015, France, [3]CNRS URA 2182 "Genes, synapses and cognition", Pasteur Institute, Paris 75015, France, [4]Human Genetics and Cognitive Functions, Université Paris Diderot, Sorbonne Paris Cité, Paris 75013, France, [5]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm 17177, Sweden, [6]GIP Cyceron, Normandy University, Caen 14074, France, [7]Child and Adolescent Psychiatry, Stockholm County Council, Stockholm 11330, Sweden, and [8]School of Occupational Therapy, Social Work and Speech Pathology, Curtin University, Perth, Western Australia 6102, Australia

Correspondence should be addressed to Annelies van't Westeinde, CAP Research Center, Center of Neurodevelopmental Disorders at Karolinska Institutet, Gävlegatan 22B, S-113 30 Stockholm, Sweden; E-mail: annelies.vant.westeinde@ki.se
[†]Equal contribution.

Abstract

A female advantage in social cognition (SoC) might contribute to women's underrepresentation in autism spectrum disorder (ASD). The latter could be underpinned by sex differences in social brain structure. This study investigated the relationship between structural social brain networks and SoC in females and males in relation to ASD and autistic traits in twins. We used a co-twin design in 77 twin pairs (39 female) aged 12.5 to 31.0 years. Twin pairs were discordant or concordant for ASD or autistic traits, discordant or concordant for other neurodevelopmental disorders or concordant for neurotypical development. They underwent structural magnetic resonance imaging and were assessed for SoC using the naturalistic Movie for the Assessment of Social Cognition. Autistic traits predicted reduced SoC capacities predominantly in male twins, despite a comparable extent of autistic traits in each sex, although the association between SoC and autistic traits did not differ significantly between the sexes. Consistently, within-pair associations between SoC and social brain structure revealed that lower SoC ability was associated with increased cortical thickness of several brain regions, particularly in males. Our findings confirm the notion that sex differences in SoC in association with ASD are underpinned by sex differences in brain structure.

Key words: autism; twins; social cognition; brain structure; sex difference

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Introduction

Autism spectrum disorder (ASD) has been associated with social cognition (SoC) challenges (Happé and Frith, 2014; Isaksson *et al.*, 2019). SoC encompasses both implicit and explicit mental processes involved in understanding agents and their interactions, as well as the ability to attribute mental states to one self and others (Heyes and Frith, 2014; Happé *et al.*, 2017). Implicit SoC refers to mechanisms of unconsciously and automatically attributing mental states, while explicit SoC requires deliberate and conscious considerations (Heyes and Frith, 2014). SoC is a complex capacity that depends on a variety of cognitive functions, including emotion recognition, social attention, social orienting, social motivation, learning from others, empathy and verbal abilities (Happé *et al.*, 2017). These abilities are supported by an elaborate brain network including temporal, inferior parietal, frontal and midline structures (Wolf *et al.*, 2010; Schurz *et al.*, 2014). Differences between autistic and typically developing (TD) individuals have been observed in activation of these regions during tasks operationalizing SoC (Kana *et al.*, 2014; White *et al.*, 2014; Kim *et al.*, 2016; Patriquin *et al.*, 2016), alongside structural differences of some of these areas, including the superior temporal sulcus, insula, fusiform face area and inferior frontal gyrus (Patriquin *et al.*, 2016). One study showed that alterations in short-range white matter connections, specifically reduced fractional anisotropy, in the insula and temporal lobe correlated with self-reported challenges in social awareness and cognitive empathy in adult autistic males (d'Albis *et al.*, 2018). Interestingly, a recent study showed that ASD might be divided into different subtypes based on neuroanatomy, with subtypes being related to the severity of autism symptom domains and the 'increased cortical thickness' group specifically having less problems in the social domain (Hong *et al.*, 2018). However, thus far, no study has directly linked performance on SoC tasks to gray matter alterations of the brain in individuals along the autistic trait continuum, from normative autistic-like traits to full-blown clinical ASD.

A skewed sex ratio is commonly found in ASD, with males being three times more often diagnosed than females (Loomes *et al.*, 2017). A prominent hypothesis to account for observed sex differences in autism is related to superior SoC performance in females compared to males, providing a protective effect from ASD-related impairments (Baron-Cohen *et al.*, 2005; Christov–Moore *et al.*, 2014). Sex differences in brain structure involved in SoC might predispose females to either more effective SoC in general, or to certain SoC components (Good *et al.*, 2001; Chen *et al.*, 2007; Sowell *et al.*, 2007; Wood *et al.*, 2008; Yamasue *et al.*, 2008; Cheng *et al.*, 2009). In TD samples, sex-specific differences in brain structure related to SoC have been observed in white matter of inferior parietal and temporal regions (Chou *et al.*, 2011; Takeuchi *et al.*, 2013). However, sex differences in the relationship between SoC and social brain structure have neither been studied across the autistic trait continuum, nor in clinical ASD. Some research suggests that both quantitative and qualitative sex differences in brain structure can be found between males and females with ASD (Lai *et al.*, 2013; Cauvet *et al.*, 2019), but such differences have never been correlated with SoC. Importantly, even though a female advantage in SoC might protect women from impairments associated with autism phenotypes, those females that do get an ASD diagnosis might perform similar to ASD males regarding SoC. However, studies have thus far mostly shown that females do have a general advantage in SoC even within individuals diagnosed with ASD (Zwaigenbaum *et al.*, 2012; Messinger *et al.*, 2015; Constantino, 2016; Hull *et al.*, 2017). The latter finding could be an indication that the phenotypic expression of ASD is different in females compared to males. If females in the extreme end of the autism spectrum outperform males, SoC might be expected to be associated with fewer differences in brain structure in females compared to males. On the other hand, if males and females have comparable problems with SoC, the female protective effect hypothesis would expect that there should be more biological adversity, i.e. neurological differences to reach the same level of autistic features and related impairments in females. At the same time, qualitative differences reflecting sex differences in SoC-related brain structure in the general population might be expected in any case. Thus, investigating sex differences in SoC-related brain structure along the autism continuum might provide insights into the neurobiology of ASD and its phenotypic expression in females.

Thus far, most studies addressing SoC in ASD have used tasks of relatively low ecological validity and low sensitivity to subtler SoC challenges (Dziobek *et al.*, 2006). To tap into the complex nature of daily life social situations, entailing both implicit and explicit components of SoC simultaneously, the Movie for the Assessment of Social Cognition (MASC) was developed (Dziobek *et al.*, 2006). The MASC can discriminate between IQ-matched individuals with ASD and non-autistic controls (Müller *et al.*, 2016), and has been shown to correlate well with other tests of SoC in a Spanish sample (Lahera *et al.*, 2014).

This study examined the relationship between structural social brain alterations and variation in SoC in a sample of male and female twins along the autistic trait continuum enriched for clinical variants of autism, using the MASC to operationalize SoC. This study explored qualitative and quantitative brain structure associated with SoC, targeting regions of the social brain network to reduce the number of comparisons (Schurz *et al.*, 2014). We employed a co-twin control design, i.e. using the co-twin as the best possible control, thereby inherently accounting for many shared genetic and environmental factors, such as variation in age, sex, socio–economic status and other shared environmental factors that usually cause a high degree of heterogeneity and noise in ASD brain research (Katuwal *et al.*, 2016).

Methods

Participants

All participants and/or their legal guardians gave written informed consent. The sample was recruited from the Roots of Autism and attention deficit hyperactivity disorder (ADHD) Twin Study Sweden (RATSS) (Bölte *et al.*, 2014), approved by the Local Ethical Review Board in Stockholm. From $N = 335$ participants hitherto collected in RATSS, only same-sex pairs were included of which structural magnetic resonance imaging (MRI) scans of both twins had good raw and processed image quality, and who were able to perform the MASC (age > 12 years). Thus, the final subsample included in this study consisted of 154 twins (77 pairs), 98 monozygotic (MZ) and 56 dizygotic (DZ) twins, with 78 females and 76 males, average age = 19.6 years (12.5–31.0). These included 28 (16 females, 12 males) individuals with an ASD diagnosis, belonging to 18 (8 female pairs, 10 male pairs) pairs that were discordant and 5 (4 female pairs, 1 male pair) pairs concordant for ASD diagnosis. See Table 1.

Table 1. Whole-group and sex-specific sample characteristics, mean scores and between-sex statistical comparisons on all behavioral variables.

Demographics	All ($n = 154$)	Females ($n = 78$)	Males ($n = 76$)	*P*-value
Number of pairs	77	39	38	
Age mean (*s.d.*)	19.58 (4.60)	2.52 (5.02)	18.61 (3.92)	.046*
Age range	12.52–31.00	12.86–29.00	12.52–31.00	
Zygosity MZ/DZ	98/56	54/24	44/32	.196
ASD diagnosis	28 ASD/126 no ASD	16 ASD/62 no ASD	12 ASD/64 no ASD	.582
ASD diagnosis per MZ/DZ	14/14	9/7	5/7	
Pairs concordant for ASD	5 pairs	4	1	
Pairs discordant for ASD	18 pairs	8	10	
Pairs ASD concordant per MZ/DZ/?	3 pairs/2 pairs	3/1	0/1	
Pairs ASD discordant per MZ/DZ/?	7 pairs/11 pairs	2/6	5/5	
ADHD diagnosis	24	10	14	.341
Other NDD	19	6	13	.077
ID diagnosis	7	2	5	.235
No diagnosis	77	36	41	.336
Mean scores				
IQ mean (*s.d.*)	99.26 (16.59)	10.67 (16.81)	97.82 (16.35)	.315 ($d = .172$, $r = .086$)
Range	62–142	63–142	62–131	
Verbal IQ mean (*s.d.*)	99.45 (17.16)	10.32 (17.51)	98.55 (16.86)	.369 ($d = .103$, $r = .051$)
Range	59–134	64–134	59–133	
MASC score mean (*s.d.*)	3.66 (5.95)	31.92 (4.77)	29.37 (6.75)	.023* ($d = .436$, $r = .213$)
Range	10–41	17–39	10–41	
SRS-2 total score mean (*s.d.*)	34.81 (29.27)	34.38 (3.28)	35.24 (28.38)	.419 ($d = -.029$, $r = -.015$)
Range	0–131	0–122	4–131	
Whole BV (*s.d.*) *in* cm^3	1195 (119)	1136 (98)	1255 (108)	<.001* ($d = -1.154$, $r = -.450$)
Range	911–1475	915–1421	911–1475	
Within-pair differences				
Within-pair difference IQ (*s.d.*)	9.77 (8.65)	9.44 (8.21)	1.11 (9.18)	.878 ($d = -.077$, $r = -.038$)
Range	0–39	0–31	0–39	
Within-pair difference Verbal IQ (*s.d.*)	1.95 (9.24)	11.15 (8.46)	1.74 (1.09)	.484 ($d = .044$, $r = .022$)
Range	0–39	0–36	0–39	
Within-pair difference MASC (*s.d.*)	3.87 (4.15)	3.59 (2.95)	4.16 (5.12)	.647 ($d = -.136$, $r = -.068$)
Range	0–22	0–10	0–22	
Within-pair difference SRS-2 total score (*s.d.*)	2.52 (24.45)	19.49 (23.40)	21.58 (25.76)	.854 ($d = -.086$, $r = -.043$)
Range	0–101	0–101	0–87	
Within-pair difference Whole BV (*s.d.*) *in* cm^3	45 (55)	42 (42)	48 (65)	.951 ($d = -.110$, $r = -.055$)
Range	.58–351	.58–154	1.14–351	

Number of pairs, age in years with mean and standard deviation and range, zygosity, ASD diagnoses (see diagnostic assessments), discordancy status (discordant when one twin has been diagnosed with ASD, concordant when both twins have been diagnosed with ASD), discordance per zygosity, other diagnoses (ADHD, Other NDD, ID or no diagnosis). Mean scores and standard deviations are given for IQ total score from Wechsler Intelligence Scale for Children-fourth edition/Wechsler Adult Intelligence Scale-fourth edition (WISC-IV/WAIS-IV), Verbal IQ from WISC-IV/WAIS-IV, SoC score (D-MASC-MC), autistic traits measured by Social Responsiveness Scale-2 (SRS-2) total raw score and Whole BV (FreeSurfer). Within-pair differences (mean, standard deviation and range) for all variables are given, indicating the difference on the specific scale between the twins of a pair. Statistics used to compare the demographics are described in the statistical analyses section. *D* = Cohen's d, *r* = effect size.
*indicates a significant effect ($p < 0.05$)

Procedures

Clinical assessment. The comprehensive assessment protocol of RATSS is described elsewhere in detail (Bölte *et al.*, 2014). Briefly, clinical consensus diagnosis of ASD and other neurodevelopmental disorders, or absence of clinical diagnosis, is based on DSM-5 criteria (American Psychiatric Association, 2013) and consensus of experienced clinicians, supported by information from the Autism Diagnostic Interview—Revised (Rutter *et al.*, 2003), the Autism Diagnostic Observation Schedule-2 (Lord *et al.*, 2012), the Kiddie Schedule for Affective Disorders and Schizophrenia (Kaufman *et al.*, 1997) or the Diagnostic Interview for ADHD in Adults (Kooij, 2010). Full-scale IQ was assessed using the Wechsler Intelligence Scales for Children or Adults, Fourth Editions (Wechsler, 2003; Wechsler *et al.*, 2008).

Movie for the assessment of SoC. The twins were assessed with the Swedish version of the MASC (Bölte *et al.*, 2011a). The MASC consists of a 15-min film clip of two females and two males meeting on a Saturday night and having dinner together. The participants were instructed to carefully observe the film. The film is paused at 43 time-points, at which the twins were asked 44 multiple choice questions regarding the characters' mental states, such as their emotions, thoughts and intentions. Four possible answer options are given, of which one is a generally expected attribution of SoC. The other options are unexpected answers, referring to either excessive mental state attribution (hypermentalizing), reduced SoC (hypomentalizing) or a 'preference for non-SoC in a social context (concrete cognition)'. Total mentalizing scores range from 0 to 44, where a higher score indicates increasing SoC (in a previous study, the TD population

mean was 34.8, while the range for ASD in the normative IQ range was $M = 24.4$) (Dziobek *et al.*, 2006).

Autistic trait measure. The extent of autistic traits was measured with the parent-report Social Responsiveness Scale-2 (SRS-2) standard child or adult versions (Constantino, 2012). The SRS-2 assesses autistic-like behaviors in the general population and quantifies their severity during the past six month, operationalizing social communication, social motivation, social awareness, social use of language and rigid inflexible behaviors. It comprises 65 Likert-scaled items scored 0 to 3 generating a total score ranging from 0 to 195, with higher scores indicating more autistic traits. Raw scores were used in all analyses as recommended for research settings (Constantino, 2012). The SRS-2 (normative population mean 23.45, ASD population mean 103.9 (Bölte *et al.*, 2011b)) has demonstrated good to excellent psychometric properties across several cultures and superior psychometric properties compared to other measures of autistic traits (Bölte *et al.*, 2008, 2011b).

Structural MRI

Image acquisition. T1-weighted images were acquired on a 3 Tesla MR750 GE scanner at Karolinska Institutet MR center (Inversion Recovery Fast Spoiled Gradient Echo—IR-FSPGR, 3D-volume, 172 sagittal slices, 256 × 256, FOV 24, voxel size 1 mm3, flip angle 12, TR/TE 8200/3.2, using a 32-channel coil array). T1-weighted acquisition was part of a 50-min scanning protocol, preceded by a 5–7-min mock-scan training for self-control of head movements.

Surface-based cortical volumetry, cortical thickness and surface area (FreeSurfer). Raw images were processed in FreeSurfer 6 (http://surfer.nmr.mgh.harvard.edu/). The standard pipeline was run on the original T1-weighted images (Dale *et al.*, 1999; Fischl *et al.*, 1999). Briefly, the intensity of the images was normalized, the brain was skull stripped and brain tissues were segmented. A white matter volume was generated from which a surface tessellation was created. Meshes were constructed for gray and white matter out of approximately 150 000 vertices per hemisphere, then parcellated according to the Destrieux Atlas (Destrieux *et al.*, 2010). Next, mean cortical thickness, volume and surface areas were obtained for each region in each hemisphere. From initially 335 twins in RATSS, 312 had completed MR scanning. From those, 13 were not processed successfully in FreeSurfer, due to excess movement; in addition, we excluded 8 different-sex pairs ($n = 16$), 1 pair from a quadruplet, 1 subject from a triplet and 4 subjects with a radiologist report (indicating some brain abnormality), as well as all subjects from incomplete pairs left after this exclusion process, resulting in 258 FreeSurfer processed images of complete same-sex twin pairs. After quality check, a further 54 twins were removed (those with insufficient quality and their co-twins), in addition to 50 subjects from the resulting sample that did not have MASC scores. This attrition resulted in 154 participants (77 complete pairs) with three neuroanatomical outputs each (cortical volume, surface area and cortical thickness) and MASC scores. A whole brain volume (BV) estimate, including all gray matter and white matter but excluding cerebrospinal fluid (ventricles and extra-axial), was used as a covariate in surface- and volume-based analyses except for cortical thickness, as it has been shown that cortical thickness is not related to total BV (Toro *et al.*, 2008).

Regions of interest selection for the neocortical social network. Using the Destrieux atlas from FreeSurfer (Destrieux *et al.*, 2010), we selected a priori neocortical areas that have been shown to be involved in SoC from a meta-analysis, selecting the networks that were associated with the 'mind in the eyes', 'social animations' and 'false belief vs photos' tests (Schurz *et al.*, 2014). Our final estimates included cortical volumes, surface area and thickness of in total 20 bilateral regions of interest (ROIs) in the following broader regions: the bilateral superior and middle temporal, supramarginal, angular, insula, inferior, middle and superior frontal, temporo-occipital, fusiform and posterior cingulate gyri and sulci (Table 2). To check that our findings are specific to the social brain network, we randomly selected three bilateral regions outside our network of interest from the Destrieux atlas in FreeSurfer, namely the cuneus, subcallosal and inferior precentral sulcus.

Statistical analysis

All statistical analyses were performed in R v3.4.1 (https://www.r-project.org/). *P*-values for the anatomical associations are FDR-corrected for 40 ROIs per estimate (volume, surface area, thickness) per analysis to control Type I errors, with a significance threshold set to $q < .05$. *P*-values for the associations between autistic traits and SoC are not corrected for multiple comparisons, and we employed a threshold of $P < .05$. Associations below a threshold of q or $P < .10$ are also reported to not miss potentially relevant associations. The sample size was comparable to recently published studies using similar co-twin designs reporting small to medium effect sizes (Wilson *et al.*, 2015; Picchioni *et al.*, 2017).

Sex differences in demographics and association between autistic traits and SoC. We first examined possible confounding demographic differences between females and males. Comparisons between the sexes were conducted using χ^2 tests for categorical variables (zygosity, diagnosis) and Wilcoxon tests for continuous, non-normally distributed variables (age, MASC, IQ, SRS-2, BV; Table 1). To determine if any observed relationship between SoC, measured by the MASC, and social brain structure in our sample would be meaningful for dimensional autism, we assessed if SoC was associated with autistic traits and if this association was influenced by IQ or age. We assessed the relationships between SoC and autistic trait severity, while controlling for IQ, using the co-twin design that is also employed in the main analyses. Within-twin pair associations were estimated using a conditional linear regression model within the generalized estimating equations (GEE) framework, using the drgee package from R (Zetterqvist and Sjölander, 2015). We assessed the within-pair relationship between autistic traits and SoC in the whole group, hypothesizing that within pairs, the twins with higher autistic traits would exhibit lower SoC capacity compared to their co-twins. The same was carried out within pairs for each sex separately, with an additional chi-square test investigating if these associations were significantly different between the sexes.

Association between SoC and neuroanatomy of the neocortical social brain network within twin pairs. A twin/co-twin design was implemented to investigate the association between SoC (predictor) and neuroanatomy (outcome) of the social brain, while controlling for confounding factors shared within twin pairs (e.g. genetic factors, demographics). For all analyses, IQ and

Table 2. List of all included bilateral (20 × 2) ROIs in the social brain mask, based on the Destrieux atlas in FreeSurfer. The left column shows regions that were associated with SoC either males (M), females (F) or both (MF). The right column shows the regions included in the mask that were not associated with SoC in either of the sexes.

ROIs associated with SoC from MASC	ROIs not associated with SoC from MASC
Anterior occipital sulcus (MF)	Mid posterior cingulate gyrus and sulcus
Superior circular insula sulcus (F)	Dorsal posterior cingulate gyrus
Anterior circular insula sulcus (M)	Inferior frontal operculum gyrus
Insula lg gyrus cent sulcus (M)	Middle frontal gyrus
Inferior frontal orbital gyrus (M)	Superior frontal gyrus
Inferior frontal triangular gyrus (M)	Insula short gyrus
Angular gyrus (M)	Lateral anterior fissure
Supramarginal gyrus (M)	Intermediate prim Jensen sulcus
Fusiform gyrus (M)	Lateral superior temporal gyrus
Middle temporal gyrus (M)	Superior temporal sulcus

BV (except for cortical thickness) were included as covariates in the models since these have been shown to vary in clinical ASD populations. Within pairs, we tested whether the twin with higher performance on SoC displayed more gray matter in the social brain regions, compared to the lower performing co-twin. Thus, a within-pair association was estimated by correlating the difference in SoC to the difference in brain structure, within each pair. We first assessed this across the whole continuum of autistic traits, regardless of biological sex, by testing the relationship between SoC and brain structure in the whole group, pooling male and female twin pairs together. Secondly, we tested the clinical relevance of such an association by running the same analyses in the ASD-discordant pairs, i.e. twin pairs where only one twin has an ASD diagnosis ($n = 18$ pairs, 8 female and 10 male pairs). A significant association between SoC and social brain structure within ASD-discordant twin pairs gives an indication that this relationship is relevant for having clinical ASD. Thirdly, we assessed sex-specific associations between SoC and social brain structure by splitting the whole group into males and females. To determine if the association was significantly different between the sexes, we ran a χ^2 test (Wald). By assessing if the association between brain structure and SoC differs between the sexes in this way, confounding factors are allowed to vary between males and females, i.e. confounding factors such as IQ were also corrected for in each sex independently.

Results

Behavior

Sex differences for SoC, autistic traits and IQ. Group means for the whole sample and all variables are provided in Table 1, and separately for ASD-discordant pairs in Table 3. On average, females displayed better SoC compared to males ($P = .02$), and this effect was observed between typical males (mean 30.27) and females (mean 32.66) ($P = .01$), and between males (mean 24.58) and females (mean 29.06) with ASD at a trend level of $P < .10$. The distribution of SoC (MASC scores) for participants with an ASD diagnosis is displayed in Figure 1.

There were no significant differences between males and females regarding autistic trait severity (SRS-2 total raw score, $P = .42$), overall IQ level ($P = .32$) and verbal IQ ($P = .37$), in the total sample, nor when restricting the analyses to subjects with ASD (SRS-2: $P = .92$, IQ: $P = .75$, verbal IQ: $P = .83$).

Within-pair differences were comparable between males and females for SoC ($P = .65$), autistic traits (SRS-2 total raw score, $P = .85$), IQ ($P = .88$) and verbal IQ ($P = .48$), indicating that male pairs were similarly discordant in SoC compared to female pairs. The distribution of within-pair difference of SoC for all males and females is displayed in Figure 2. Finally, females had 9.5% smaller total BVs ($P < .001$) and were slightly older ($M = 20.5$ years) compared to males ($M = 18.6$ years) ($P = .046$).

Within-pair associations between autistic traits and SoC. See Table 4. Within pairs, increased autistic traits were associated with reduced SoC ($\beta = -.059$, 95% confidence interval (CI) 0.101, −0.018, $P = .005$), while higher IQ predicted better SoC skills ($\beta = .121$, 95% CI 0.016, 0.225, $P = .024$). Thus, within a pair, the twin with more autistic traits performed poorer on the SoC compared to her/his co-twin, and this was true across the whole continuum of autistic traits. Further, within ASD-discordant pairs, ASD diagnosis was negatively associated with SoC ($\beta = -3.590$, 95% CI 6.778, −0.408, $P = .027$), indicating that having an ASD diagnosis was associated with a reduction of 3.59 points on the SoC test. Finally, when splitting by sex, ASD diagnosis was associated with SoC only in males ($\beta = -4.880$, 95% CI 9.500, −0.255, $P = .039$). However, the magnitude of the association between autistic traits and SoC was not significantly different between males and females ($P = .34$), indicating that the association in females was going in the same direction and we therefore cannot rule out that they are the same.

Within-pair associations of SoC skills with neuroanatomy of the neocortical social brain network

Within-pair results for the association between SoC and neuroanatomy are presented in Tables 5 and 6. Within pairs and along the autism trait continuum, the twin with lower SoC had increased thickness of the right fusiform gyrus ($B = -.0090$, $q = .014$), right supramarginal gyrus ($B = -.0158$, $q = .007$), right superior temporal sulcus ($B = -.0073$, $q = .030$), left inferior frontal orbital ($B = -.0164$, $q = .007$) and triangularis gyri ($B = -.0010$, $q = .014$).

In order to test the clinical relevance of the relationship between SoC and brain structure, i.e. to test if the association is also found at the most affected end of the autism continuum, we restricted the analyses to pairs that were discordant for ASD diagnosis. We observed that within-pair reductions in SoC were associated with increased thickness in the same regions as in the whole group. In addition, within ASD-discordant pairs, lower SoC was associated with increased thickness of the left superior temporal sulcus ($B = -.0082$, $q = .021$), long insula gyrus ($B = -.0193$, $q = .021$) and anterior circular insula sulcus ($B = -.0114$, $q = .047$) as well as the right inferior frontal orbital ($B = -.0201$, $q = .001$) and

Table 3. Mean (*s.d.*) and range of SoC, autistic traits, full-scale IQ and verbal IQ in ASD-discordant pairs. The average scores for the twins diagnosed with ASD and the twin without ASD diagnosis are displayed.

ASD-discordant pairs $n = 18$ pairs (8 female, 10 male) mean age 18.24 (4.14)		
Variable	ASD-diagnosed subjects	Non-ASD subjects
MASC	26.72 (8.34)	31.17 (6.85)
Range	10–36	16–41
SRS-2	78.83 (3.35)	35.17 (24.21)
Range	21–131	4–93
IQ total	93.50 (2.93)	97.50 (12.47)
Range	65–138	65–120
IQ verbal	94.11 (23.06)	10.28 (13.90)
Range	59–129	71–126

Of the 18 co-twins without ASD diagnosis, 11 did not have any diagnosis. From the other 7, 6 had a psychiatric diagnosis, 2 had an ADHD diagnosis, 2 had other NDD diagnosis and 1 had intellectual disability (subjects could have more than one diagnosis).

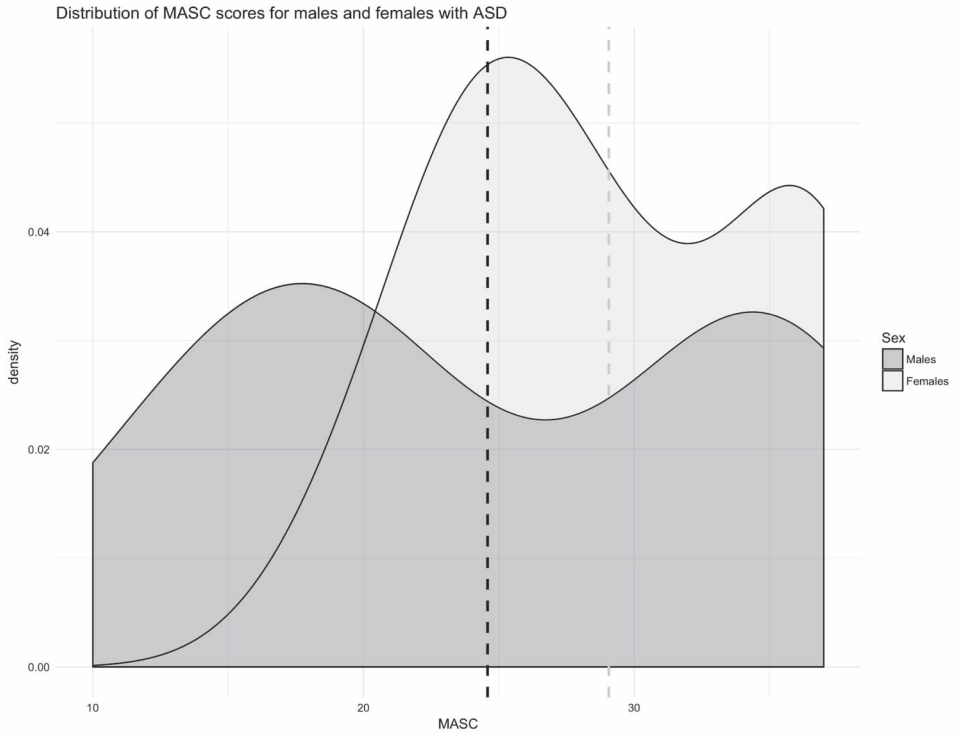

Fig. 1. Distribution of SoC scores in males and females with an ASD diagnosis. Males are shown in dark gray, females in light gray. Males with ASD seem to display a larger variation of performance on the SoC task compared to females with ASD. Females with ASD tended to perform better compared to males with ASD on SoC ($P = 0.098$). The dotted vertical line indicates the mean SoC score per group.

triangularis ($B = -.0122$, $q = .021$), lateral superior temporal gyri ($B = -.0172$, $q = .021$), anterior occipital sulcus ($B = -.0099$, $q = .021$) and the bilateral superior frontal (Left: $B = -.0087$, $q = .047$; Right: $B = -.0069$, $q < .001$), angular (Left: $B = -.0211$, $q = .004$; Right: $B = -.0181$, $q = .002$) and middle temporal gyri (Left: $B = -.0155$, $q = .021$; Right: $B = -.0217$, $q = .047$). Finally, in ASD-discordant pairs, low SoC was associated with decreased surface area of the right long insula ($B = 10.74$, $q = .039$) as well as the left short insula gyri ($B = 5.31$, $q = .017$).

When assessing sex-specific effects along the whole autistic trait continuum, lower SoC within a pair was associated with increased thickness in very similar regions, but mostly in males. In males, 11 out of 40 (bilateral, 2×20) ROIs were associated with SoC, while in females only 2 out of 40 ROIs were associated with SoC. Table 2, listing all included ROIs, indicates the areas that were associated with SoC in either males or females. In the male pairs, the twin with low SoC had a thicker cortex compared to his co-twin in the bilateral inferior frontal orbital (Left: $B = -.0192$, $q = .001$; Right: $B = -.0159$, $q = .001$) and angular gyri (Left: $B = -.0207$, $q = .003$; Right: $B = -.0134$, $q = .024$), the right fusiform ($B = -.0085$, $q = .038$) and supramarginal gyri ($B = -.0221$, $q < .001$), and the left inferior frontal triangular gyrus ($B = -.0143$, $q < .001$) and anterior circular insula sulcus ($B = -.0137$, $q = .014$). Additionally, low SoC was associated with increased volume of the right supramarginal gyrus ($B = -73.03$, $q = .03$), but reduced surface area of the right anterior occipital sulcus ($B = 8.12$, $q = .017$). Figure 3 displays an example of the within-pair association per sex between SoC and thickness of the left inferior orbital frontal gyrus. In females, on the other hand, the twin with lower SoC only showed reduced volume

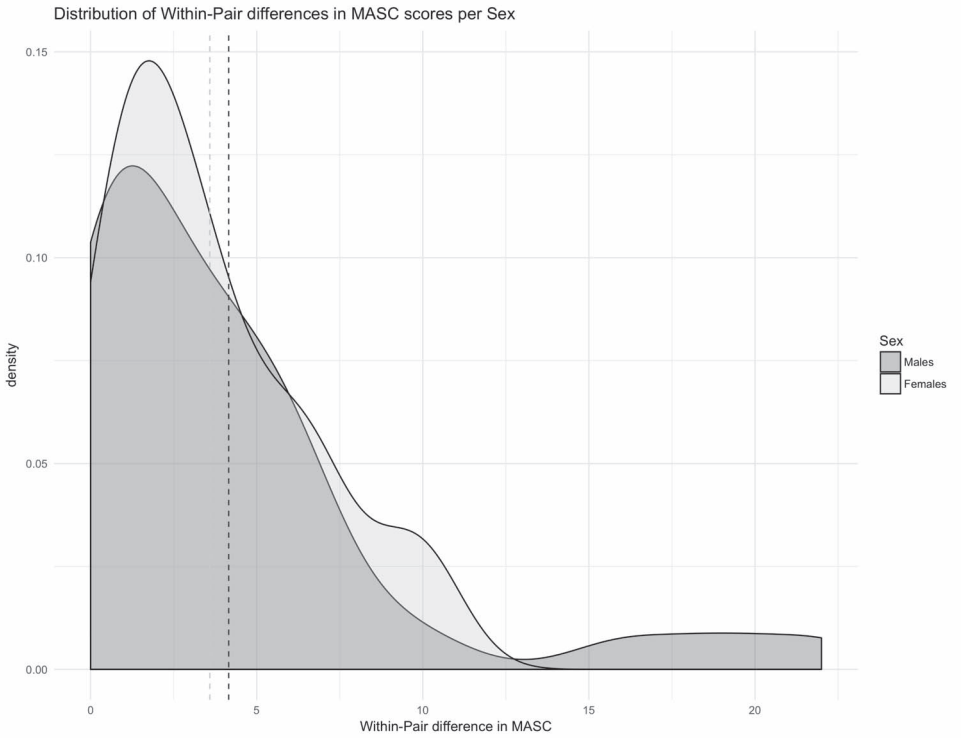

Fig. 2. Distribution of SoC scores within male and female twin pairs. A within-pair difference of 1 point indicates that one twin scored 1 point higher on the SoC task compared to the co-twin. Within male pairs, there were larger differences on SoC, but the within-pair differences in males were not significantly different from the within-pair differences in females ($P > 0.05$, see Table 1). The dotted vertical line indicates the mean SoC score per group.

Table 4. Behavioral outcomes: within-pair associations in the whole group and split by sex, between SoC and autism, with (A) autistic traits predicting SoC and (B) ASD diagnosis predicting SoC in ASD-discordant pairs.

Outcome: SoC			Outcome: SoC		
(A)	B (SE) *P*-value	95% CI	(B)	B (SE) *P*-value	95% CI
Whole group	ASD-discordant				
SRS-2	−.059 (.021) .005**	−.101, −.018	ASD diagnosis	−3.590 (1.63) .077*	−6.778, −.409
IQ	.121 (.053) .024*	.016, .225	IQ	.210 (.092 .020*	.033, .392
Males	ASD-discordant males				
SRS-2	−.072 (.031) .018*	−.132, −.013	ASD diagnosis	−4.880 (2.36) .039*	−9.450, −.255
IQ	.183 (.074) .014*	.037, .329	IQ	.298 (.119) .012*	.066, .531
Females	ASD-discordant females				
SRS-2	−.050 (.030) .102	−.109, .010	ASD diagnosis	−1.940 (2.02) .338	−5.907, 2.027
IQ	.050 (.071) .481	−.090, .191	IQ	.110 (.091) .217	−.066, .290

*$P < .05$, $P < .1$.
**$P < .001$.

of the left superior circular insula sulcus ($B = 28.73$, $q = .011$) and increased thickness of the right anterior occipital sulcus ($B = -.0157$, $q = .040$). Finally, the association between SoC and neuroanatomy was different between males and females for thickness of the bilateral angular gyri (Right $P = .029$, Left $P = .009$) and for thickness and volume of the right supramarginal gyrus (thickness $P = .006$, volume $P < .001$). Figure 4 summarizes the results per sex, and also includes an overview of the ROIs that were included but that did not show associations with SoC in either sex. Supplementary analyses further revealed that most associations were present in DZ, but not MZ twins, indicating that the link between SoC and cortical thickness is mostly driven by genetics (Supplementary Results). Finally, there was no association between SoC and either volume, surface area or thickness of the three randomly picked control regions outside the selected social brain network (bilateral cuneus, superior precentral sulcus and subcallosal gyrus) (Table 7).

Discussion

This study is the first to investigate associations between SoC assessed by the MASC test and social brain structure along the autistic trait continuum from the normative to the clinical spectrum. In particular, we addressed sex-specific effects while controlling for shared genetic and environmental factors by using a co-twin control design. Having an ASD diagnosis as well as having more autistic traits were associated with lower SoC

Table 5. Within-pair associations between cortical volume, surface area and thickness of neocortical ROIs and SoC in the whole group and for males and females separately.

Region of interest	Cortical volume			Surface area			Thickness		
	Whole group	Males	Females	Whole group	Males	Females	Whole group	Males	Females
	B (SE) *q*-value	B (SE) *q*-value	B (SE) *q*-value	B (SE) *q*-value	B (SE) *q*-value	B (SE) *q*-value	B (SE) *q*-value	B (SE) *q*-value	B (SE) *q*-value
Right inferior frontal orbital G.	−2.07 (7.44) *.844*	−17.37 (6.57) *.113*	27.03 (12.16) *.345*	1.2 (1.51) *.665*	−1.18 (1.26) *.553*	5.74 (2.72) *.277*	−.0105 (.0040) *.067*	**−.0159 (.0041) .001**	−.0006 (.0074) .999
Right insula long G. cent S.	16.1 (6.22) *.096*	15.12 (7.5) *.241*	17.97 (1.29) *.360*	**7.43 (2.47) .062**	8.35 (2.82) *.063*	5.69 (4.55) *.95*	−.0064 (.0059) *.474*	**−.0164 (.0070) .064**	.0123 (.0095) *.645*
Right fusiform G.	−1.15 (19.5) *.778*	−3.39 (19.22) *.917*	−23 (37.2) *.985*	4.27 (4.96) *.655*	5.15 (5.02) *.508*	2.59 (9.43) *.95*	**−.0090 (.0028) .014**	**−.0085 (.0032) .038**	−.0099 (.0046) *.262*
Right angular G.	−31.01 (3.91) *.632*	−7.6 (36.68) *.241*	44.28 (4.73) *.852*	3.64 (6.6) *.729*	1.04 (7.81) *.946*	8.57 (14.16) *.95*	−.0072 (.0040) *.196*	**−.0134 (.0047) .024**	.0044 (.0063) *.75*
Right supramarginal G.	−28.56 (22.74) *.598*	**−73.03 (21.67) .03**	56.04 (31.15) *.360*	9.94 (6.28) *.504*	1.13 (8.24) *.457*	9.59 (1.59) *.95*	**−.0158 (.0044) .007**	**−.0221 (.0046) <.001**	−.0039 (.0053) *.751*
Right anterior occipital S.	7.3 (5.87) *.598*	14.27 (5.92) *.160*	−5.96 (11.62) *.985*	5.29 (2.43) *.238*	**8.12 (2.3) .017**	−.1 (5.01) *.984*	−.0100 (.0044) *.095*	−.0071 (.0056) *.369*	**−.0157 (.0048) .040**
Right superior temporal S.	−54.59 (24.18) *.192*	−4.71 (31.33) *.352*	−8.99 (43.93) *.360*	−9.78 (8.94) *.638*	−3.2 (1.78) *.876*	−22.31 (21.04) *.95*	**−.0073 (.0025) .030**	−.0076 (.0030) *.051*	−.0068 (.0040) *.506*
Left inferior frontal orbital G.	−1.82 (6.18) *.844*	−2.7 (8.33) *.877*	−.15 (6.43) *.989*	1.7 (1.3) *.559*	1.8 (1.63) *.506*	1.51 (1.99) *.95*	**−.0164 (.0045) .007**	**−.0192 (.0048) .001**	−.0113 (.0074) *.506*
Left inferior frontal triangular G.	3.06 (14.56) *.878*	−1.96 (18.48) *.939*	12.6 (26.98) *.985*	4.26 (3.9) *.638*	5.07 (4.8) *.506*	2.72 (6.68) *.95*	**−.0100 (.0031) .014**	**−.0143 (.0034) <.001**	−.0019 (.0053) *.844*
Left angular G.	−71.75 (39.6) *.400*	−11.77 (53.25) *.241*	2.48 (34.21) *.989*	−5.08 (7.64) *.698*	−5.82 (9.32) *.710*	−3.67 (11.63) *.95*	−.0119 (.0051) *.095*	**−.0207 (.0059) .003**	.0045 (.0079) *.773*
Left lateral superior temporal G.	18.48 (18.4) *.632*	21.3 (22.29) *.522*	13.1 (29.17) *.985*	**1.33 (3.49) .062**	1.93 (4.32) *.146*	9.17 (4.95) *.425*	−.0034 (.0052) *.742*	−.0023 (.0071) *.846*	−.0054 (.0065) *.751*
Left middle temporal G.	−3.61 (27.31) *.617*	−57.31 (32.48) *.259*	2.19 (35.76) *.985*	−2.19 (5.74) *.780*	−5.99 (7.16) *.620*	5.02 (8.04) *.95*	−.0078 (.0036) *.124*	**−.0075 (.0031) .064**	−.0085 (.0078) *.737*
Left anterior circular insula S.	2.04 (3.92) *.778*	−1.88 (4.11) *.809*	9.51 (5.89) *.426*	1.46 (1.63) *.655*	.63 (1.89) *.868*	3.03 (2.44) *.95*	−.0088 (.0043) *.141*	**−.0137 (.0045) .014**	.0004 (.0079) *.999*
Left superior circular insula S.	17.38 (5.99) *.096*	11.41 (8.4) *.332*	**28.73 (7.88) .011**	6.05 (2.55) *.177*	5.31 (3.58) *.351*	7.46 (2.98) *.165*	.0013 (.0022) *.764*	−.0020 (.0026) *.614*	.0074 (.0035) *.262*
Left superior temporal S.	−49.82 (34.75) *.598*	−69.83 (45.22) *.294*	−11.74 (4.07) *.989*	−15.03 (14.12) *.638*	−24.09 (19.2) *.457*	2.19 (13.35) *.983*	**−.0060 (.0024) .070**	−.0064 (.0028) *.073*	−.0052 (.0044) *.678*

Surface-based cerebral estimates for the within-pair associations between SoC skills and brain structure in the whole group, and males and females separately, using either cortical volume, surface area or cortical thickness as outcome. All brain measures are computed from the FreeSurfer pipeline using the Destrieux Atlas. A positive estimate corresponds to brain measures affected positively (increase) by an increase in SoC skill. Regions are reported in this table only if at least one of the estimates was significant ($q < 0.05$) or had a q-value < 0.1 (FDR-corrected). In each cell, the first line corresponds to the estimate, the second line in parenthesis corresponds to the standard error and the last line in italic is the *P*-value. Estimates with a q-value < 0.05 are indicated in bold, estimates with a q-value < 0.1 are indicated in gray. G. = gyrus, S. = sulcus.

performance within twin pairs, but this effect was only significant in males, despite similar autistic trait severity (and similar within-pair differences in the latter) in females and males. Further, within pairs, reduced SoC predicted increased thickness of parts of the social brain network. Importantly, these associations were also present in twin pairs discordant for ASD and therefore valid even for clinical autism variants, not only broader autism phenotypes and normative autistic trait variation. Interestingly, these effects seemed to be largely driven by the males. Male-specific effects were found in the bilateral angular and right

Table 6. Within-pair associations between cortical volume, surface area and thickness of neocortical ROIs and SoC in ASD-discordant pairs (8 female pairs, 10 male pairs).

Region of interest Right	Cortical volume	Surface area	Thickness	Region of interest Left	Cortical volume	Surface area	Thickness
	B (SE) *q*-value	B (SE) *q*-value	B (SE) *q*-value		B (SE) *q*-value	B (SE) *q*-value	B (SE) *q*-value
Right fusiform G.	−21.9	1.11	**−.0095**	Left insula short G.	14.68	**5.31**	−.0108
	(33.47)	(8.46)	**(.0036)**		(6.13)	**(1.5)**	(.0056)
	.760	*.972*	**.021**		*.133*	**.017**	.099
Right anterior occipital S.	8.67	6.47	**−.0099**	Left anterior circular insula S.	−4.65	−.66	**−.0114**
	(6.11)	(2.97)	**(.0037)**		(3.6)	(1.73)	**(.0049)**
	.328	*.149*	**.021**		*.392*	*.934*	**.047**
Right insula lg G. cent S.	23.76	**1.74**	−.0101	Left insula lg G. cent S.	4.31	3.33	**−.0193**
	(9.84)	**(3.46)**	(.0062)		(8.63)	(1.46)	**(.0073)**
	.133	**.039**	*.172*		*.852*	*.129*	**.021**
Right angular G.	−84.84	−.27	**−.0181**	Left angular G.	−96.79	−4.22	**−.0211**
	(44.7)	(7.72)	**(.0050)**		(65.14)	(1.41)	**(.0062)**
	.258	*.972*	**.002**		*.321*	*.934*	**.004**
Right supramarginal G.	−64.94	13.53	**−.0252**	Left supramarginal G.	39.81	23.06	**−.0122**
	(28.89)	(8.42)	**(.0058)**		(41.53)	(16.6)	**(.0059)**
	.164	*.333*	**<.001**		*.588*	*.424*	**.073**
Right middle temporal G.	−74.74	12	**−.0217**	Left middle temporal G.	−77.33	−4.21	**−.0155**
	(41.37)	(4.58)	**(.0095)**		(31.65)	(8.26)	**(.0059)**
	.258	*.077*	**.047**		*.133*	*.872*	**.021**
Right superior temporal S.	−48.93	1.5	**−.0118**	Left superior temporal S.	−71.25	−17.25	**−.0082**
	(39)	(12.41)	**(.0044)**		(45.03)	(21.14)	**(.0029)**
	.399	*.972*	**.021**		*.321*	*.754*	**.021**
Right lateral superior temporal G.	−2.12	1.38	**−.0172**	Left lateral superior temporal G.	42.69	**16.74**	−.0081
	(16.34)	(4.46)	**(.0063)**		(28.79)	**(5.86)**	(.0080)
	.955	*.129*	**.021**		*.321*	**.057**	*.402*
Right superior frontal G.	.61	19.08	**−.0069**	Left superior frontal G.	27.9	32.57	**−.0087**
	(6.92)	(15.48)	**(.0017)**		(74.16)	(21.85)	**(.0038)**
	.992	*.484*	**<.001**		*.859*	*.389*	**.047**
Right middle frontal G.	−72.39	1.32	**−.0098**	Left middle frontal G.	−73.83	−5.77	**−.0073**
	(42.54)	(11.15)	**(.0037)**		(42.72)	(7.63)	**(.0035)**
	.273	*.972*	**.021**		*.273*	*.782*	**.070**
Right inferior frontal orbital G.	−2.76	2.59	**−.0202**	Left inferior frontal orbital G.	−11.69	.36	**−.0214**
	(7.41)	(1.42)	**(.0053)**		(6.43)	(1.39)	**(.0049)**
	.859	*.250*	**.001**		*.258*	*.972*	**<.001**
Right inferior frontal triangular G.	2.01	9.3	**−.0122**	Left inferior frontal triangular G.	1.02	8.64	**−.0164**
	(27.69)	(6.77)	**(.0046)**		(15.22)	(4.1)	**(.0044)**
	.760	*.424*	**.021**		*.760*	*.156*	**.002**
Right Inferior frontal operculum G	**43.56**	**12.26**	−.0014				
	(13.54)	**(4.73)**	(.0066)				
	.052	**.077**	*.872*				

Surface-based cerebral estimates for the within-pair associations between SoC skills and brain structure in ASD-discordant pairs, using either cortical volume, surface area or cortical thickness as outcome. All brain measures are computed from the FreeSurfer pipeline using the Destrieux Atlas. A positive estimate corresponds to brain measures affected positively (increase) by an increase in SoC skill. Regions are reported in this table only if at least one of the estimates was significant ($q < 0.05$) or had a q-value < 0.1 (FDR-corrected). In each cell, the first line corresponds to the estimate, the second line in parenthesis corresponds to the standard error and the last line in italic is the *P*-value. Estimates with a q-value < 0.05 are indicated in bold, estimates with a q-value < 0.1 are indicated in gray. G. = gyrus, S. = sulcus

supramarginal gyri. Moreover, similar associations were found only in DZ and not MZ twins, suggesting a strong impact of genetics on the relationship between SoC and brain structure.

No previous study has directly assessed the relationship between SoC and neuroanatomy in ASD. However, our results correspond to a previous study that investigated a SoC network, derived from a meta-analyses of functional neuroimaging studies of SoC in ASD compared to controls, and found increased thickness of the inferior frontal gyrus in participants with autism (Patriquin *et al.*, 2016). Although the relationship

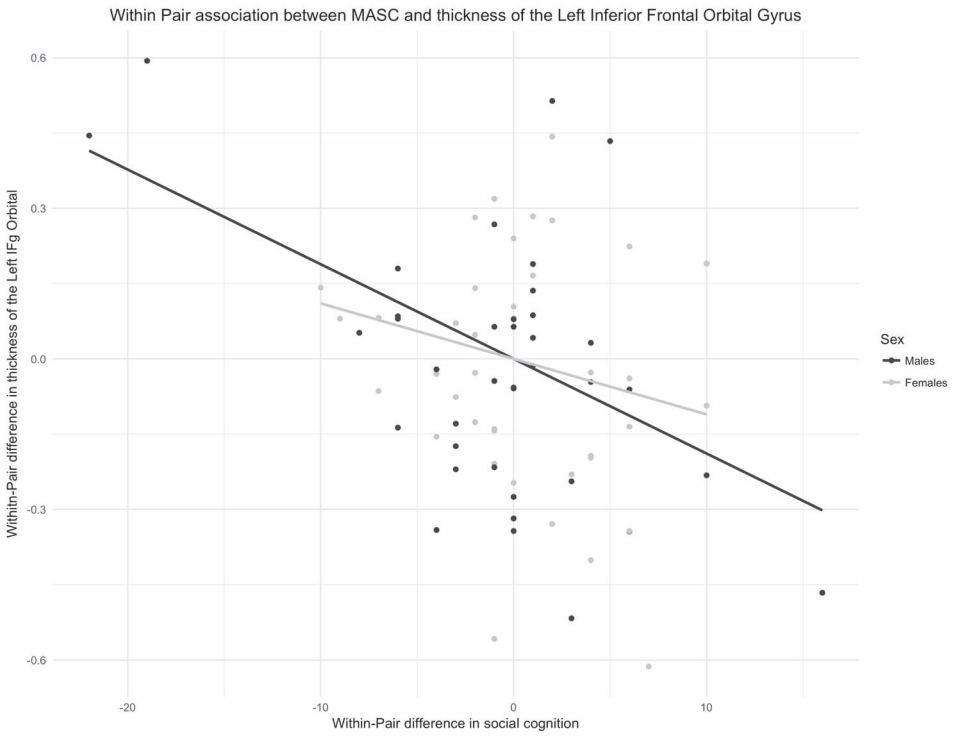

Fig. 3. This is an example of the within-pair association between SoC and brain structure. Displayed is the association between within-pair differences in SoC (on the x-axis) and within-pair differences on thickness of the left inferior frontal orbital gyrus (on the y-axis). Each dot represents one twin pair. In males, there is a significant correlation between differences in SoC, and differences in brain structure, with better SoC being associated with reduced thickness of the left orbital inferior frontal gyrus.

Table 7. Within-pair associations between cortical volume, surface area and thickness of three control regions (cuneus, subcallosal and inferior precentral sulcus) and SoC for males and females separately.

Region of interest	Cortical volume		Surface area		Thickness	
	Males B (SE) *q*-value	Females B (SE) *q*-value	Males B (SE) *q*-value	Females B (SE) *q*-value	Males B (SE) *q*-value	Females B (SE) *q*-value
Left cuneus	−11.71 (14.92) *.432*	−2.76 (14.43) *.848*	−3.00 (4.38) *.493*	.290 (6.00) *.962*	−.003 (.005) *.534*	.002 (.005) *.668*
Left subcallosal gyrus	2.35 (11.64) *.840*	−8.94 (13.11) *.495*	.872 (4.91) *.859*	−4.39 (5.39) *.415*	.003 (.010) *.758*	.010 (.016) *.529*
Left inferior precentral sulcus (superior part)	−1.52 (2.72) *.612*	.75 (17.90) *.967*	−1.75 (9.39) *.852*	3.65 (7.90) *.644*	.001 (.005) *.783*	−.007 (.007) *.334*
Right cuneus	−22.66 (17.78) *.203*	6.81 (19.01) *.720*	−2.49 (8.83) *.778*	−3.19 (6.62) *.630*	−.006 (.004) *.091*	.006 (.004) *.072*
Right subcallosal gyrus	−8.03 (9.76) *.410*	7.86 (1.71) *.463*	−1.03 (4.85) *.832*	3.26 (5.39) *.545*	−.013 (.015) *.394*	−.013 (.019) *.493*
Right inferior precentral sulcus (superior part)	−14.33 (12.44) *.249*	−24.54 (21.03) *.243*	−3.57 (5.24) *.496*	−6.97 (8.78) *.427*	−.004 (.003) *.241*	.003 (.008) *.744*

Surface-based cerebral estimates for the within-pair associations between SoC skills and brain structure in males and females separately, using either cortical volume, surface area or cortical thickness as outcome. Three brain regions outside the social brain network were chosen at random and included the bilateral cuneus, subcallosal gyrus and inferior precentral sulcus (superior part). All brain measures are computed from the FreeSurfer pipeline using the Destrieux Atlas. A positive estimate corresponds to brain measures affected positively (increase) by an increase in SoC skill. In each cell, the first line corresponds to the estimate, the second line in parenthesis corresponds to the standard error and the last line in italic is the *P*-value. Estimates with a *q*-value < 0.05 are indicated in bold, estimates with a *q*-value < 0.1 are indicated in gray. G. = gyrus, S. = sulcus

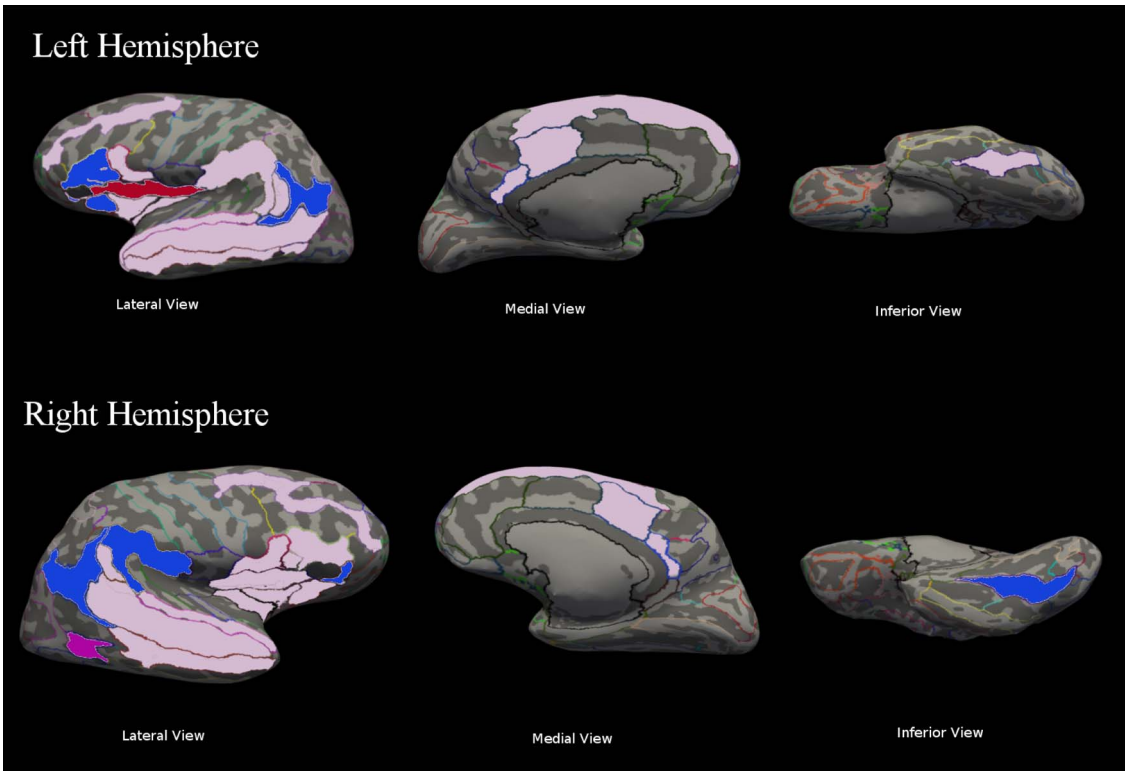

Fig. 4. Illustration of surface-based morphometric results displayed on inflated brain. The pink indicates areas that were included in the ROIs but that were not significantly associated with SoC. In red are the regions with significant association between SoC and brain estimates in females: increased volume of the left superior circular insula sulcus and reduced thickness of the right anterior occipital sulcus. In blue are the regions associated with SoC for males: reduced thickness of the right inferior frontal orbital gyrus, fusiform gyrus, angular gyrus, supramarginal gyrus and the left inferior frontal orbital and triangular gyri, angular gyrus and anterior circular insula sulcus in males, in addition to reduced volume of the right supramarginal gyrus. In purple is the region associated with SoC in both sexes: the right anterior occipital sulcus, which is associated with reduced thickness in females, and increased surface area in males.

between brain structure and function is not straightforward, structural differences might underlie alterations in SoC observed in ASD (Patriquin *et al.*, 2016; Kana *et al.*, 2017). Previous functional imaging studies using the MASC demonstrated activation in similar brain regions known to be involved in explicit SoC, face processing and language abilities in typical development (Wolf *et al.*, 2010). Moreover, a recent study found associations between white matter microstructure of short-range fibers in regions of the social brain network and scores on social awareness and empathy in ASD males (d'Albis *et al.*, 2018). Thus, structural alterations as reported in this study could affect the functioning of these regions and hence alter SoC skills, thereby influencing the development of autistic phenotypes.

Significant associations between SoC and social brain structure were observed mostly in males, with 25% of ROIs being associated with SoC in males, as opposed to 5% in females, while group sizes were comparable and therefore yielded similar statistical power to detect the differences. This finding is in line with the behavioral link between autistic traits and SoC in the males in our sample, while the overall level of autistic traits did not differ between the sexes. However, importantly, the difference in performance on MASC between males and females with an ASD diagnosis did not survive significance testing. The score distribution showed that within the male group, a few participants scored poorly on the MASC, while for females the distribution of scores appeared to be narrower. Thus, although females with ASD seem to have problems with SoC, they might have been less likely to perform at the extreme end of the SoC score distribution. Moreover, the lack of significant association between both ASD diagnosis and autistic traits and SoC in females suggests that problems with SoC were less pronounced in autistic females. The observation that females with more autistic traits still perform relatively well on SoC tasks corresponds to the idea that, even among subjects with ASD, sex differences in SoC exist similar to those seen in TD populations (Zwaigenbaum *et al.*, 2012; Messinger *et al.*, 2015; Constantino, 2016; Hull *et al.*, 2017). Indeed, scores on the MASC are likely to reflect intrinsic status SoC, and hence not the result of behavioral camouflaging (Lai *et al.*, 2016). Further, societal bias might both impact our expectations from female behavior, thereby conditioning their behaviors, and at the same time stimulate the social brain network more in females compared to males. Such a bias would alter the development of SoC and their underlying neuroanatomy in females in general. Thus, better performance on SoC and less changes in brain structure in females related to SoC might be a result of environmental influences from society rather than biological determination.

On balance, however, low variance of SoC performance in our study could have contributed to limited social brain related findings in females. Still, cortical thickness was associated with SoC in the ASD-discordant pairs, of which 40% were female pairs. Even though it is possible that the observed associations in the discordant pairs were driven by the male pairs, the pattern of result does suggest that in females with full-blown ASD, as opposed to those along the TD range of the trait continuum,

the relationship between social brain structure and SoC appears more prominent.

Despite more indicated regions in males, neuroanatomical sex differences in relation to SoC were only significant in the angular and supramarginal gyri in our study. These areas are part of the temporo–parietal junction, which is involved in integrating complex sensory information about self and others, and therefore contributes crucially to SoC processing (Mostofsky and Ewen, 2011; Eddy, 2016). Previous studies on TD individuals reported sex differences in white matter of the inferior parietal and temporal lobes in relation to SoC (Chou *et al.*, 2011; Takeuchi *et al.*, 2013). In addition, gray matter of the ventromedial prefrontal cortex has been related to being more feminine, which in turn correlated with higher performance on a social perceptiveness task (Wood *et al.*, 2008). Moreover, interaction effects between sex and ASD diagnoses have been observed for gray (Beacher *et al.*, 2012) and white (Lai *et al.*, 2013) matter in the right inferior parietal lobule, which comprises of the angular and supramarginal gyri, as well as white matter connectivity of the temporal lobe, temporo–parieto–occipital junction and medial parietal lobe (Irimia *et al.*, 2017). A recent study investigating camouflaging in ASD reported hypoactivity of the right temporo–parietal junction during mentalizing only in autistic males compared to neurotypical males, but not in autistic females (Lai *et al.*, 2019). Thus, sex-specific effects in association with ASD, potentially related to SoC abilities, are consistently found in the inferior parietal lobe and temporo–occipital–parietal junction (TPJ). The qualitative brain structure differences observed in our study might therefore reflect sex-specificity of these areas in the general population. As the TPJ is involved in regulation of internal representations by updating those using contextual information, and hence adjusting top-down expectations (Geng and Vossel, 2013), we could speculate that a female advantage in this brain region might contribute to their hypothesized increased sensitivity to environmental and social influences.

The twin design inherently controls for factors shared within a twin pair, including 50 (DZ twins) or 100% genetics (MZ twins), age and socio–economic status, and therefore the produced estimates may be less biased than the results from conventional across cohort regression analyses. Our study showed that most effects were driven by the DZ twins, thus indicating that differences in genetics were underlying the associations between SoC and the brain. Since the observed associations were primarily driven by DZ twins, it is possible that the SoC–brain relationship was affected by genes in males. Similarly, this would correspond to an enhanced sensitivity of females to environment factors that could potentially stimulate their SoC skills. However, due to the size of our sample, splitting the group by both gender and zygosity would not have led to interpretable results. Larger twin cohorts need to address if the relationship between brain and autistic behavior is differentially affected by genes vs non-shared environment in males compared to females. Furthermore, recently the assumption that MZ and DZ twins have equal environments has been challenged, with environmental differences found between MZ and DZ twins that go even beyond evocative gene–environment correlations (Fosse *et al.*, 2015). This entails that the environment is more different for DZ compared to MZ twins, and as such, the associations between SoC and brain structure in DZ twins might still be influenced by differential environments rather than genetics.

Moreover, this study includes a cohort with a wide age and IQ range. Ideally, we would have investigated sex differences in brain structures in separate age and IQ bins, in particular considering that the shared environmental factor might vary between younger and older participants, with younger twins being on average more likely to share their environment. However, that type of analyses would require a substantially larger sample size and these questions are therefore left for future studies to explore.

Finally, it is important to mention that, although we selected regions of the social brain network a priori, our analyses are rather exploratory in character. Three randomly selected regions outside the social brain network were not associated with SoC in any of the sexes, suggesting that our observations are specific for the social network. However, this does not exclude the possibility that structure of other brain regions is also associated with SoC abilities. Replication in a larger and non-twin sample, and including more severely affected autistic females, is required before any firm conclusions can be drawn.

Conclusion

Using co-twin design, we show that SoC is associated with brain structure of the social network across the autistic trait continuum into the clinical spectrum of ASD. In addition, despite similar autism trait and clinical levels in both sexes, these associations seemed to be specific for males in the present sample. Our findings urge further research to elucidate sex differences in the underlying neurobiological mechanisms of SoC and autism.

Supplementary material

Supplementary material is available at *SCAN* online.

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