Selective Disruption of Sociocognitive Structural Brain Networks in Autism and Alexithymia

Boris C. Bernhardt1,2, Sofie L. Valk1,1, Giorgia Silani2,3, Geoffrey Bird2,4, Uta Frith2 and Tania Singer1,2

1Department of Social Neuroscience, Max-Planck-Institute of Human Cognitive and Brain Sciences, Leipzig, Germany, 2Institute of Cognitive Neurosciences, University College London, London, UK, 3Cognitive Neuroscience Sector, International School for Advanced Studies SISSA-ISAS, Trieste, Italy and 4Social, Genetic and Developmental Psychiatry Centre (MRC), Institute of Psychiatry, King’s College London, London, UK

Address correspondence to Tania Singer, PhD, Department of Social Neuroscience, Max-Planck-Institute of Human Cognitive and Brain Sciences, Stephanstraße 1a, D-04103 Leipzig, Germany. Email: singer@cbs.mpg.de

Both authors contributed equally to this work.

Autism spectrum conditions (ASC) are neurodevelopmental disorders characterized by abnormal social cognition. A core feature of ASC is disrupted Theory of Mind (ToM), our ability to take the mental perspective of others. ASC is also associated with alexithymia, a trait characterized by altered emotional interoception and empathy. Here, we applied structural MRI covariance analysis to assess whether ASC and alexithymia differentially affect structural brain networks associated with sociocognitive and socioaffective functions. Based on previous functional MRI findings, we expected disrupted ToM networks (centered on dorsomedial prefrontal cortex [dmPFC], and temporo-parietal junction [TPJ]) in ASC, while alexithymia would affect networks centered on fronto-insular cortex (FI), regions associated with interoception of emotion and empathy. Relative to controls, ASC indeed showed reduced covariance in networks centered on dmPFC and TPJ, but not within FI networks. Irrespective of ASC, covariance was negatively modulated by alexithymia in networks extending from FI to posterior regions. Network findings were complemented by self-reports, indicating decreased perspective taking but normal empathic concern in ASC. Our results show divergent effects of ASC and alexithymia on inter-regional structural networks, suggesting that networks mediating socioaffective processing may be separable from networks mediating sociocognitive processing.

Keywords: ASD, connectivity, cortical thickness, insula, social brain

Introduction

Autism spectrum conditions (ASC) are a group of neurodevelopmental disorders which persist into adulthood and are characterized by abnormalities of language and social interaction, together with stereotyped and repetitive behavior. One source of the social cognition difficulties seen in ASC is thought to be an impairment in “Theory of Mind” (ToM), the ability to infer the mental states of others (Castelli et al. 2002; Frith and Happé 2005). A second potential source of the social difficulties encountered by individuals with ASC is the presence of co-occurring alexithymia within this population (Berthoz and Hill 2005; Silani et al. 2008; Bird et al. 2010). Alexithymia is a subclinical trait associated with reduced emotional awareness and empathizing. In contrast to ToM, which has also been referred to as mentalizing or cognitive perspective taking, empathy refers to our ability to share and understand affective states with others (de Vignemont and Singer 2006) and is typically associated with brain networks subserving interoception and emotional awareness (Singer and Lamm 2009; Bernhardt and Singer 2012; Singer 2012).

Alexithymia is significantly more prevalent in the population of individuals with ASC, with more than 50% showing this trait, than in the typical population, where the prevalence is ~10% (Hill et al. 2004; Berthoz and Hill 2005; Silani et al. 2008; Bird et al. 2010). Several recent studies suggest that some of the difficulties in socioemotional processing thought to be characteristic of ASC may instead be due to co-occurring alexithymia within this group. These deficits include: emotional interoception (Silani et al. 2008), empathy (Bird et al. 2010), appropriate eye and mouth fixation (Bird et al. 2011), and the recognition of emotion in others (Cook et al. 2013).

The clinical distinction between ASC and alexithymia contrasts with accounts which specify that difficulties in emotional empathy and cognitive perspective taking cannot be separated; that both relate to faults in the same brain network (Chakrabarti and Baron-Cohen 2006; Lombardo et al. 2007). Conversely, different outcomes of ASC and alexithymia are theoretically supported by claims that cognitive and affective networks in the social brain diverge (Singer 2006, 2012; Shamay-Tsoory et al. 2009; Hooker et al. 2010). In line with this work, one may assume that processes involved in cognitive perspective taking and in emotional interoception and empathy are likely embedded within differentially distributed and interconnected networks (Singer 2006, 2012; Lamm et al. 2011). Several task-based functional MRI studies have shown atypical activations in dorsal medial prefrontal cortex (dmPFC) and temporo-parietal junction (TPJ) during cognitive perspective taking tasks in ASC (Castelli et al. 2002; Kennedy and Courchesne 2008; Kana et al. 2009; Lombardo et al. 2011). As these areas are among the most consistently activated areas during mentally tasks in typically developing adults (Saxe and Kanwisher 2003; Mitchell et al. 2006; Van Overwalle 2009; Mar 2011; Bzdok et al. 2012), these findings indicate disruptions in ToM networks in ASC. In contrast, previous functional imaging studies have demonstrated that alexithymia relates to hypoactivity of fronto-insular (FI) cortices in both typical adults and those with ASC during empathy and interoception, irrespective of ASC diagnosis (Silani et al. 2008; Bird et al. 2010). These previous findings suggest dissociation between social cognitive deficits in ASC and alexithymia. Accordingly, atypical ToM is thought to be a core deficit in ASC, whereas failures in socioaffective processing such as emotional interoception and empathy seem instead to be associated with alexithymia.

To test this hypothesis and to extend previous findings that were based only on analysis of localized functional brain
activity in the context of affective tasks (Silani et al. 2008; Bird et al. 2010), we investigated whether ASC and its core deficits in ToM may be further discriminated from alexithymia and its specific deficits in socioaffective processing at the level of inter-regional brain networks. To this end, we investigated typical adults and adults with ASC that exhibited comparable levels of alexithymic traits. This conservative design permitted to study the effects of ASC relatively unconfounded by the presence of alexithymia, and vice versa. Inter-regional structural networks were assessed using covariance analysis of MRI-based cortical thickness data. This technique has previously been used to map inter-regional structural networks in humans, where invasive anatomical tract-tracing techniques cannot be used (Lerch et al. 2006; Bullmore and Sporns 2009; Zilinski et al. 2010; Bernhardt et al. 2011; Raznahan et al. 2011; Khundrakpam et al. 2013). This approach rests on the assumption that positive correlations indicate connectivity, as axionally connected regions are believed to have common trophic, developmental, and maturational influences (Cheverud 1984; Zhang and Sejnowski 2000; Raznahan et al. 2011).

Cortical thickness measurements offer the advantage of reflecting in vivo intrinsic characteristics of intracortical morphology including cell size, density, and cell arrangement in a topologically and biologically meaningful way (Lerch et al. 2006; Winkler et al. 2010). In previous work, structural covariance network mapping has been used to identify network alterations during brain development (Zilinski et al. 2010; Khundrakpam et al. 2013), in neurological conditions (Bernhardt et al. 2011), and psychiatric disorders (Bullmore et al. 1998; Mitelman et al. 2005; Bassett et al. 2008); in ASC, a recent covariance analysis revealed atypicalsities of face perception networks (Dziobek et al. 2010).

In the current study, the structural covariance of networks involved in ToM was investigated by seeding from TPJ and dmPFC; while the networks involved in empathy and interception impacted by alexithymia were examined by seeding from FI. Seed coordinates were derived from previous functional MRI meta-analyses in the domain of ToM (Bzdok et al. 2010), based on the tessellated surfaces using a 20-mm full-width-at-half-maximum.

Patients and Methods

Subjects

We assessed structural MRI data of 16 high-functioning individuals with ASC (4 females) and 16 healthy controls (7 females), who were initially recruited at the Institute of Cognitive Neuroscience, University College London. All subjects were right-handed. Diagnosis was performed by an independent clinician according to the standard Diagnostic and Statistical Manual of Psychiatric Disorders-IV (American Psychiatric Association 2000). Twelve participants had received a diagnosis of Asperger’s Syndrome and 4 of autism. In addition to the clinical diagnosis, we used the Autism Diagnostic Observational Schedule (ADOS-G; Lord et al. 2000) to characterize the current level of functioning for the ASC group. The mean ADOS score for our ASC sample was 8.7 ± 4.8. For more details on the ASC sample, please see Table 1. Control participants were pre-screened for any neurological or psychiatric disorders and did not exhibit autistic features.

ASC and control groups were statistically matched for age (ASC: 21–60 years, mean ± SD 34.8 ± 13.3 years; Controls: 23–63 years, mean ± SD 36.2 ± 13.0 years), gender, full-scale IQ (ASC: mean ± SD 119.8 ± 15.2, range: 91–140; Controls: 113.4 ± 12.3, range: 98–149), measured using the Wechsler Adult Intelligence Scale, WAIS-III UK (Wechsler 1999), self-reported empathy (13 ASC: 33 29 M AS 12 (5/7) 101 46 54.6 ± 16.5; 10 Controls: 41 28 M AS 10 (3/7) 125 59 51 M AS 7 (3/4) 132 61 5.8 ± 4.8). For more details on the ASC sample, please see Table 1. The diagnosis refers to the original clinical assessment provided by a qualified psychologist or psychiatrist (AS, Asperger’s syndrome; AU, Autism). Scores on the ADOS-G (social interaction, cutoff = 4; communication, cutoff = 2) are derived from the diagnostic algorithm and represent the behavior of the participant at the time of the study. TAS represents scores on the TAS-20 Alexithymia questionnaire. IQ represents scores by the Wechsler Adult Intelligence Scale. *Only total ADOS scores were available at time of study.

MRI Acquisition

MRA data acquisition was performed on a 1.5 T Siemens Sonata scanner (Siemens Medical Systems, Erlangen) using a 3D IR/GR MDEFT T1-weighted sequence (TR = 20.66 ms; TE = 8.42 ms; TI = 640; flip angle = 25°; 256 coronal slices; matrix size = 176 × 224; FOV = 224 mm; slice thickness = 1 mm), yielding a final voxel size of 1.0 × 1.0 × 1.0 mm.

MRI-Based Cortical Thickness Measurements

FreeSurfer (Version 5.0.0; http://surfer.nmr.mgh.harvard.edu) was used to generate models of the cortical surface and to model cortical thickness from the T1-weighted images. Previous work has validated FreeSurfer by comparing it with histological analysis (Rosas et al. 2002) and manual measurements (Kuperberg et al. 2003). The processing steps have been described in detail elsewhere (Dale et al. 1999; Fischl et al. 1999; Han et al. 2006). Following surface extraction, sulcal and gyral features across individual subjects were aligned by morphing each subject’s brain to an average spherical representation, fsaverage7, that allows for accurate matching of cortical thickness measurement locations among participants, while minimizing metric distortion. The entire cortex in each subject was visually inspected and segmentation inaccuracies were manually corrected by a single rater blind to the diagnosis (S.L.V.). For whole-brain analysis, thickness data were smoothed on the tessellated surfaces using a 20-mm full-with-at-half-maximum.
Statistical Analysis


Mapping Structural Networks

To map structural covariance networks, we correlated the cortical thickness of each seed (i.e., bilateral dMPFC, TPJ, FI) across participants with thickness measures of all other points of the entire cortical surface. Analyses were restricted to networks ipsilateral to the respective seed regions.

Mapping Modulations of Covariance by ASC

We used linear interaction models to compare the covariance strength in our group of individuals with ASC to controls. These models contained simple terms for seed thickness and group, together with a seed thickness x group interaction term. To control for effects of alexithymia, we added a simple term for the individual TAS-score in the same statistical model.

Mapping Modulations by Alethymia

We furthermore assessed the modulation of covariance strength by alexithymia. These models contained simple terms for seed thickness and TAS-score as well as a parametric interaction term for seed thickness x TAS-score. To control for diagnosis of ASC, we added a simple factor for group in the statistical model.

Results

Structural Covariance Analysis of Social Cognition Networks in Controls

Structural covariance analysis in controls indicated that each seed region (i.e., dMPFC, TPJ, FI) was embedded within relatively specific, and distinct networks of brain regions (Fig. 1). Considering the left dMPFC seed, correlations included large portions of lateral and medial prefrontal and fronto-central neocortices, predominantly on the superior aspects (P < 0.001, FWE). Correlations of right dMPFC seed were similar to those of its left counterpart, but additionally encompassed regions in right lateral occipito-parietal regions (P < 0.01, FWE).

Structural networks of the left TPJ seed included posterior opercular, supramarginal, lateral parieto-occipital regions, together with lateral temporal and posterior midline cortices (P < 0.03, FWE). Networks identified using the right TPJ seed were slightly less extended, but had overall a similar topography than those of left TPJ, including lateral parietal, supramarginal, and lateral temporal cortices.

Networks seeded from left FI included other insular segments, together with ventrolateral and dorsolateral prefrontal cortex. In the posterior quadrant, structural correlations extended to lateral and medial occipital regions, together with retrosplenial cortex (P < 0.005, FWE). Networks of right FI included medial PFC regions; but significant correlations were not observed with posterior regions.

Modulation of Covariance by ASC

The direct comparison of structural covariance networks between the control and ASC groups revealed decreased but not increased structural covariance networks centered on seeds related to ToM (i.e., dMPFC and TPJ) in the ASC group (Fig. 2). Individuals with ASC displayed markedly reduced structural covariance between the left dMPFC seed and a target region in lateral and medial premotor regions (P < 0.05, FWE). A trend for a similar modulation was also seen in the right hemisphere. Analysis of the network derived from the TPJ seed revealed a reduction of covariance strength between left TPJ and large portions of left superior temporal cortices extending into the posterior parietal lobe (P < 0.002, FWE). In contrast, there were no effects of ASC on FI networks.

The above ASC-related modulations of ToM networks were based on models that statistically controlled for alexithymia; yet, comparable patterns of network disruptions were observed in a model did not contain TAS scores as a nuisance regressor. In addition, a separate analysis that also included global mean cortical thickness or age as control variables yielded virtually identical results. Indeed, post hoc analysis between seed and target regions from the main analysis confirmed strong effects for the covariance modulation between the left dMPFC seed and fronto-central regions and between the left TPJ seed and ipsilateral superior temporal and parietal cortices by ASC (t > 3.2), even when correcting for global mean thickness or age.

For completeness, networks identified in the ASC group are shown in the Supplementary Figure 2. For an illustration on
the mean effect in clusters of findings, please see Supplementary Figure 3A,B.

**Relationship Between Covariance Strength and Alexithymia**

The modulation of seed covariance by the degree of alexithymia (irrespective of ASC diagnosis) was assessed by testing the parametric interaction between TAS score and seed covariance strength across all participants, controlling for group differences between ASC and controls in the same model (Fig. 3). This analysis revealed a negative modulation of left FI covariance with left supramarginal and anterior temporo-parietal ($P < 0.03$, FWE), together with lateral occipital regions ($P < 0.05$, FWE). These findings indicated that participants with higher degrees of alexithymia had a lower structural covariance between FI and these target regions than those with low degrees of alexithymia. Similar to the group analysis (above), the modulatory effect of alexithymia remained strong when correcting for global mean cortical thickness or age confounds in the statistical model in a post hoc framework ($t > 3.6$). Conversely, and in line with our hypotheses, no modulatory effect of Alexithymia on ToM networks derived from seeding from the TPJ and dmPFC was observed (FWE > 0.1).

For an illustration of the mean effect in clusters of significant findings, please see Supplementary Figure 3C.

**Relationship to Self-Reported Perspective Taking**

By design, our ASC and control groups had comparable overall IRI scores ($t = -0.6$, $P > 0.3$). Moreover, analysis of IRI sub-scales showed that the ASC group did not differ from controls on the IRI subscales fantasy ($t = 0.4$, $P > 0.3$), empathic concern ($t = -0.88$, $P > 0.2$), and personal distress ($t = 1.56$, $P > 0.1$) after correction for multiple comparisons. As expected, however, the ASC group did score significantly lower on the perspective taking subscale ($t = -2.53$, $P < 0.04$, Bonferroni-corrected) relative to controls. Although the above analysis was based on models that statistically controlled for alexithymia, an equivalent pattern of findings was observed in a simple model that did not include TAS scores.

**Absence of Simple Cortical Thickness Differences Between ASC and Controls**

We did not observe any significant difference in mean cortical thickness between individuals with ASC and controls, regardless of whether TAS was included in the model, or not.

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**Figure 1.** Structural covariance analysis seeding from (A) dorsomedial PFC (dmPFC), (B) temporo-parietal junction (TPJ), (C) and fronto-insular cortex (FI) in 16 healthy control subjects. Significant correlations between cortical thickness in the seed and a cortical target region across the sample were interpreted as structural networks. Vertex-level colors indicate uncorrected $P$-values. Significant regions after multiple comparisons correction at a cluster level of FWE < 0.05 (thresholded using random field theory for nonisotropic images; cluster threshold $t = 2.2$, extent threshold = 2.3 resels) are surrounded by solid black outlines. To illustrate trends, findings at $P < 0.02$, uncorrected (no black outlines, semitransparent) are also shown.
(Controls mean ± SD = 2.41 ± 0.10 mm, range = 2.18–2.62 mm; ASC 2.47 ± 0.08 mm; range = 2.25–2.58, t<1, P>0.2). Analyzing vertexwise cortical thickness data, we also did not find any significant differences in vertexwise thickness between ASC and controls (Supplementary Fig. 4).

Reproducibility: Leave-One-Out Analysis

We furthermore assessed the robustness of our findings with respect to outliers. To this end, we carried out a leave-one-out approach. In this step, our main surface-based analyses (for assessing a group differences between ASC and controls as in Fig. 2; and for assessing the modulation of covariance by alexithymia as in Fig. 3) were carried out repeatedly. Each iteration involved the removal of one subject followed by the analysis on the basis of the remaining 31 subjects, leading to a total of 32 surface-based maps of findings for each analysis. This analysis revealed that our main effects remained consistent. Indeed, ASC was associated with decreased covariance of left TPJ to regions in left superior temporal and left dmPFC to left fronto-central regions in all 32 iterations (Supplementary Fig. 5A,B); likewise, alexithymia was associated with FI network decreases to supramarginal and occipital regions in all iterations (Supplementary Fig. 5C). These results suggest that our main findings, namely, a disruption of dmPFC and TPJ covariance networks by ASC diagnosis and a disruption of FI covariance networks by alexithymia, were not driven by the presence of single outliers in these samples.

Discussion

We studied structural brain networks involved in ToM and empathy in groups of autistic and typical volunteers with high and low levels of alexithymia. Our structural MRI covariance analysis aimed to test the hypothesis that autism would be associated with atypicalities in networks associated with ToM (dmPFC and TPJ), while alexithymia would be associated with deficiencies in networks centered on FI, a region subserving affective processes, such as interoception on emotions and empathy (Singer 2006, 2012; Craig 2009; Singer et al. 2009; Bird et al. 2010; Lamm et al. 2011). Results supported these predictions; reduced covariance within networks centered on both dmPFC and TPJ was observed in individuals with ASC, but no impact of ASC was observed on FI networks. Conversely, the degree of alexithymia was shown to impact upon covariance networks including FI (irrespective of whether alexithymia was accompanied by ASC), but not those networks centered upon dmPFC and TPJ seeds. Our findings, therefore, suggest a divergence between ASC and alexithymia at the level of inter-regional structural covariance networks. The observation of a dissociation between deficits in socioaffective and...
sociocognitive networks in ASC and alexithymia provide novel insights that may promote a clearer differentiation between different social cognition networks in the typical human brain.

Covariance networks in the current study were centered on 3 key regions involved in social cognition: dmPFC, TPJ, and FI. For all 3 seeds, network patterns were in overall agreement with data from previous animal tract-tracing studies (Mesulam and Mufson 1982; Mufson and Mesulam 1982; Averbeck and Seo 2008) and functional connectivity mapping in humans (Margulies et al. 2007; Deen et al. 2011; Taren et al. 2011). Indeed, dmPFC mainly covaried with lateral and medial prefrontal, and premotor/motor regions, a finding in accordance with task-free functional connectivity data showing marked intrinsic functional signal correlations between medial and lateral prefrontal regions (Taren et al. 2011), and between dmPFC and premotor areas (Margulies et al. 2007). For the TPJ, covariance patterns with lateral temporal, parietal and occipital regions, together with the precuneus resembled functional connectivity data of more posterior TPJ regions (Mars et al. 2011), with the notable exception of the medial prefrontal cortex which was only observed at a subthreshold level in our data. This lack of sensitivity may, in part, relate to the modest sample size studied in the current study. Last, FI covariance networks in our data showed a fronto-limbic and posterior pattern that again largely resembled previous functional connectivity data of this region (Cauda et al. 2011; Deen et al. 2011). In addition to extending our understanding of structural networks centered on these regions, observing divergent covariance patterns of these regions in the current study lends further support to the hypothesis that these regions play complimentary yet distinct functional roles in socioaffective and cognitive processes (Singer 2006, 2012; Van Overwalle 2009; Lamm et al. 2011; Mar 2011; Bzdok et al. 2012). Specifically, dmPFC with its more prefrontal and premotor/motor connectual pattern may, thus, represent and predict outcomes of actions, together with traits, norms, and behavioral strategies at a more abstract level (Amodio and Frith 2006; Hampton et al. 2008; Van Overwalle 2009; Yoshiida et al. 2010). On the other hand, connectivity patterns of TPJ may contribute to its role in perspective taking, self-other distinction, and early integration of sensory stimuli (Saxe and Kanwisher 2003; Decety and Lamm 2007; Mitchell 2008).

Between-group comparisons of structural covariance strength across the entire neocortex showed that the ASC group displayed reduced covariance patterns of networks centered on ToM regions. Specifically, we observed decreased dmPFC covariance to premotor cortices, and decreased TPJ covariance to large portions of lateral temporal neocortex extending into adjacent posterior parietal cortex. These findings were robust even when correcting for differences in global mean cortical thickness, suggesting that network alterations were specific to these inter-regional links and likely not driven by a diffuse mechanism that affects the connectivity fingerprint of our seeds in general. Our inter-regional structural covariance data, thus, suggest that ToM deficits in ASC are linked to an underlying reduction in brain network integration,
encompassing both core ToM networks and other areas such as the premotor cortex. Our findings are in accord with data from previous task-free functional connectivity analysis (Anderson et al. 2011; Gotts et al. 2012) and support of the concept of a general connectional alteration in ASC (Frith 2003; Just et al. 2004, 2012; Rapin and Tuchman 2008; Kana et al. 2011; Muller et al. 2011) which may involve instances of both under- as well as overconnectivity in large-scale and localized brain networks (Kana et al. 2011; Muller et al. 2011). In the current data, we specifically observed covariance disruptions indicative of underconnectivity, a finding in overall agreement of a previous study that has also suggested diffuse decreases in inter-regional covariance networks based on grey matter volume measurements (McAlonan et al. 2005). Although the physical substrate of reduced covariance and functional connectivity in ASC are unknown, our findings likely indicate abnormal maturational processes in ASC (Zilbovicius et al. 1995; Alexander-Bloch et al. 2013), possibly secondary to a developmental disruption on inter-regional brain networks in this condition. Moreover, although the relationship between covariance patterns and structural connectivity data inferred from diffusion MRI tractography may be complex (Gong et al. 2012), our data may also relate to diffusion MRI findings indicative of architectural alterations in multiple white matter tracts in children, adolescents, and adults with ASC (Barnea-Goraly et al. 2004; Sundaram et al. 2008; Bloemen et al. 2010; Fletcher et al. 2010; Jeong et al. 2011; Shukla et al. 2011). Interestingly, a recent study showed a similar structural compromise in children with autism and their unaffected siblings, suggesting a genetic basis for connectivity abnormalities in ASC (Barnea-Goraly et al. 2010).

In our group analysis, we failed to observe any noteworthy modulations by ASC alone on networks centered on FI, a region mediating interoception, emotional awareness, and empathy (Singer 2006, 2012; Craig 2009; Singer et al. 2009; Bird et al. 2010; Lamm et al. 2011). These findings, therefore, seem to diverge from previous functional MRI work on FI that has shown altered activation patterns as well as changes in its connectivity in large-scale and localized brain networks (Kana et al. 2011; Muller et al. 2011) which may involve instances of both under- as well as overconnectivity in large-scale and localized brain networks (Kana et al. 2011; Muller et al. 2011). In the current data, we specifically observed covariance disruptions indicative of underconnectivity, a finding in overall agreement of a previous study that has also suggested diffuse decreases in inter-regional covariance networks based on grey matter volume measurements (McAlonan et al. 2005). Although the physical substrate of reduced covariance and functional connectivity in ASC are unknown, our findings likely indicate abnormal maturational processes in ASC (Zilbovicius et al. 1995; Alexander-Bloch et al. 2013), possibly secondary to a developmental disruption on inter-regional brain networks in this condition. Moreover, although the relationship between covariance patterns and structural connectivity data inferred from diffusion MRI tractography may be complex (Gong et al. 2012), our data may also relate to diffusion MRI findings indicative of architectural alterations in multiple white matter tracts in children, adolescents, and adults with ASC (Barnea-Goraly et al. 2004; Sundaram et al. 2008; Bloemen et al. 2010; Fletcher et al. 2010; Jeong et al. 2011; Shukla et al. 2011). Interestingly, a recent study showed a similar structural compromise in children with autism and their unaffected siblings, suggesting a genetic basis for connectivity abnormalities in ASC (Barnea-Goraly et al. 2010).

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Analysis of self-report questionnaire data revealed that individuals with autism, regardless of whether they were also alexithymic, reported problems on the cognitive perspective-taking subscale of the Interpersonal Reactivity Index (IRI, Davis 1983); but not on the other subscales, such as empathic concern. This pattern of findings based on self-report measures alone was supportive of our structural covariance findings that showed a selective disruption of cognitive perspective taking networks in ASCs without evident disruptions in networks subserving empathy and interoception. Nevertheless, it is of note that regions such as TPJ and dmPFC do not only subserve ToM functions (Amadio and Frith 2006; Mitchell et al. 2006; Decety and Lamm 2007; Mitchell 2008; Christoff et al. 2009), as much as FI is not only involved in empathy and interoception, respectively (Craig 2009; Singer et al. 2009; Chang et al. 2012; Kelly et al. 2012; Zaki et al. 2012). Indeed, these regions are anatomically and functionally connected to multiple functional networks, allowing these regions to flexibly participate in a wide range of functional processes (Margulies et al. 2007; Cauda et al. 2011; Mars et al. 2011; Bernhardt et al. 2014). Future studies will be needed to qualify the specificity of our findings for impairments of mentalizing functions on the one hand and affective interoception and empathy on the other hand in ASCs and alexithymia. Ideally, these studies would include large batteries of behavioral tasks that quantify impairments in perspective taking capacities more objectively than the IRI self-report data used in the current study (Castelli et al. 2002; Samson et al. 2004; Dziobek et al. 2008), and that assess individual differences in a variety of further cognitive and affective domains of social cognition.

A limitation of the present work is the relatively modest sample size of our ASC and control groups. This limitation may have led a reduced power in detecting covariance alterations between groups, and also in revealing several previously observed structural covariance patterns within each group. For example, in the current sample, our controls did not show significant structural covariance patterns between FI and anterior cingulate cortices, a finding that may otherwise be expected given previous structural covariance as well as functional connectivity findings (Seeley et al. 2007, 2009). These limitations related to the small sample size are, in part, due to the conservative nature of our design, for which we had to recruit an equal amount of typical adults as well as adults with ASC that exhibited similarly high and low levels of trait alexithymia. Such a well-controlled procedure is rather difficult to achieve as the prevalence rate of people with high alexithymia in healthy populations and with low alexithymia in ASCs, respectively, is relatively low and thus oversampling in both populations was necessary. However, to assess the robustness of our findings, we performed a leave-one-out cross-validation analysis. Using such
an approach allowed us to ensure that our main effects, namely, the disruption of left TPJ and left dmPFC covariance by ASC and the modulation of FI covariance by TAS scores, remained consistent, even when individual subjects were removed from the analysis. These results make us confident that single outliers could not have driven our main findings.

In summary, our data revealed disruptions in structural covariance networks mediating ToM functions in ASC when compared with healthy controls, but not those networks relating to emotional awareness and empathy. In contrast, the degree of alexithymia in ASC and controls was associated with a modulation of FI networks mediating emotional awareness and empathy, but not of those subserving ToM. Therefore, while awaiting replication and further behavioral testing in larger samples, our data may support a dissociation between ASC and alexithymia at the level of inter-regional structural covariance networks, and also provide novel insight into variations in brain network configurations that shape different types of social cognition in adults.

Supplementary Material
Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes
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References