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Decreased centrality of cortical volume covariance networks in autism spectrum disorders

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ABSTRACT

Autism spectrum disorders (ASD) are a group of neurodevelopmental conditions characterized by atypical structural and functional brain connectivity. Complex network analysis has been mainly used to describe altered network-level organization for functional systems and white matter tracts in ASD. However, atypical functional and structural connectivity are likely to be also linked to abnormal development of the correlated structure of cortical gray matter. Such covariations of gray matter are particularly well suited to the investigation of the complex cortical pathology of ASD, which is not confined to isolated brain regions but instead acts at the systems level. In this study, we examined network centrality properties of gray matter networks in adults with ASD (n = 84) and neurotypical controls (n = 84) using graph theoretical analysis. We derived a structural covariance network for each group using interregional correlation matrices of cortical volumes extracted from a surface-based parcellation scheme containing 68 cortical regions. Differences between groups in closeness network centrality measures were evaluated using permutation testing. We identified several brain regions in the medial frontal, parietal and temporo-occipital cortices with reductions in closeness centrality in ASD compared to controls. We also found an association between an increased number of autistic traits and reduced centrality of visual nodes in neurotypicals. Our study shows that ASD are accompanied by atypical organization of structural covariance networks by means of a decreased centrality of regions relevant for social and sensorimotor processing. These findings provide further evidence for the altered network-level connectivity model of ASD.

1. Introduction

Autism spectrum disorders (ASD) are a group of neurodevelopmental conditions in which the diversity of symptoms is now viewed as a manifestation of a neural systems disorder that is accompanied by differences in brain anatomy and connectivity (Ecker et al., 2013c). Although the specific neurobiological mechanisms of ASD remain unknown, it has been noted that a

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dysregulation to the developmental trajectory of the brain is likely to affect not only the neuroanatomical makeup of isolated regions, but also the formation of the global anatomical circuitry required for functional integrative processing (Belmonte et al., 2004; Geschwind and Levitt, 2007a). However, the impact of ASD on the integrated development of the brain as a connected neural system remains largely unknown.

To date, insights into abnormal anatomical connectivity in ASD have been mainly derived from neuroimaging studies examining white-matter differences using voxel-based morphometry or diffusion tensor imaging (DTI). Combined with data from functional connectivity magnetic resonance imaging (Just et al., 2012) these findings have contributed to the general notion of global hypo-connectivity in the brain in ASD. For instance, individuals with ASD have widespread reductions in the volume of white matter during childhood, adolescence and adulthood compared to age-matched neurotypical controls (McAlonan et al., 2009; Ecker et al., 2012). Altered fiber tract connectivity in ASD is also frequently observed in the neurocognitive systems that are likely to mediate autistic symptoms and traits, such as limbic and language pathways, frontostriatal circuitry and the corpus callosum (Vissers et al., 2012). The widely spatially distributed nature of these previous findings further supports the notion of ASD as a 'developmental disconnection syndrome' (Geschwind and Levitt, 2007b). Moreover, it has also been suggested that atypical anatomical connectivity of the brain in ASD may not be restricted to white-matter but may also affect gray-matter (Abrahams and Geschwind, 2010; Ecker et al., 2013b). However, there are only a few studies to date exploring differences in putative measures of gray-matter connectivity in ASD (Zielinski et al., 2012).

In order to explore gray-matter neuroanatomy as a connected neural system, an increasing number of studies have proposed the use of structural covariance MRI techniques (Evans, 2013). The analysis of structural covariance can be used to define anatomical relationships among a set of brain regions based on the interregional statistical associations of different morphometric gray-matter features, such as cortical thickness or gray-matter density (Mechelli et al., 2005; Lerch et al., 2006; He et al., 2007). Although the neurobiological interpretation of these associations remains vague, it has been demonstrated that networks of gray-matter covariance are highly heritable (Schmitt et al., 2008), and resemble patterns of coordinated structural maturation (Zielinski et al., 2010; Raznahan et al., 2011; Alexander-Bloch et al., 2013b). Alternatively, it has been showed that structural covariance may also reflect disease propagation effects, since brain regions showing volumetric reductions in patient' populations also exhibit increased anatomical covariance (Seeley et al., 2009). Therefore, the distinction between increased correlation due to connectivity or common pathological factors is important because both measurements might represent different factors affecting the organization of gray matter covariance networks.

Given the association between synchronized developmental change in distributed cortical regions and patterns of inter-regional anatomical correlations, one would likewise expect ASD to be associated with differences in anatomical gray-matter covariance especially because the emergence of autism symptomatology occurs in a critical period for brain maturation (i.e. before the age of 3). Indeed, preliminary findings suggest that the association between behavioral autistic features and changes in brain morphology can be expressed as atypical patterns of shared anatomical variance between brain regions. For example, (McAlonan et al., 2005) reported differences in gray-matter covariance between brain regions of the limbic-striatal 'social' brain systems in children with ASD. Moreover, (Sato et al., 2013), using a machine learning approach, have shown that correlations between cortical thickness measures in frontal and temporal regions are associated with the presence of autistic symptoms. However, it has not yet been established whether differences in the organization of these gray-matter covariance networks are a characteristic feature of ASD.

Recently, complex network analysis based on graph theory has been used to characterize various organizational properties of the large-scale functional and structural networks of the brain (Alexander-Bloch et al., 2013a). These approaches use properties of network dynamics to describe the brain as a complex network composed of regions (i.e. nodes) and the connections between them (i.e. edges) (Bullmore and Sporns, 2009). The application of graph theory metrics of centrality to brain networks based on neuroimaging data have revealed a set of specific brain regions that tend to be highly connected (i.e. hubs), which express the increased capacity of these regions in interacting with many other regions, thus facilitating the integration of information across the network (Rubinov and Sporns, 2010). Regions with high centrality, however, are also likely to be more vulnerable to pathological factors, as suggested by evidence showing that hub regions are more likely to present morphometric differences than non-hubs in many brain disorders, including ASD (Crossley et al., 2014).

In the present study, we therefore examined differences in the organization of networks of cortical gray-matter volume covariance in ASD. Specifically, we investigated whether ASD would affect network centrality structure. For this purpose, we used graph theory-derived closeness centrality measures. In order to capture the influence of both connectivity-driven and disease-related factors on structural covariance, we computed two different metrics: connectivity-closeness and integrity-closeness. In neurotypicals, a central position in structural and functional networks has consistently been reported for medial parietal, frontal, and temporal regions (Bassett et al., 2008; Hagmann et al., 2008), which are classically described as multi-modal associative cortical areas involved in a broad range of cognitive processes (Mesulam, 1998). As previous findings have suggested that individuals with ASD show under-connectivity when compared to normal controls in several neurocognitive systems, we would expect to see reductions in structural covariance network centrality in those cortical regions which appear to be adversely associated with autistic symptoms and traits.

2. Method

2.1. Participants

Eighty-four right-handed men with ASD and 84 matched controls aged 18–42 years (Table 1) were recruited by advertisement and subsequently assessed at 1 of 3 centers: the Institute of Psychiatry, King's College London; the Autism Research Centre, University of Cambridge; and the Autism Research Group, University of Oxford. Approximately equal ratios of cases to controls were recruited at each site: London, 38:38; Cambridge, 31:29; and Oxford, 15:17. Data from these samples has already been published in Ecker et al. (Ecker et al., 2012, 2013a), where further details on this specific set of patients can be found.

Exclusion criteria for all participants included a history of major psychiatric disorder, head injury, genetic disorder associated with autism, or any other medical condition affecting brain function. We excluded participants with substance abuse and participants on antipsychotic medications, mood stabilizers, or benzodiazepines. All participants with ASD were diagnosed according to International Classification of Diseases (ICD)-10 research criteria and confirmed using the Autism Diagnostic Interview–Revised (Lord et al., 1994) to ensure that all participants with ASD met the

Table 1
Participants characteristics.

Characteristic	Mean (SD) [range]		
	ASD (n = 84)	Control (n = 84)	p-value
Age (years)	26 (7) [18–43]	28 (6) [18–43]	0.07
WASI full IQ score	110 (14) [73–135]	114 (12) [77–137]	0.07
ADI-R score			
Social	18.04 (5.31) [9–28)	NA	NA
Communication	14.08 (4.29) [8–25]	NA	NA
Repetitive behavior	4.97 (2.16) [2–10]	NA	NA
ADOS total score[a]	9.26 (4.49) [3–21]	NA	NA
AQ total score[b]	30.59 (8.49) [4–46]	14.48 (6.08) [3–34]	<0.001

Abbreviations: ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, Autism Spectrum Disorder, NA, Not Applicable; WASI, Wechsler Abbreviated Scale of Intelligence; AQ, Autism Spectrum Quotient.
[a] Information was available for 82 individuals with ASD.
[b] Information was available for 81 individuals with ASD and for all 84 controls.

criteria for childhood autism. All cases of ASD reached ADI-R algorithm cutoffs in the 3 domains of impaired reciprocal social interaction, communication, and repetitive behavior/stereotyped patterns, although failure to reach cutoff in 1 of the domains by 1 point was permitted. We also assessed autistic traits in both case and control participants, using the Autism Spectrum Quotient (Baron-Cohen et al., 2001).

2.2. MRI data acquisition

Details of the acquisition protocol have been previously described by (Ecker et al., 2012, 2013). All participants were scanned with contemporary magnetic resonance imaging (MRI) scanners operating at 3T and fitted with an 8-channel receive-only head coil (GE Medical Systems HDx at the Autism Research Centre, University of Cambridge and the Institute of Psychiatry, King's College London; Siemens Medical Systems Trim Trio at the Autism Research Group, University of Oxford). A specialized acquisition protocol with quantitative imaging (driven-equilibrium single-pulse estimation of T1) was used to ensure standardization of structural MRI scans across the 3 scanner platforms. This protocol has been validated and is described elsewhere (Deoni et al., 2008).

2.3. Imaging processing

Scans were initially screened by a radiologist to exclude clinically significant abnormalities and to assess the existence of movement. Scans of insufficient quality were excluded from the analysis. Brain anatomy of the data has already been investigated with other approaches in previous studies (Ecker et al., 2012, 2013a). The volume of brain regions was estimated using the FreeSurfer software package (version 5, https://surfer.nmr.mgh.harvard.edu). These well validated and fully automated procedures have been extensively described elsewhere (Dale et al., 1999; Fischl and Dale, 2000). Briefly, the analysis involved non-uniform intensity correction, intensity normalization and removal of non-brain tissue. The cortical boundaries between gray and white matter, and between gray matter and cerebrospinal fluid (CSF), were tracked, tessellated and smoothed to produce a surface mesh. Topology correction and surface deformation were applied and cortical thickness (CT) was estimated by considering the closest distance from the gray/white matter boundary to the gray matter/CSF boundary at each vertex on the tessellated surface. The cortical surface of each hemisphere was then parcellated based on gyral and sulcal landmarks according to the Desikan–Killiany atlas (Desikan et al., 2006). The surface area (SA) was calculated by taking the sum of the area of the vertices in each parcellation. Cortical volume was then calculated as the product of the SA and CT for each region. The estimated volume of these 68 parcellated regions was then used in further analyses. For each region, the effects of age were removed by using linear multiple regression (and keeping the residuals).

2.4. Structural covariance and graph measures

In order to compare differences between individuals with ASD and neurotypical controls, undirected weighted cortical networks were obtained for each group by structural covariance (pairwise Pearson correlation coefficient between the volumes of cortical regions, estimated by FreeSurfer). Since homologous-region interhemispheric centrality could be explicable by asymmetric patterns of regional covariance (Mechelli et al., 2005) rather than by any more fundamental network organizational property, we averaged the volumes of homologous regions in the left and right hemispheres. The correlation matrix of volumes within each group describes the structural covariance between regions. The correlation matrix A_i (i = 1,2; 1 = control; 2 = ASD) defines an undirected weighted graph G_i in which the strength of the edge linking one node to another is given by the absolute value of the correlation between them. For each node (i.e. brain region), closeness centrality measures were computed in order to quantify the relevance of the node in the context of the whole network (Freeman, 1978). The closeness index measures how close a node is to the rest of the nodes in the brain, and reflects the node's integration capacity (Rubinov and Sporns, 2010).

The connectivity-closeness assumes that the observed volumetric correlations mirror functional and/or structural brain connectivity. In this case, we define the distance between the nodes i and j as the inverse of the absolute values of the correlation coefficient between i and j, i.e., the greater the correlation, the shorter is the distance. Thus, the connectivity-closeness measures how close a change in the volume of one brain region is to the changes in the volumes of other regions. This coefficient is suitable in order to investigate functional network effects on structural covariance, since it reflects the efficiency of communication (i.e., shortest paths). On the other hand, integrity-closeness assumes that increased interregional correlations are primarily associated with common impairment in distinct brain regions, which is driven by pathological conditions. We defined the integrity-closeness considering the absolute values of the correlation coefficient as the distances between nodes. Note that this distance definition is the inverse of the one in connectivity-closeness. In this sense, the shortest paths reflect the less affected paths between brain regions, i.e., brain integrity at each node.

2.5. Statistical analysis

Statistical significance of the group differences of closeness measures at each node was assessed using permutation testing that allowed us to assign a probability value to each node of the graph. In the permutation test, the group labels were randomly distributed across individuals between groups, and the correlation matrix of each group were recalculated 100 000 times. This allowed for the non-parametric estimation of the null distribution for the observed group difference at each node. The significance level was set at 5% following false discovery rate (FDR) correction for multiple comparisons.

3. Results

Participant demographic characteristics are shown in Table 1. There were no differences (2-tailed) between people with ASD and

controls in age ($t166 = -1.82$; $P = .07$) and full-scale IQ ($t166 = 1.78$; $P = .07$). As expected, individuals with ASD scored high in autistic traits ($t166 = 10.36$; $P < .001$).

Table 2 presents the closeness centrality measures for all nodes in the structural covariance network estimated for each group of individuals. Significant group differences (FDR corrected $p < 0.05$) were identified only in the integrity-closeness. This measure was reduced for the ASD network in seven brain regions (Fig. 1), including the superior parietal and paracentral lobule, lingual, fusiform and parahippocampal cortices, and lateral orbitofrontal and precuneous cortices.

In a subsequent post-hoc analysis, we assessed the integrity-closeness of these regions in networks estimated for subgroups of control and ASD individuals, categorized as scoring either high or low on the Autism Spectrum Quotient (using the median as a cut-off; ASD = 31, Controls = 13). Note that an increased number of autistic traits in controls was associated with reduced integrity-closeness in the lingual and fusiform gyri (Fig. 2).

The box plots in Fig. 3 show that the pattern of structural covariance in ASD is characterized by stronger positive interregional correlations compared to controls, suggesting that the observed reduced integrity-closeness in the ASD network may indeed reflect the coordinated effects of disease-related factors on cortical volume.

4. Discussion

In this study, we examined centrality properties of networks of cortical gray matter covariance in adults with ASD and neurotypical controls using graph theoretical analysis. We derived an anatomical brain network for each group using interregional correlation matrices of cortical volumes, extracted from a surface-based parcellation scheme. Using permutation testing, we identified several brain regions in the medial frontal, parietal and temporo-occipital cortices with reductions in the proposed integrity-closeness graph-centrality descriptor within the ASD network. These findings suggest that differences in the organization of key brain regions in the structural covariance network in ASD may be influenced by common diseased-related factors affecting cortical volume correlations across multiple brain regions.

Recent theoretical models have highlighted the need to consider ASD as a disorder of several large-scale neuro-cognitive networks (Belmonte et al., 2004; Welchew et al., 2005; Geschwind and Levitt, 2007b). Our results support this notion by demonstrating structural abnormalities at the system level, generated by disruptions in connectivity between multiple spatially distributed brain regions. We found decreased integrity-centrality in sensorimotor, unimodal, multimodal and paralimbic hubs. All of these network components have been previously identified as clinical hallmarks in ASD. For example, functional differences in parahippocampal, fusiform and lingual cortices have previously been linked to impairments in face and visuospatial processing (Kleinhans et al., 2008; McGrath et al., 2012); the precuneus has a role in emotion, self-referential thinking and projection processes critical for social development (Cavanna and Trimble, 2006) and has also been linked to atypical mentalizing or theory of mind in ASD (Castelli et al., 2002; Wang et al., 2007); the paracentral and superior parietal cortices are part of the network alleged to be the basis of imitative and empathic behavior (Rizzolatti and Craighero, 2004), and have also been proposed to underpin ASD deficits in motor control,

Table 2
Integrity and connectivity-closeness values of the brain regions used to derive group structural covariance networks for ASD and control subjects. Significant differences (FDR corrected) between groups were observed only for the integrity-closeness measure. These regions are highlighted in bold.

Region	Integrity-closeness			Connectivity-closeness		
	Control	ASD	P-value	Control	ASD	P-value
Superior parietal lobule	**0.530**	**0.114**	**0.050**	0.008	0.009	0.679
Caudal anterior cingulate gyrus	0.216	0.152	0.694	0.010	0.010	0.922
Cuneus cortex	0.391	0.143	0.188	0.008	0.009	0.783
Lingual gyrus	**0.497**	**0.111**	**0.050**	0.010	0.010	0.835
Isthmus – cingulate gyrus	0.480	0.137	0.077	0.009	0.011	0.546
Rostral anterior cingulate gyrus	0.275	0.143	0.412	0.009	0.013	0.546
Middle temporal gyrus	0.171	0.097	0.438	0.011	0.013	0.582
Transverse temporal gyrus	0.441	0.158	0.140	0.008	0.010	0.546
Caudal middle frontal gyrus	0.535	0.213	0.098	0.008	0.009	0.582
Fusiform gyrus	**0.500**	**0.112**	**0.042**	0.009	0.012	0.546
Pars triangularis	0.418	0.122	0.077	0.009	0.010	0.688
Temporal pole	0.598	0.220	0.077	0.005	0.007	0.546
Postcentral gyrus	0.182	0.130	0.705	0.011	0.014	0.546
Superior temporal gyrus	0.424	0.188	0.140	0.011	0.014	0.546
Pericalcarine cortex	0.242	0.108	0.243	0.009	0.010	0.783
Entorhinal cortex	0.392	0.155	0.188	0.008	0.009	0.716
Rostral middle frontal gyrus	0.185	0.094	0.438	0.011	0.013	0.546
Pars orbitalis	0.230	0.106	0.412	0.009	0.011	0.582
Inferior temporal gyrus	0.330	0.099	0.183	0.010	0.012	0.582
Frontal pole	0.577	0.227	0.077	0.006	0.006	0.898
Posterior cingulate gyrus	0.212	0.182	0.705	0.010	0.011	0.815
Medial orbital frontal gyrus	0.257	0.095	0.305	0.010	0.014	0.546
Lateral occipital gyrus	0.209	0.116	0.522	0.008	0.011	0.546
Paracentral lobule	**0.584**	**0.134**	**0.042**	0.008	0.011	0.546
Insula	0.300	0.159	0.243	0.011	0.014	0.546
Supramarginal gyrus	0.379	0.152	0.187	0.010	0.014	0.546
Parahippocampal gyrus	**0.522**	**0.119**	**0.050**	0.009	0.010	0.679
Pars opercularis	0.456	0.096	0.077	0.008	0.011	0.546
Inferior parietal lobule	0.422	0.149	0.112	0.010	0.011	0.922
Precentral gyrus	0.259	0.162	0.577	0.010	0.013	0.546
Superior frontal gyrus	0.252	0.090	0.279	0.011	0.015	0.546
Lateral orbital frontal gyrus	**0.566**	**0.163**	**0.029**	0.012	0.014	0.679
Precuneus	0.561	0.105	0.041	0.012	0.013	0.783

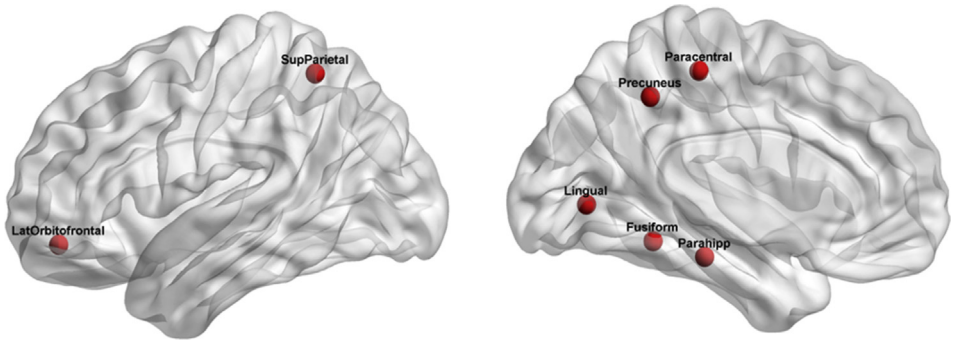

Fig. 1. Brain regions with significant reductions in integrity-closeness in the structural covariance network estimated for the group of individuals with ASD (corrected p-value < 0.05). The findings highlight an impaired central role of these regions in the context of the structural covariance network in ASD.

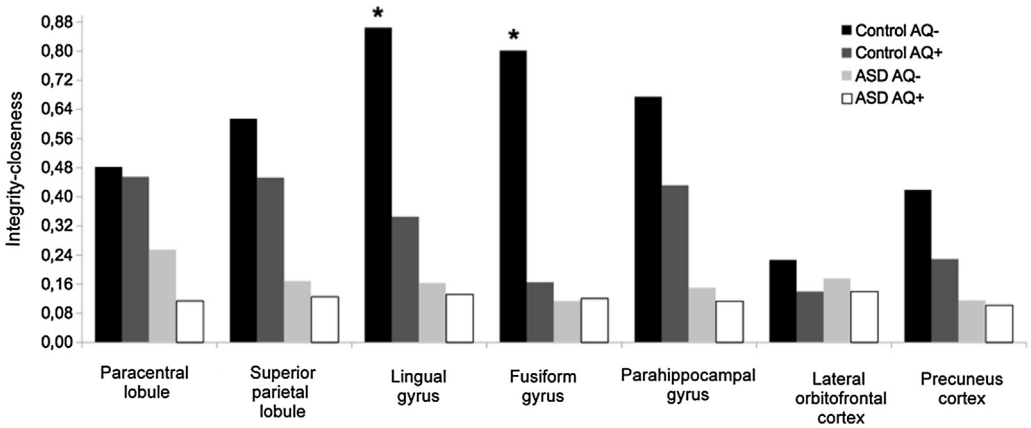

Fig. 2. Closeness centrality of regions in the covariance networks estimated for groups of neurotypical controls and individuals with ASD, with low AQ and high AQ. Note that the integrity-closeness of the lingual and fusiform cortices decreases significantly in the network derived from the group of control subjects with a high number of autistic traits. AQ− = Autism Spectrum Quotient score below the median. AQ+ = Autism Spectrum Quotient score above the median. *Control AQ− > Control AQ+.

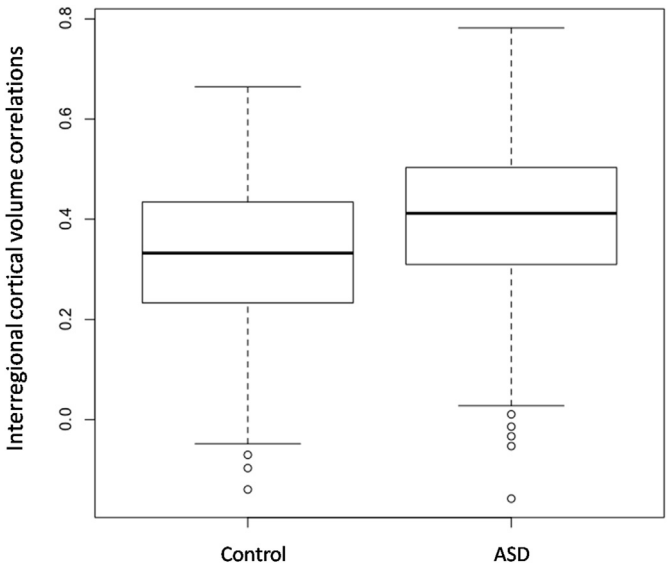

Fig. 3. Box plots of interregional cortical volume correlations across the ASD and control groups. The horizontal line near the middle of each box indicates the median, while the top and bottom borders of the box mark the 25th and 75th percentiles, respectively. The whiskers above and below the box mark the range of the distribution (maximum and minimum, respectively).

communication, and social abilities (Kana et al., 2011); finally, the orbitofrontal cortex has been implicated in repetitive behavior (Atmaca et al., 2007). Therefore, our study supports the notion that these network components are 'core' brain structures underlying ASD, and that interregional structural variations in these regions may mediate autistic behaviors and traits.

Our results, which point to a reduced integrity but no connectivity-closeness centrality of distributed hubs of the gray-matter covariance networks of the brain in adults with ASD, can also be interpreted in light of existing previous evidence showing that spatial patterns of disease-specific gray-matter differences mirror normal functional connectivity and structural covariance patterns. For example, in neurodegenerative diseases, including Alzheimer disease, it was shown a spatial colocalization of regional atrophy with the topography of structural and functional brain networks (Seeley et al., 2009). In the ASD literature, previous studies have reported ASD-associated reductions in gray matter volume (McAlonan et al., 2005), and/or cortical thickness (Hyde et al., 2010; Ecker et al., 2013a) in similar regions as those highlighted in our study, and have also reported abnormalities in the white-matter tracts connecting these core regions (Pugliese et al., 2009; Bloemen et al., 2010). Our current findings thus extend these prior regional neuroanatomical studies to the system level, although the neurobiological mechanisms linking morphological abnormalities and global network disorganization remain unknown. One possible interpretation of our findings is that patterns

of global network dysfunction arise as a result of gray matter abnormalities at the local level. For example, a recent study using proxy measures of the length of intra-area intrinsic cortico-cortical connectivity reported reductions in the wiring costs in ASD in regions that were also identified as being atypical in our study (i.e. the prefrontal, temporo-parietal and sensorimotor cortices) (Ecker et al., 2013b). These reduced cortico-cortical wiring costs (and potentially shorter intrinsic connections) may arise from a fundamentally different morphology of the brain in ASD (Nordahl et al., 2007), which in turn, can alter the topological organization of interregional gray-matter associations.

Although there remains substantial controversy regarding the nature of connectivity impairment in autism, with researchers arguing in favor of under-connectivity (Abrams et al., 2013), over-connectivity (Supekar et al., 2013) or unique patterns of both underconnectivity and over-connectivity depending on the brain region, our results might be viewed in light of under-connectivity models of ASD that are based on the notion of atypical network integration, e.g. between frontal and parietal nodes (Just et al., 2012; Rudie et al., 2012b). According to network theory, the efficient integration within the brain is supported by nodes with high centrality that facilitate the convergence of neuronal signals from different sensory modalities or cognitive domains (Van den Heuvel and Sporns, 2013). It has also been suggested that these specialized brain hubs have anatomical and functional connections that can span longer distances, thus being more metabolically costly and particularly vulnerable to insults in comparison to non-hub regions (Collin et al., 2014). ASD may therefore reflect an atypical maturation of these hubs, and consequently, the reduced network integrity-centrality may indicate a preference of these network components for establishing local over global connections (Courchesne and Pierce, 2005; Anderson et al., 2011), which may underpin many of the characteristically detail-oriented perceptual-cognitive styles observed in ASD (Happé and Frith, 2006).

It remains undetermined, however, if our observed pattern of hub disruption is a specific phenotype of ASD or whether it applies to all individuals on the autism spectrum. Indeed, a recent study (Crossley et al., 2014) revealed that various distinct psychiatric and neurological disorders are associated with damage to hubs, and a disruption of these central brain regions may therefore be a common factor contributing to wider neural dysfunction. In this regard, it would be important to associate our metrics indexing hub dysfunction with different behavioral, cognitive, and clinical phenotypes of ASD. However, as we derived a covariance network for each group separately, rather than for individuals, inter-individual differences in symptom profiles could not be statistically linked to inter-individual differences in cortical networks. We therefore also explored covariance networks for subgroups of neurotypicals, and individuals with ASD, that were categorized according to the number of ASD traits. Significant reductions in the integrity-closeness centrality of nodes in the visual cortices were associated with a greater number of ASD traits within the control but not ASD group, suggesting that subclinical features, which may also be observed in the general population, may also be expressed as differences in network organization. Future work is however needed to establish a more direct link between disruptions of hub nodes and the core clinical features of ASD.

An important future question for the presented results derived from the structural covariance analysis is also the extent to which the observed GM correlation network differences in ASD compare with those derived from other neuroimaging techniques, such as DTI or functional connectivity. Among the few studies that have examined alterations of local graph-theoretical metrics in ASD so far, one study using functional networks reported increased centrality for nodes within the occipital and sensorimotor networks, and reductions in the fronto-parietal and cingulo-opercular networks (Itahashi et al., 2014). Another study suggested that ASD may have differences in the balance of local and global efficiency between functional and structural networks derived from diffusion-weighted imaging during development (Rudie et al., 2012a). However, node-centrality measures derived from different imaging modalities have yet to be compared in the context of ASD. Future investigations of this nature would thus provide important new insights into the highly inter-dependent nature of cortical structure and brain function, particularly in individuals with ASD, which show highly heterogeneous abnormalities in complex cognitive functions that are thought to result from subtle and spatially distributed neuroanatomical differences arising during development.

Our interpretation of the current findings must also consider that the neurobiological mechanisms that result in interregional gray-matter volumetric correlations are not fully understood. Previous investigations note that phenomena of structural covariance may be attributable to activity-related morphological plasticity (i.e. learning) (McAlonan et al., 2005). There are also suggestions about the contribution of heredity (Thompson et al., 2001) as well as environment-related plasticity (Draganski et al., 2004). As ASD is a group of conditions in which both causative and phenotypic heterogeneity is a dominant theme (Abrahams and Geschwind, 2008), it is therefore difficult to speculate about what specific factors may cause the shared neuroanatomical variation observed here. However, our findings lend further support to the notion that differences in brain anatomy can be captured by the structural organization of the brain (He et al., 2007).

The present study has some methodological limitations. First, we investigated the organization of structural covariance networks in a sample of high-functioning men diagnosed with the ADI-R as having ASD. As ASD is a spectrum condition, our sample therefore represents a specific subpopulation of the autistic phenotype and results might not generalize to other groups on the autism spectrum (eg, individuals with intellectual disability) or to females with the condition. Second, structural connectivity was inferred from measures of covariation among regional cortical volumes. Evidence suggests that the two constituents of gray matter volume (i.e. cortical thickness and surface area) have different cellular components and developmental determinants (Rakic, 1988). Future work is thus needed to determine which specific aspects of the cortical morphology are causing the observed differences in inter-regional structural covariance in ASD. In addition, the volumes of homologous regions were averaged across hemispheres, preventing us from examining laterality effects in network organization. Evidence suggests that an abnormal lateralization pattern of functional connectivity between language and default mode regions exists in ASD (Nielsen et al., 2014), but the extent to which these differences can be observed at the level of structural networks is currently unknown.

In conclusion, our results suggest that adults with ASD have a consistent pattern of decreased integrity-closeness centrality in multiple distributed cortical regions within the context of structural covariance networks, which is in agreement with theories of ASD as a brain disconnectivity/underconnectivity syndrome.

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Contributors

CE, DM, DA, CM, ED and MRC AIMS Consortium designed the study and wrote the protocol. MRC AIMS Consortium collected the data. JB, WEC, CE and JRS wrote the manuscript. JRS undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

Conflicts of interest

None.

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