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Idiosyncratic organization of cortical networks in autism spectrum disorder

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ABSTRACT

Neuroimaging studies of Autism Spectrum Disorder (ASD) have yielded inconsistent results indicating either increases or decreases in functional connectivity, or both. Recent findings suggest that these seemingly divergent results might be underpinned by greater inter-individual variability in brain network connectivity in ASD. We tested the hypothesis that the spatial patterns of intrinsic connectivity networks (ICNs) are more idiosyncratic in ASD, and demonstrated that this increased variability is associated with symptomatology.

We estimated whole brain functional connectivity based on resting state functional magnetic resonance imaging (fMRI) data obtained from the Autism Brain Imaging Data Exchange I & II (ABIDE I & II) repository: 422 (69 females) participants with ASD and 424 (59 females) typically developing (TD) participants between 6 and 30 years of age. We clustered individuals' patterns of resting state functional connectivity into seven networks, each representing an ICN, and assessed the heterogeneity of each vertex on the cortical surface across individuals in terms of its incorporation into a particular ICN.

We found that the incorporation of individual anatomical locations (vertices) to a common network was less consistent across individuals in ASD, indicating a more idiosyncratic organization of ICNs in the ASD brain. This spatial shifting effect was particularly pronounced in the Sensory-Motor Network (SMN) and the Default Mode Network (DMN). We also found that this idiosyncrasy in large-scale brain network organization was correlated with ASD symptomatology (ADOS).

These results support the view that idiosyncratic functional connectivity is a hallmark of the ASD brain. We provide the first evidence that the anatomical organization of ICNs is idiosyncratic in ASD, as well as providing evidence that such abnormalities in brain network organization may contribute to the symptoms of ASD.

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by difficulties in social communication and restricted, repetitive behaviors and/or interests (DSM-5). The neurobiological basis of ASD remains unclear. Increasing evidence, however, indicates that alterations in brain connectivity are an important contributing factor in ASD (Dajani and Uddin, 2016; Kennedy and Courchesne, 2008; Minshew and Williams, 2007). Although many studies have reported atypical functional connectivity in the ASD brain, they are often contradictory regarding whether this involves hypoconnectivity, hyperconnectivity, or both (for review see Mohammad-Rezazadeh and Frohlich, 2016).

Intrinsic connectivity networks (ICNs), derived from large-scale correlation structure in spontaneous hemodynamic activity, appear to be altered in ASD with little consensus on the direction of the alterations. Some studies indicate a pattern of underconnectivity (Cheng et al., 2017; Damarla et al., 2010; Just et al., 2012). Others suggest a general or local increase in connectivity (Cerliani et al., 2015; Supekar et al., 2013), and some studies report both hypoconnectivity and hyperconnectivity (Lynch et al., 2013; Maximo et al., 2014; Monk et al., 2009; Müller et al., 2011), or no differences in global connectivity (Nomi and Uddin, 2015; Tyszka et al., 2014).

Recent research suggests that rather than a characteristic directionality of atypicalities of brain network connectivity, such as a consistent increase or a decrease across individuals with ASD, the critical characteristic of the ASD brain is variability of functional connectivity across individuals, often referred as idiosyncrasy (Hahamy et al., 2015). In this view, it is the idiosyncrasy of connectivity that contributes to ASD symptomatology. This is an attractive hypothesis in that apparently contradictory findings might be reconciled by supposing that greater variability of connectivity is characteristic of the ASD brain, rather than under- or over-connectivity *per se*. This perspective is also consistent with

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reports of increased variability across trials in ASD. For example, Dinstein et al. (2012) reported non-significant differences in the evoked related amplitudes but statistically significant lower reliability in the ASD group. Spatio-temporal responses during stimuli have also been reported to be more variable across ASD individuals (Byrge et al., 2015; Hasson et al., 2009). In the view that idiosyncrasy underlies apparently contradictory functional connectivity results in ASD, increased temporal variability of correlation strength between nodes of a network could also drive differences between groups in either direction, particularly when sample sizes are low. Studies of dynamic functional connectivity in ASD have reported typical connectivity but increased intra-individual variability that seems to be a contributing factor in static functional underconnectivity results in ASD (Falahpour et al., 2016). From this perspective, inherent idiosyncrasy or variability in brain network communication may be a largely overlooked feature of the ASD brain which underpins observed symptomatology, and could be mischaracterized as either underconnectivity or overconnectivity in particular studies.

It remains unclear if idiosyncratic functional connectivity is manifested in the spatial organization of large-scale ICNs which are implicated in cognition, development and atypical neurocognitive function in ASD. Specifically, it is not clear if the incorporation of specific anatomical locations into particular ICNs is more variable in ASD. In this study, we tested the hypotheses that the spatial organization of ICNs in ASD is more heterogeneous, and that such idiosyncrasy in spontaneous large-scale network connectivity is associated with ASD symptomatology. To test these hypotheses, we used a clustering algorithm similarly applied in Yeo et al. (2011) with a large data-set from the Autism Brain Imaging Data Exchange (ABIDE I & II) repository: 422 (69 females) participants with ASD and 424 (59 females) typically developing (TD) participants between 6 and 30 years of age. This method is better suited for estimating the spatial variability of ICNs relative to more conventional approaches such as seed-based connectivity analysis. Seed-based connectivity analysis can be biased by the seed selection, and reflects connectivity of one seed with other voxels. Conversely, clustering analysis parcellates brain areas into clusters that highly correlate between each other and renders a spatial map of the topographies of the networks which can be used to measure spatial consistency across subjects. Recent studies on cingulate cortex connectivity (Balsters et al., 2016a,b) and basal ganglia connectivity (Balsters et al., 2016a,b) support the evidence that in ASD brain parcellation techniques improve network detection in comparison with seed-based approaches due to more variable spatial topographies. To assess if ICNs are spatially shifted in ASD, spatial maps were derived for every subject and we measured how much they differed from their group norm map to obtain a variability measure. This variability was later correlated with age, IQ and ADOS.

Material and methods

Data acquisition

Data were selected from the Autism Brain Imaging Database Exchange (ABIDE; Martino et al., 2014) repository (ABIDE I and II releases), which combines data across multiple imaging centers (Table 1). We employed structural (MPRAGE T1) and resting state functional MRI scans. Details of acquisition and protocols are available at http://fcon_1000.projects.nitrc.org/indi/abide/. Based on visual inspection, we excluded participants with compromised quality of structural MRI scans, such as having movement artifacts or not having full brain coverage. The final sample included 424 typically developing (TD) individuals (aged between 6 and 64, mean 16.05 ± 7.19 years of age; 59 females) and 422 participants with ASD (aged between 6 and 64, mean 16.56 ± 8.66 years

Table 1
Description of number of participants per center, mean and standard deviation of age, total Framewise Displacement (mean displacement between volumes) and IQs. For the total means we indicate if statistically significant (*). Full names of the centers available at: http://fcon_1000.projects.nitrc.org/indi/abide/.

Centers	Group	Subjects	Age		Framewise Displacement		Full IQ		Verbal IQ		Performance IQ	
			Mean	STD	Mean	STD	Mean	STD	Mean	STD	Mean	STD
KKI	ASD	18	9.96	1.52	1.09	0.75	96.61	18.00	N/A	N/A	N/A	N/A
	CTR	21	9.97	1.16	0.88	0.42	112.48	9.32	N/A	N/A	N/A	N/A
MAX MUN	ASD	22	29.55	13.86	0.62	0.39	109.83	15.64	N/A	N/A	111.50	10.85
	CTR	24	24.64	8.77	0.67	0.78	111.75	9.29	N/A	N/A	110.87	13.82
NYU I & II	ASD	93	13.14	7.10	0.45	0.37	107.84	16.30	105.90	15.76	108.59	17.20
	CTR	93	15.79	6.28	0.43	0.37	113.53	12.74	113.25	12.16	110.63	13.56
OHSU	ASD	12	11.43	2.18	0.18	0.07	106.01	22.01	N/A	N/A	N/A	N/A
	CTR	14	10.09	1.12	0.49	0.51	114.97	11.12	N/A	N/A	N/A	N/A
OLIN	ASD	15	17.33	3.17	1.03	1.40	109.70	22.10	N/A	N/A	N/A	N/A
	CTR	14	16.93	3.63	0.81	0.52	116.36	13.94	N/A	N/A	N/A	N/A
PITT	ASD	27	19.13	7.43	0.55	0.41	110.63	14.22	107.11	13.75	111.41	13.74
	CTR	26	19.07	6.69	0.53	0.35	110.04	9.56	107.46	11.08	109.73	9.16
SBL	ASD	14	35.29	10.76	0.39	0.26	109.20	13.63	111.36	12.57	114.27	12.74
	CTR	13	35.38	5.22	0.41	0.20	N/A	N/A	N/A	N/A	N/A	N/A
SDSU	ASD	11	15.25	1.70	0.54	0.33	118.88	18.91	117.00	18.42	116.00	17.13
	CTR	12	14.08	1.94	0.54	0.47	108.20	11.01	106.30	10.88	108.50	12.47
STANDFORD	ASD	15	10.23	1.63	0.62	0.44	114.71	15.44	113.64	20.30	112.71	12.52
	CTR	17	9.92	1.58	1.04	2.03	114.12	13.60	114.35	16.83	111.00	16.60
TRINIT	ASD	22	16.81	3.17	0.64	0.53	108.91	15.55	107.86	14.35	107.57	15.72
	CTR	25	17.08	3.77	0.47	0.55	110.88	12.20	109.60	13.70	110.32	10.95
USM	ASD	28	23.46	8.33	1.15	1.94	99.72	16.56	94.98	19.27	104.65	16.73
	CTR	25	21.29	8.35	0.70	0.58	115.36	15.14	113.60	16.00	112.84	14.19
YALE	ASD	26	12.75	3.11	0.62	0.51	95.26	21.68	97.11	23.30	92.26	19.61
	CTR	27	12.68	2.75	0.54	0.38	104.96	17.39	106.79	15.97	101.25	16.51
UCLA	ASD	47	13.12	2.42	0.88	0.99	100.87	13.35	102.10	13.70	100.21	13.97
	CTR	42	12.93	1.91	0.57	0.79	106.48	10.67	107.19	11.22	104.43	11.62
LEUVEN	ASD	27	18.03	5.08	0.51	0.31	109.43	13.09	100.19	20.35	103.37	17.41
	CTR	29	18.69	5.04	0.62	0.52	114.80	12.86	115.84	11.12	107.42	13.47
UM I & II	ASD	45	14.88	1.55	0.63	0.44	114.12	12.92	115.85	18.22	112.38	15.49
	CTR	42	16.71	3.97	0.78	1.13	111.12	9.51	113.48	11.85	107.62	12.13
Total	**ASD**	**422**	**17.36**	**4.87**	**0.66**	**0.61**	**107.45**	**16.63**	**106.65**	**17.27**	**107.91**	**15.26**
	CTR	**424**	**17.02**	**4.14**	**0.63**	**0.64**	**111.79**	**12.03**	**110.79**	**13.08**	**108.60**	**13.13**
Significance			**$p > .05$**		**$p > .05$**		**$p < .01$***		**$p < .01$ ***		**$p < .05$ ***	

of age; 69 females). Participants per center where matched and a chi proportion statistical test indicated that there were no significant differences in the proportion of ASD and TD participants across centers. The Autism Diagnostic Observation Schedule (ADOS) scores were provided for 158 participants for ADOS total, 134 for ADOS communication and social, and 109 for ADOS behavioral scores. For the ADOS multilinear regression, 109 participants with ASD were included.

Data preprocessing

Structural MRI images were preprocessed using FreeSurfer 5.1 (Fischl, 2012). Functional MRI data was preprocessed using the Configurable Pipeline for the Analysis of Connectomes (C-PAC, Cameron et al., 2013). The first four volumes were removed to ensure magnetic stability was reached. All volume slices were time corrected and head motion was regressed on 24 parameters (Friston et al., 1996). Sources of spurious signal were removed, regressing out the global, linear, motion and quadratic signals, CompCor was applied calculating 5 components derived from nuisance signals from the white matter and cerebrospinal fluid. Then the functional images were temporally filtered between 0.1 Hz and 0.01 Hz.

Next, we co-registered functional images with the cortical surfaces, defined by gray-white boundary and pial surface, using FreeSurfer. Specifically, a boundary-based registration algorithm was applied (Greve and Fischl, 2009), available in the FsFast FreeSurfer toolbox (http://surfer.nmr.mgh.harvard.edu/fswiki/FsFast). Centers for which acquisition parameters led to the algorithm failure to co-register were discarded. Individuals with a cost function above 0.6 were visually inspected and realigned if necessary or discarded. The surface functional MRI was smoothed with an FMHW of 5 mm for a better group-space co-registration and then was projected into a common group space composed of 10,242 vertices per hemisphere, ~ 4 mm mesh (fsaverage5). For our analysis, the non-cortical vertices were masked out, rendering 18,715 vertices for the whole cortex (See Fig. 1 for data analysis overview).

Network clustering

Brain functional connectivity was parcelled into seven clusters based on correlations between fMRI signals. We first selected the time series of 1170 regions of interest (ROIs), which were sampled equidistantly on the cortical surface at approximately 16 mm apart. Then, for each ROI the Pearson correlation was calculated with all the vertices of the cortical surface (18715 vertices), resulting in an 18715×1170 correlation matrix. Each 18715 vertices were associated with a point in a 1170-dimentional space. A von Mises-Fisher clustering algorithm (Lashkari et al., 2010) was applied to parcel the cortical vertices into seven clusters, separately for each participant, similar to what was done in a previous study (Yeo et al., 2011), except that individual's correlation matrices were used rather than a group-averaged one. Using this technique, each vertex in the cortex was assigned to a label associated with one cluster. The number of clusters selected was set at seven following the successful application of this technique in Yeo et al. (2011).

To start the clustering algorithm from a common point rather than a random location, we computed the posterior assignment probabilities (the probabilities of vertices to belong to a cluster) using a group correlation matrix and used its values as initialization parameters (*a priori* assignment probabilities) for the individual correlation matrices. First, all the individual correlation matrices were summed to form a group correlation matrix and we clustered the group activity obtaining the initialization parameters. Then, for every participant we initiated the algorithm with a common assignment probability distribution that was then iteratively adjusted to the correlation values of the participant. We obtained one parcellation for every participant, and to match the cluster labels between participants, separately for each group, a Hungarian Matching combinatorial algorithm was applied, available in the toolbox Thomas-Yeo-lab toolbox (https://github.com/ThomasYeoLab/CBIG/). Once the parcellations for every participant were obtained, three analyses were performed: a network proportion analysis, a group mode matching analysis and a network area analysis.

Network proportion analysis

In the network proportion analysis, we tested the hypothesis that the anatomical organization of ICNs is more idiosyncratic in ASD by analyzing the proportion of participants for which any given vertex is associated with a specific network in each group. Alternatively stated, this investigates if a particular ICN membership of a given cortical location is more variable across individuals with ASD, relative to TD participants. The number of participants for whom a given ICN label was assigned to each vertex was calculated and a chi-square test was used to test the equality of proportions. Thus, for every vertex we had the number of times a cluster was labeled across participants, i.e. for vertices in the visual area the percentage of participants with a visual network label would be around 80–90% and in frontal vertices should be less than 5%. To find associations between network-specific idiosyncrasy and symptomatology, we measured how many vertices in each participant matched the group mode for a given network. This measure was then correlated with ADOS scores and a multilinear regression was conducted

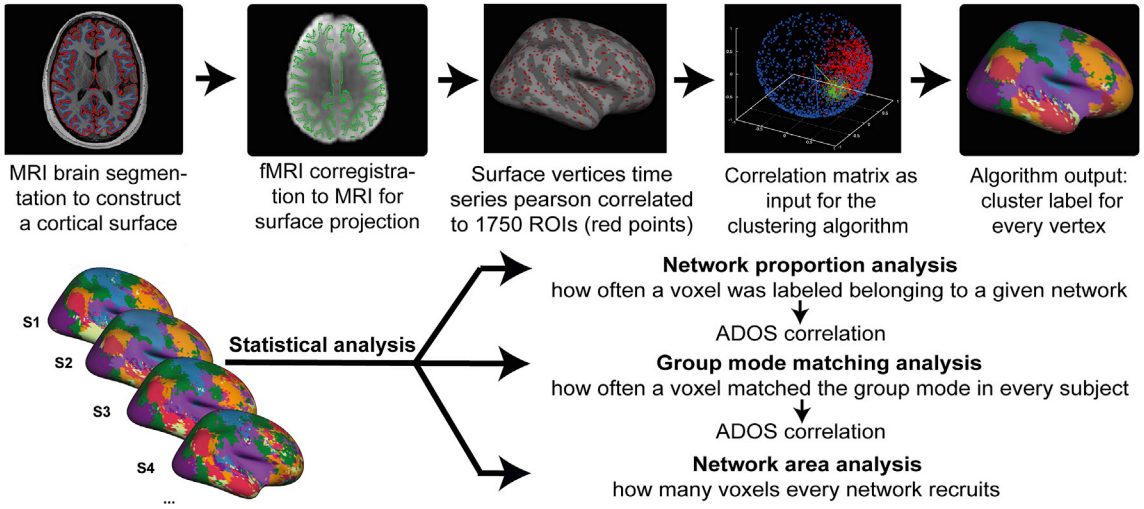

Fig. 1. Overview of the data analysis.

to find which subscales predicted better this measure.

Group mode matching analysis

In the group mode matching analysis, we aimed to determine on a whole-cortex level if certain vertices were more stable or variable in terms of being assigned to a specific network, and more variability would indicate higher idiosyncrasy across participants. We explored the mode of the ICN cluster label at each vertex and its deviance to support the so-called 'regression to the mean' effect. This effect, as described by Hahamy et al. (2015), refers to individual topographical misalignments rather than magnitude changes that in the group level is reflected by group statistical differences such as increase or decrease in connectivity when apparently these differences are driven by topographical misalignments. For each group, the most frequent label (mode) in each vertex was calculated, and the group spatial organization of the cortical networks was obtained. To investigate group differences, a chi-square test was conducted, separately for each vertex, to test for equality of proportions of the participants matching the mode for a given vertex. The chi-square test p-values were corrected for multiple comparisons using FDR with a $q = 0.05$. Then, correlations and multilinear regression with ADOS subscales for the ASD group were conducted, as well as associations between age and IQ with the number of vertices in a given participant that matched the mode.

To further test if the results of this analysis were driven by inter-site variability, we repeated this analysis calculating the mode for every center and matching each participant to its center mode. To determine if the observed results might be driven by structural differences we also measured major sulcus-gyrus differences between groups by using Freesurfer sulcal values, wherein each vertex a value is given by its distance of the midpoint between a sulci and gyri, and positive if it is closer to the sulcus and negative if to the gyrus. We performed a T-test for every vertex and corrected with FDR $q = 0.05$.

Network area analysis

In the network area analysis, we aimed to assess if any group differences observed in the previous analyses were driven by a reduced incorporation of vertices into a given cluster or if the number of vertices in a given cluster are equal between groups but more spatially variable. The null hypothesis would suggest that there is an increased or decreased overall connectivity in some networks, for example, that some networks recruit more vertices in one group than the other, thus not supporting the idiosyncrasy hypothesis. Alternatively, a similar recruitment number would support the 'regression to the mean' effect where spatial misalignment would drive the results obtained in the previous analysis. To test this, we measured how many vertices were incorporated into each network for every participant, a network-specific consistency score, and performed a two-sample *t*-test comparing the number of vertices recruited for each cluster between the two groups.

Analysis of covariance of the consistency scores

For every subject, we obtained a consistency score of how many vertices matched the group mode, for the group mode matching analysis, and for network proportion analysis we obtained a consistency score for the SMN and for the DMN, the two networks statistically significant in the network proportion analysis. In order to control for confounding variables, we conducted an ANCOVA for each of the three consistency scores. As potentially confounding variables we included mean total Framewise Displacement, which is the mean of the sum of the absolute values of the derivatives of six realignment parameters between one volume and the previous one and converted to total millimeters moved, IQ (full, verbal and performance), age and center.

Results

Network proportion analysis

In the network proportion analysis, we obtained the percentage of times a given cluster was labeled at every vertex. For both TD and ASD groups we found that the seven clusters corresponded well to the well-established topology of the ICNs representing the visual network (VN), somatomotor network (SMN), dorsal attention network (DAN), ventral attention network (VAN), frontoparietal network (FPN), default mode network (DMN) and the limbic system network (LSN) (Fig. 2).

The network proportion analysis revealed network-specific idiosyncrasy in the SMN and DMN in ASD, in which significant vertices were labeled more often as belonging to these networks in the TD group (Fig. 3). The VAN had 27 significant vertices out of 2723 total vertices from the group mode map, and was discarded as non-significant given that the significant vertices were very few <0.01%. In the SMN the vertices which differed significantly between groups were located mostly in the mid precentral gyrus and the postcentral gyrus. Out of 3215 vertices labeled as SMN in the group mode map, 512 were significantly different between the two groups. In the DMN the areas which significantly differed between the ASD and TD groups were in the posterior cingulate cortex, frontal pole, angular gyrus and anterior temporal pole. These differences were represented by 931 vertices significantly different out of 4080 vertices labeled as the DMN in the mode group map. In both cases, these two networks were labeled more frequently in the control group, i.e. in the ASD these vertices were less consistent across participants. All reported differences were significant $p < .05$, FDR corrected.

Group mode matching analysis

In the group mode matching analysis, a group spatial map was obtained by taking the most frequent label for every vertex (the mode). The group mode maps for both groups were visually similar, although some areas incorporated into the DMN in TD participants were instead associated with the LSN in the ASD group. This was particularly pronounced in the anterior temporal pole and the superior temporal gyrus. The control group mode map is highly qualitatively similar to the results obtained in Yeo et al., (2011), validating the method employed in this study, and replicating the results of Yeo et al. (2011) using an independent dataset.

The group modes were used to measure how often participants matched the group norm. We obtained a consistency score by calculating how many vertices in each participant matched the group mode. This mode matching analysis revealed similar differences as found in the previous analysis. Out of 18715 total vertices 2452 were identified as significantly different between TD and ASD groups ($p > .05$, FDR corrected). The significant vertices were concentrated in the posterior cingulate cortex, somatomotor network, mid-frontal, angular gyrus and anterior temporal pole, all of them with a higher proportion in the control group (Fig. 4). Conversely, in the calcarine sulcus, some vertices are significantly more consistent within the ASD group ($p < .05$, FDR corrected). In the network proportion analysis, however, we did not find evidence of higher stability in these visual areas, thus we did not consider this small cluster as relevant in our analysis.

When matching each participant to its own center mode to assess if the results depicted in Fig. 4 were driven by intersite variability, the overall significant vertices found in Fig. 4 C did not differ substantially albeit diminished activation and percentages of statistical difference (see Supplementary Fig. 1). Given that the group mode is more representative than the specific center mode, we decided to use the group mode as our core analysis. In addition, we performed a sulci-gyri comparison between groups and no vertex survived multiple comparison correction, and before FDR correction the voxels below $p = .05$ did not resemble the significant areas found in this analysis, thus we have evidence that our results are not driven by coarse anatomical differences.

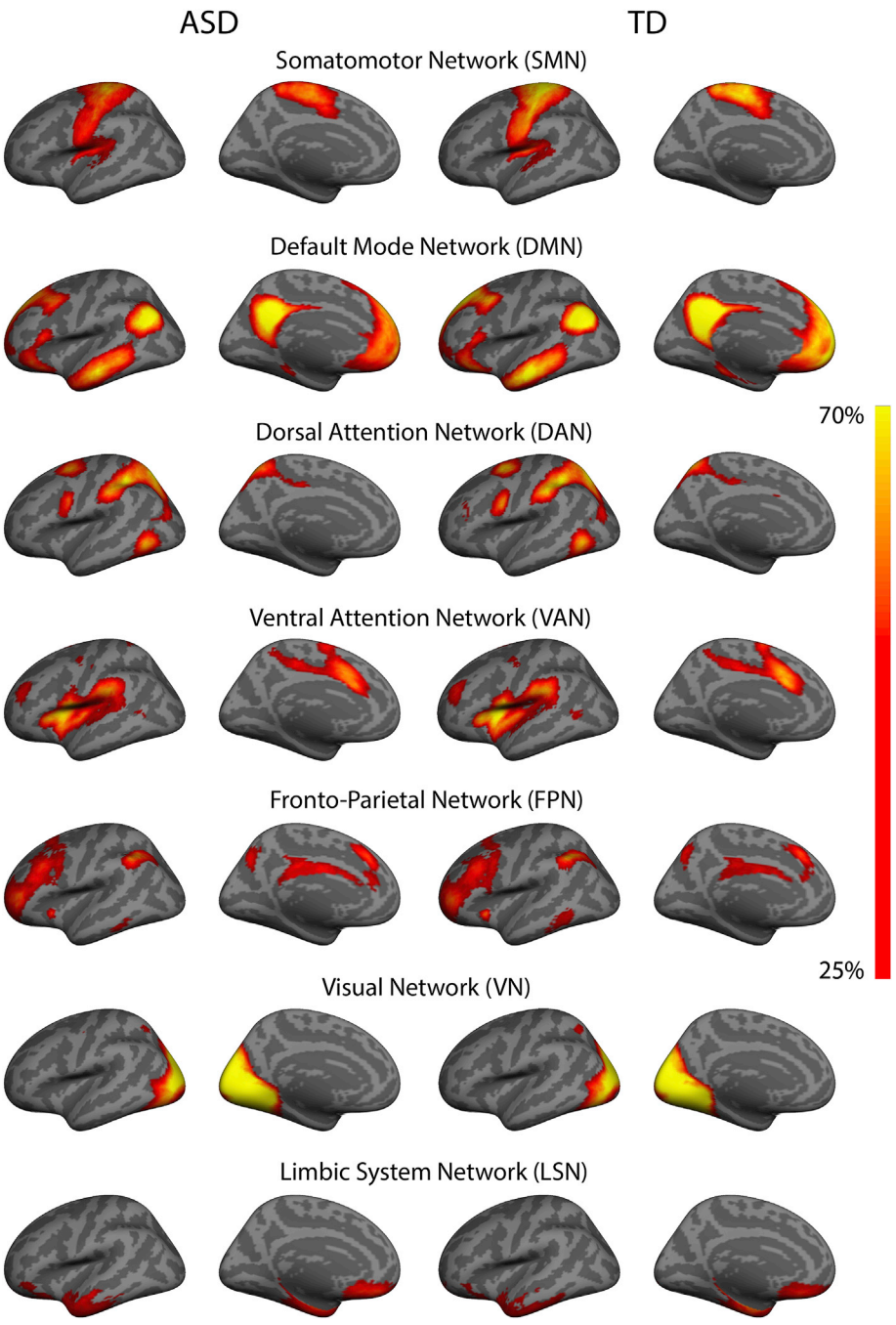

Fig. 2. Spatial maps for every network showing the percentage of participants that matched each network for a given voxel in the left hemisphere for ASD (left two columns) and TD (right two columns).

Correlations with ASD symptomatology

We tested if cortical and network-specific consistency scores (how many vertices matched the group mode) of the participants were associated with age or IQ, but no significant correlations were observed. We found significant correlations with ADOS scores for whole-cortex consistency and for the SMN network consistency score, but not for the DMN with only a trend of $p = .09$. For the whole brain and the SMN, correlations indicated a negative association with ADOS scores, the more consistency the lower the ADOS scores, i.e. more idiosyncrasy is associated to higher symptomatology (Table 2). To assess the contributions of ADOS subscales, a multilinear regression was conducted. ADOS total was discarded due to collinearity (it is the sum of ADOS social and communication). For the two consistency scores, we found that ADOS social can significantly predict it independently of the other predictors (Table 2).

Network area analysis

In the network area analysis, we aimed to identify if the differences found in the previous analyses in the SMN and DMN vertices were driven by spatial variability generating a 'regression to the mean' in which the differences were caused by topographical misalignment or if these differences were driven by reduced recruitment of vertices by these networks. For each network, we measured how many vertices were recruited in every participant. All networks did not differ significantly between groups except the limbic system, adjacent to the DMN with a $p < .01$ and a mean difference of 138 more vertices recruited in the ASD, and the DMN with a p-value $< .01$ with a mean difference of 150 more vertices in the control group.

A few vertices of the DMN were labeled as the LSN in the ASD group and visual analysis of the mode group suggested that this exchange

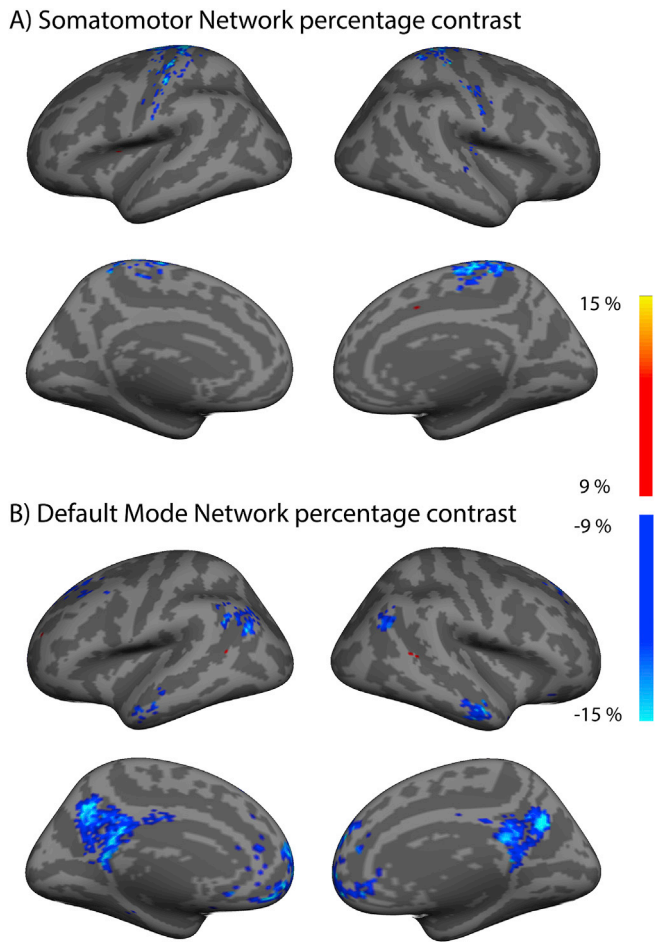

Fig. 3. Chi-square contrast of the frequency of a voxel being labeled as belonging to a specific network across groups. Blue represents increased idiosyncrasy of ICN membership in ASD: A) the SMN contrast, B) the DMN contrast.

occurred in the anterior temporal lobe. To test this, we measured how many vertices labeled as the DMN in the TD group mode were labeled as the LSN in the ASD group mode. The results indicated that in the ASD group mode 233 vertices were labeled as the LSN whereas in the TD group mode they were labeled as DMN (Supplementary Fig. 2). Furthermore, in the previous two analyses, these areas were not statistically significant, indicating that this reduced recruitment in the boundary between the DMN and LSN is not generalizable in the rest of the cortex. Taking this into account, there is evidence that the total area of the ICNs are not significantly different in ASD supporting the hypothesis that the differences found in the previous analysis are driven by spatial variability rather than spatially reduced recruitment.

Table 2
Correlation values for ADOS scales and multilinear regression relation, p-value and significant independent predictors for whole-cortex and SMN consistency scores. P-values for bi-variate correlations are not multiple comparisons corrected.

	ADOS bi-variate correlation			
	Total	Communication	Social	RR Behavior
Whole-cortex consistency	$r = -0.32$ $p < .001$	$r = -0.23$ $p < .01$	$r = -0.36$ $p < .001$	$r = -0.26$ $p < .01$
SMN consistency	$r = -0.27$ $p < .001$	$r = -0.17$ $p < .01$	$r = -0.30$ $p < .001$	$r = -0.19$ $p < .01$
	ADOS multilinear regression			
	Relation	p-value	Indep. predictor	p-value
Whole-cortex consistency	$R = .46$	$p < .001$	ADOS Social	$p < .001$
SMN consistency	$R = .34$	$p < .01$	ADOS Social	$p < .01$

Analysis of covariance of the consistency scores

We conducted three ANCOVAs, one for the global consistency score (how well subjects matched the group mode), one for the SMN and one for the DMN consistency score (how well subjects matched the group network). For the global consistency scores, we obtained a $F = 23.21$, $p < .001$, for the SMN an $F = 33.05$, $p < .001$, and for the DMN an $F = 20.67$, $p < .001$. For the three ANCOVAs the interactions group*-center were not significant in any of them.

Discussion

The present study provides the first demonstration that the organization of ICNs in neuroanatomical space is idiosyncratic in ASD. This idiosyncrasy was concentrated in regions associated with the DMN and SMN, suggesting that variability of connectivity involving regions typically associated with these networks may be particularly relevant for altered brain function in ASD. We also show for the first time that the degree of ICN idiosyncrasy is associated with ASD symptomatology. These findings support the view that idiosyncratic spatial organization of cortical networks may contribute to ASD and its symptoms, and that the often-contradictory neuroimaging findings in ASD may be reconciled through a framework of considering between-participant variability in functional connectivity rather than overconnectivity or underconnectivity *per se*.

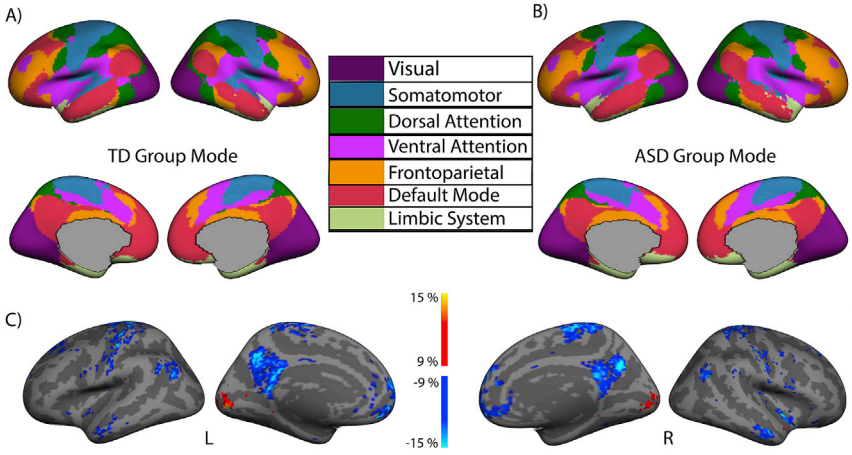

Fig. 4. Group spatial map obtained by taking the most frequent network label in each vertex for A) the TD group, and B) the ASD group. C) Chi square contrast revealing group differences mostly in the DMN and SMN being more stable in the TD group and some visual vertices more stable in the ASD group.

We performed three analyses in which we measured how frequently a particular anatomical vertex was labeled as belonging to a particular network across individuals, how much participants matched the group mode labeling for every vertex, and how many vertices were incorporated into each network in each participant. All three analyses supported the hypothesis of increased heterogeneity in the organization of cortical networks in ASD. For the network area analysis, a small number of vertices in the ASD group were labeled as limbic system whereas in the TD group were labeled as DMN, although these vertices were not related to areas with more idiosyncrasy, it is known that the areas labeled as limbic system are more prone to signal drop out, field inhomogeneities and distortions by air-filled cavities (Devlin et al., 2000). Notwithstanding these small number of vertices, we found that increased network idiosyncrasy was not explained by reduced or increased number of vertices recruited, suggesting spatial shifting of ICNs in the ASD group, particularly in areas belonging to the SMN and DMN, networks particularly relevant in ASD symptomatology.

The DMN has been linked to social and self-referential cognitive processes including the ability to attribute mental states to other people, the ability to understand narrative and figurate communication, future prospecting, emotional processing and tasks involving mentalizing (Buckner and Carroll, 2007; Cato et al., 2004; Gilbert et al., 2006; Greicius and Menon, 2004; Iacoboni et al., 2004; Miall and Robertson, 2006). Our results indicate that some areas of the DMN showed reduced propensity towards organizing into a coherent network that is consistently expressed across individuals in the ASD group. Specifically, the precuneus, medial prefrontal cortex, anterior temporal lobe and angular gyrus showed more idiosyncratic incorporation into functional networks in the ASD group. Previous studies in ASD have reported alterations in these areas of the DMN, such as medial prefrontal cortex and precuneous with overconnectivity and underconnectivity (Fishman et al. 2014); decreased global, ipsilateral and contralateral functional connectivity in the medial prefrontal cortex, precuneous, anterior cingulate and sensorimotor areas (Lee et al, 2016); decreased connectivity in the mirror system and social cognition-related midline structures with reduced gyrification (Bos et al., 2015; Schaer et al., 2013); and decreased connectivity between DMN hubs, the precuneous and medial prefrontal cortex, revealed by ICA derived sub-networks of the DMN (Assaf et al., 2010). Based on the results of our analysis, alterations in these DMN areas cannot be explained merely by reduced within-network connectivity, as between groups the number of vertices recruited per network did not vary significantly. Our results suggest that the topographies of the networks are rather more idiosyncratic in terms of their organization in neuroanatomical space in ASD, and when group averaging this variability might lead to increased or decreased connectivity.

Another network found more idiosyncratic in ASD was the SMN which might be related to sensory-motor alterations in ASD. People with ASD often experience impairments in domains such as motor control, skilled movements and postural stability (Fournier et al., 2010; Haswell et al., 2009), and somatosensory alterations that include hypersenstivity and hyposensitivity to pain, temperature and textures (Baum et al., 2015; Rogers et al., 2003; Tomchek and Dunn, 2007). Neuroimaging studies have found connectivity abnormalities in the SMN during motor task performance (Mostofsky et al., 2009), in vibrotactile stimulation with reduced feedback connectivity at rest (Khan et al., 2015), reduced sensorimotor GABA inhibition that leads to altered excitatory-inhibitory balance (Puts et al., 2017), decreased inter-hemispheric connectivity between sensory motor areas (Anderson et al., 2011; Martino et al., 2014), and increased connectivity between primary sensory and subcortical ICA derived networks associated with symptom severity (Cerliani et al., 2015). Hahamy et al., 2015, found evidence for both under- and over connectivity involving sensorimotor cortex caused by topographic distortions across ASD participants. Our clustering analysis also showed that the SMN is more idiosyncratic, especially involving the post-central gyrus, and also indicated that this idiosyncratic organization of the SMN is associated with ADOS symptomatology.

A multilinear regression indicated that ADOS scores are significant predictors of whole-brain network idiosyncrasy and that ADOS Social is a significant predictor of whole-brain idiosyncrasy when considering covariance with the other subscales. At the level of individual ICNs, we found significant relations with ADOS scores in the SMN, but not the DMN. This association with symptomatology suggess that the idiosyncratic organization of the SMN might be relevant for difficulties in social cognition in individuals with ASD. Based on this hypothesis, idiosyncratic organization of ICNs would be a direct manifestation of symptomatology, and idiosyncrasy could potentially be a reliable indicator of symptom severity. Another plausible hypothesis could be compensatory mechanisms including neuroplasticity, wherein ASD individuals use other neuronal resources as a substitute for impaired neurotypical neural resources. For example, some studies found disrupted cortical representations of the body in ASD (Coskun et al., 2009; Marco et al., 2011). Accordingly, individuals with ASD may apply alternative strategies which require alternative patterns of functional brain activations and network connectivity. For example, different forward and inverse models of action control may be used to overcome disrupted body representations and successfully perform a task. The ADOS correlation with whole-cortex and SMN consistency scores support the first hypothesis that idiosyncrasy reflects pathological functional organization of the nervous system whereas DMN consistency not associated with ADOS might suggest the latter hypothesis of compensatory plasticity. It is likely, however, that the DMN reflects both symptomatology and compensatory plasticity as the ADOS relation with whole-cortex consistency score (which includes the DMN) is higher ($R = 0.46$) than the ADOS relation with SMN ($R = 0.34$), part of the former ADOS relation could be related with vertices in the DMN. Future research will help to refine and understand the origin and causes of variability in ASD. This paper brings more evidence of idiosyncrasy in ASD and its relation to symptomatology, supporting previous finding in homotopic connectivity (Hahamy et al., 2015), maturational homotopic connectivity (Kozhemiako et al. submitted), idiosyncratic cerebellar neuromagnetic rhythms (Vakorin et al., 2017), idiosyncratic brain patterns less correlated across participants as a function of social comprehension impairment (Byrge et al., 2015), and increased variability in dynamic functional connectivity in ASD (Chen et al., 2017).

The present results indicate increased variability in the organization of functional brain networks neuroanatomical space in ASD. However, there are some noteworthy limitations in the present investigation. In this study, a clustering algorithm was used in which an *a priori* condition was set to partition the brain into seven clusters. Although this normalizes differences across participants and scan centers, it is constraining the solution in a manner that may not best reflect the data in all participants. As well, use of the ABIDE database confers certain advantages, such as a large sample that represents the heterogeneity of ASD better than a single-centre study, however, it also imposes certain limitations, such as differences among sites in inclusion/exclusion criteria, and higher variability across centers caused not only by scan parameters but age, social status and other demographic variables.

We demonstrate here that the organization of ICNs in anatomical space is idiosyncratic is ASD, and that these alterations are associated with ASD symptomatology. This expands upon earlier work by demonstrating that such idiosyncrasy is evident for large-scale network coordination understood to play a critical role in brain function, its development, and its disruption in numerous neurological and neuropsychiatric populations, including ASD. These findings support the recently emerging view that ASD may be a disorder of idiosyncratic functional brain network connectivity.

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These authors report no biomedical financial interests or potential conflicts.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2018.01.022.

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