

Cortical Dysconnectivity Measured by Structural Covariance Is Associated With the Presence of Psychotic Symptoms in 22q11.2 Deletion Syndrome

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ABSTRACT

BACKGROUND: 22q11.2 deletion syndrome (22q11DS) is the third-largest known genetic risk factor for the development of psychosis. Dysconnectivity has consistently been implicated in the physiopathology of psychosis. Structural covariance of cortical morphology is a method of exploring connectivity among brain regions that to date has not been employed in 22q11DS.

METHODS: In the present study we employed structural covariance of cortical thickness to explore connectivity alterations in a group of 108 patients with 22q11DS compared with 96 control subjects. We subsequently divided patients into two subgroups of 31 subjects each according to the presence of attenuated psychotic symptoms. FreeSurfer software was used to obtain the mean cortical thickness in 148 brain regions from T1-weighted 3T images. For each population we reconstructed a brain graph using Pearson correlation between the average thickness of each couple of brain regions, which we characterized in terms of mean correlation strength and in terms of network architecture using graph theory.

RESULTS: Patients with 22q11DS presented increased mean correlation strength, but there was no difference in global architecture compared with control subjects. However, symptomatic patients presented increased mean correlation strength coupled with increased segregation and decreased integration compared with both control subjects and nonsymptomatic patients. They also presented increased centrality for a cluster of anterior cingulate and dorsomedial prefrontal regions.

CONCLUSIONS: These results confirm the importance of cortical dysconnectivity in the physiopathology of psychosis. Moreover they support the significance of aberrant anterior cingulate connectivity.

Keywords: Anterior cingulate, Connectome, Graph theory, Salience network, Schizophrenia, Structural covariance

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22q11.2 deletion syndrome (22q11DS) is a genetic disorder caused by a 1.5- to 3-Mb deletion of chromosome 22 (1) affecting approximately 1 per 4000 live births (2). It is associated with a complex somatic and neuropsychological phenotype. Affected patients present mild cognitive impairments together with a high prevalence of psychotic symptoms (3). By adulthood approximately 30% to 40% of patients meet diagnostic criteria for a schizophrenia spectrum disorder (4–6). 22q11DS is therefore one of the three highest risk factors for the development of psychosis (7). Furthermore, these patients are typically diagnosed before the onset of a full-blown psychosis, making 22q11DS a valuable model to study the earliest stages of the disease.

Neuroimaging studies in psychosis have contributed overwhelming evidence for the importance of dysconnectivity in the physiopathology of this disease (8). According to this hypothesis, psychosis is better understood as a disorder of the

communication among regions, rather than as a dysfunction affecting separate regions independently (9). The introduction of connectomics has provided new tools to test this dysconnectivity hypothesis (10–13). This approach consists in comprehensively describing the connections among brain regions. Connectome networks are complex and can be analyzed quantitatively and objectively using graph theory (14,15). A major contribution of connectomics is the notion that physiological brain networks display a balance between local segregation and global integration (16). Local segregation is thought to reflect information processing occurring in sub-communities of functionally specialized regions. Global integration is thought to reflect the efficient communication between these multiple subnetworks. An altered balance between integration and segregation has repetitively been found in patients with psychosis. Indeed, structural connectome studies have consistently reported deficits of global

integration mirrored by an abnormal increase in local segregation (8,17,18).

At the same time, morphological studies of psychosis have consistently reported alterations of cortical morphology, with widespread reductions of gray matter volume and thickness (19–23). Additionally, longitudinal studies have shown accelerated trajectories of cortical thinning (20,24). These mass univariate approaches, however, consider each region or cluster independently (25). It is therefore still unclear whether dysconnectivity and altered cortical morphology are somehow related or if they represent independent pathogenic factors.

Structural covariance is an alternative method for exploring cortical connectivity that could help address this issue (26) based on the assumption that regions that are functionally and structurally connected tend to covary in their morphology (27–30). It has been proposed that these structural correlations are due to the mutually trophic effect of axonal connections (31,32). Alterations of axonal connectivity could therefore directly influence cortical morphology (33), determining altered patterns of structural covariance. In the field of psychosis, structural covariance studies have reported reductions of integration and increased segregation (34,35), in line with consistent reports from tractography-based studies (8,17,18).

In 22q11DS, previous structural connectome studies from our group have confirmed deficits of integration and an increased segregation (36,37). A recent review has also highlighted the predominant impairment of long-range and midline connections (38). In parallel, morphological studies have confirmed that altered cortical morphology is associated with the psychosis phenotype (39–44). To date, however, no study has employed structural covariance in 22q11DS. This approach could help to further elucidate the role of dysconnectivity in the physiopathology of psychosis. Moreover, it could provide evidence for a relationship between dysconnectivity and altered cortical morphology.

In the present study we employed graph analysis to study structural covariance of cortical thickness in a large population of patients with 22q11DS. Patients were divided into two subgroups of 31 subjects each on the basis of the manifestation of attenuated psychotic symptoms. We hypothesized that the architecture of the brain graph would be disrupted in 22q11DS when compared with healthy control subjects, with reduced global integration and increased segregation, replicating results from tractography-based studies (36,37). We hypothesized that this alteration would be relevant to the

psychosis phenotype selectively affecting the subgroup of patients suffering from moderate-to-severe prodromal psychotic symptoms.

METHODS AND MATERIALS

Participants

Cohorts of Patients With 22q11DS and Healthy Control Subjects. All patients with 22q11DS were recruited at the University of Geneva School of Medicine in the context of a prospective longitudinal study [details about recruitment can be found in (42,45)]. In total, 108 patients were included in the present study (range, 5.4–47.4 years of age); 96 control subjects (range, 5.1–58.8 years of age) were recruited among healthy siblings of patients ($n = 46$) and from the Geneva state school system ($n = 50$). Control subjects were screened for past or present history of psychiatric or neurological disorders.

The groups did not differ in terms of age ($p = .66$), gender ($p = .63$), or handedness as defined by the Edinburgh laterality quotient ($p = .93$). Only full-scale IQ was significantly lower in patients compared with control subjects ($p < .001$; see Table 1 for details).

The presence of DSM-IV psychiatric disorders was assessed by means of the Diagnostic Interview for Children and Adolescents-Revised (46) and the psychosis supplement from the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (47) for individuals below 18 years of age. For adult participants, we used the Structured Clinical Interview for DSM-IV Axis I Disorders (48). In addition, the presence of prodromal psychotic symptoms was assessed by means of the Structured Interview for Prodromal Symptoms (49). Written informed consent was obtained for all participants, and the study was approved by the Institutional Review Board of the University of Geneva School of Medicine.

Subdivision of the Patients With 22q11DS According to the Presence of Psychotic Symptoms.

Patients were classified according to the Structured Interview for Prodromal Symptoms. Those with a score of 3 or higher on one or more positive symptom items were considered to have at least attenuated psychotic symptoms. This threshold corresponds to the intensity of symptoms necessary to have at least an attenuated positive symptoms prodromal syndrome, aside from the criteria of time and frequency (49). This threshold,

Table 1. Demographic Features of Different Populations and Relative and Statistical Significance of Differences

	Entire Cohort			PPs vs. NPPs vs. Control Subjects					
	Control Subjects	Patients With 22q11DS	p	Control Subjects	PPs With 22q11DS	NPPs With 22q11DS	PPs vs. NPPs, p	PPs vs. Control Subjects, p	NPPs vs. Control Subjects, p
Gender, n (Male/Female)	96 (49/47)	108 (49/59)	.63	31 (16/15)	31 (17/14)	31 (12/19)	.20	.80	.31
Age, Years	18 ± 5	18.47 ± 8.6	.66	19.0 ± 5.7	19.1 ± 6.1	18.5 ± 5.4	.68	.95	.71
IQ	109.8 ± 12.6	74.5 ± 12.7	<.0001 ^a	107.7 ± 12.9	73.4 ± 11.8	74.0 ± 12.0	.98	<.0001 ^a	<.0001 ^a
Right Handed, %	83	83	.93	86	76	83	.34	.19	.71

Values are expressed as mean ± SD except where indicated.

Between-group differences were tested with a two-sample t test for continuous variables and a chi-square test for discrete variables.

NPPs, nonpsychotic patients; PPs psychotic patients; 22q11DS, 22q11.2 deletion syndrome.

^aStatistically significant between-group difference.

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although less specific than traditional at-risk mental state criteria, was better suited for our mostly subclinical population, allowing comparisons among larger subgroups. Also, it was employed in a previous study of functional connectivity in 22q11DS (50). We excluded 32 patients that were too young or cognitively impaired to perform a Structured Interview for Prodromal Symptoms evaluation. Thirty-one patients presented at least attenuated psychotic symptoms (range, 12.2–34.3 years of age), and 2 of them met the DSM-IV criteria for diagnosis of a psychotic disorder. From here on, in the interest of brevity, this group will be referred to as patients with psychotic symptoms (PPs). A description of the positive symptom profile is reported in Table 2 and is consistent with previous reports on 22q11DS (6).

From the remaining 45 nonsymptomatic patients we excluded 11 patients who had presented prodromal psychotic symptoms at an earlier visit, according to longitudinal information that was available for 31 of 45 of these patients.

The remaining 34 patients were considered not to present attenuated psychotic symptoms (range, 10.1–43.34 years of age; nonpsychotic patients [NPPs]). We excluded the 2 youngest subjects and the oldest subject from the NPPs group to uniform the sample size and age range (11.6–34.8 years of age) with the PPs group. We also selected a subgroup of 31 demographically matched control subjects (range, 12.1–32.3 years of age). The groups did not differ in terms of age ($p > .83$), gender ($p > .27$), or handedness ($p > .37$), but differed in neuroleptic medication (8 of 31 in the PPs group vs. 0 of 34 in the NPPs group; $p = .001$). However, regressing for the effect of neuroleptic medication did not significantly modify our results, as reported in Supplemental Table S10. Full-scale IQ was lower in both subgroups of patients compared with control subjects ($p < .001$) but was not different between subgroups. See Tables 1 and 3 for details.

Image Acquisition and Processing

T1-weighted images were acquired employing a three-dimensional volumetric pulse sequence with a Siemens Trio 3T scanner (Siemens Corp., Erlangen, Germany). Sequence parameters were the following: repetition time = 2500 ms, echo time = 3 ms, flip angle = 8°, acquisition matrix = 256 × 256, field of view = 22 cm, slice thickness = 1.1 mm, 192 slices. The images were imported in the FreeSurfer software package, version 5.1 (Athinoula A. Martinos Center for Biomedical

Table 2. Profile of Positive Symptoms Among Symptomatic Patients ($n = 31$)

	Frequency of Moderate-to-Severe Positive Symptoms in Symptomatic Subgroup
Perceptual Abnormalities	22
Persecutory Ideas	17
Delusional Ideas	14
Disorganized Communication	6
Grandiosity	1
Two Above-Threshold Symptoms	9
Three Above-Threshold Symptoms	5
Four Above-Threshold Symptoms	4

Table 3. 22q11DS Demographics

	Entire Cohort	Psychotic	Nonpsychotic
ADHD	21	7	6
Any Mood Disorder	15	13	4
Any Anxiety Disorder	42	18	13
Other Psychiatric Disorders	18	4	5
Any Psychotic Disorder	15	8	0
≥1 Psychotropic Medication	17	9	1
Medications			
Methylphenidate	10	2	7
Anxiolytics	10	3	0
Antidepressants	12	5	3
Melatonin	5	3	2
Neuroleptics	14	8	0
Antiepileptics	3	2	0

The “Other Psychiatric Disorders” category includes oppositional disorders as well as enuresis and encopresis.

ADHD, attention-deficit/hyperactivity disorder; 22q11DS, 22q11.2 deletion syndrome.

Imaging, Charlestown, MA; <http://surfer.nmr.mgh.harvard.edu/fswiki>) to semiautomatically reconstruct precise three-dimensional representations of the internal and external cortical surfaces (51). The mean cortical thickness was extracted in a total of 148 regions using FreeSurfer software and Destrieux parcellation (52).

Structural Covariance Estimation

The effects of age, gender, and overall mean cortical thickness were regressed from the mean thickness of each brain region, and the residuals of this regression were used for the subsequent steps of the analysis. As a supplementary analysis the effects of age² and age³ were added as additional covariates. Pearson correlations between the cortical thickness of each couple of brain regions were used to construct a 148 × 148 cortical covariance matrix for each group (26).

The mean strength of the correlations was measured in terms of the number of connections that were significant at $p < .05$ before and after correcting for multiple comparisons with false discovery rate (FDR) (53) and as the mean r coefficients for both positive and negative correlations. Individual correlations were compared using Fisher’s r to z transformation and applying both FDR and network-based statistics (54) correction for multiple comparisons. The r coefficients were also averaged across connections among 12 bilateral brain lobes and after merging bilateral hemispheres. We also compared intralobar as opposed to extralobar connections.

To characterize the architectural features of the connectivity matrices we used graph theory. This mathematical framework conceptualizes the human connectome as being composed of nodes, represented by the 148 regions of the Destrieux parcellation, and edges, represented by the Pearson correlation coefficient between measures of cortical thickness. All the graph theoretical analyses were performed using the functions included in the Brain Connectivity Toolbox for MATLAB (The MathWorks, Inc., Natick, MA; <http://www.brain-connectivity-toolbox.net>). Graph analysis can be performed with either a weighted or a binary approach. Here we opted for the latter, as

we were interested in investigating the architectural features of the connectivity matrices that, irrespective of differences of overall connectivity strength, are known to influence weighted graphs (55). For binarization we employed a minimum spanning tree thresholding (55). We tested the graphs of the range of thresholds that yielded fully connected nonrandom graphs. Randomness was defined as a small-world index of less than 1.2 (56,57). All measures were then plotted as a function of the connectivity threshold and were considered equivalent to the area under the curve or integer of this function. We also employed two alternative approaches to normalize for connectivity differences, described in Supplemental Tables S7 and S8. Graph analysis was performed considering only positive correlations given that the overlap with structural connectivity has been shown to be largely specific to positive correlations (29). We include comparisons of network architecture of negative connections in Supplemental Table S4.

Graph theoretical measures were estimated at the global level on the entire connectivity matrix as well as at the local level of individual nodes. Four global measures were used: 1) mean path length, 2) efficiency, 3) mean clustering coefficient, and 4) modularity. Mean path length quantifies the average minimum number of edges separating each couple of nodes of the network. Efficiency is the inverse of mean path length and therefore expresses how efficiently the organization of the edges limits the mean distance separating individual nodes. Mean clustering coefficient measures how many of the neighbors of each node are also neighbors to each other. Modularity is a property of graphs by which subsets of nodes, defined as modules, are more densely connected to each other than to the rest of the network. Modularity can be quantified as the proportion of edges connecting nodes within each module, with respect to the total number of edges. Modularity and mean clustering coefficient are considered measures of segregation of a network, whereas efficiency and mean path length are considered measures of integration. Additionally, betweenness centrality was computed as a measure of the contribution of each local region to the architecture of the network. Betweenness centrality is defined as the fraction of shortest paths between nodes passing through each node and therefore expresses how central a node is in the network. Differences in two other commonly used local graph theoretical measures (local clustering coefficient and connectivity degree) are reported in Supplemental Figures S2, S4, and S5.

Statistical Analysis

First, patients with 22q11DS were compared with control subjects. Statistical significance was established through permutation testing. Specifically we regressed for the effects of age, gender, and mean cortical thickness in each original population and then randomly attributed each subject's residuals to two groups, for 2000 iterations. At each iteration we recomputed our measures, thereby obtaining a distribution to test our null hypothesis. Residuals, instead of the original measures of cortical thickness, were permuted due to significant age by diagnosis interactions that we observed across our groups (reported in Supplemental Figure S3), in line with previous literature (42,44). We therefore preferred to avoid regressing for the effect of age in permuted groups because

this effect would not be uniform across subjects, potentially leading to biased residuals. Subsequently, the two subgroups of patients were compared with each other and with the subgroup of control subjects using the same approach. All analyses were corrected for multiple comparisons using FDR at $p < .05$ (53) and corrected p values are reported.

RESULTS

22q11DS Patients Versus Control Subjects

Mean Correlation Strength. Patients presented increased mean correlation strength as revealed by a higher number of connections that remained significant after correction for multiple comparisons ($n = 200$ in control subjects vs. $n = 474$ in patients with 22q11DS; $p = .04$). Mean r coefficients were not significantly different. Differences affecting individual connections did not survive correction for multiple comparisons with both FDR and network-based statistics, nor did differences between mean interlobe connections (Supplemental Tables S5–S7).

Network Architecture. Global architectural parameters were not significantly different between the two groups.

Local Betweenness Centrality. No region displayed differences in betweenness centrality after correction for multiple comparisons with FDR.

Alterations Related to the Presence of Psychotic Symptoms

Mean Correlation Strength. PPs showed an increase in mean correlation strength compared with both control subjects and NPPs, as revealed by an increase in the number of significant connections ($n = 1086$ vs. $n = 750$ [control subjects; $p = .01$] vs. $n = 816$ [NPPs; $p = .028$]) as well as mean positive ($r = .1775$ [$p = .01$] vs. $r = .1564$ [control subjects; $p = .01$] vs. $r = .1598$ [NPPs]) and negative ($r = -.1768$ [$p = .029$] vs. $r = -.1628$ [control subjects; $p = .03$] vs. $r = -.1564$ [NPPs]) r coefficients (see Figure 1). Differences affecting individual connections did not survive correction for multiple comparisons with FDR or network-based statistics, nor did differences between mean lobar connections (Supplemental Tables S5–S7). However, when merging bilateral hemispheres, PPs showed a significant increase in the mean strength of more local intralobar as opposed to extralobar connections, compared with both control subjects ($p = .005$) and NPPs ($p = .01$).

NPPs were not significantly different from control subjects in terms of number of mean correlation strength.

Network Architecture. PPs presented increased mean path length compared with both control subjects ($p = .039$) and NPPs ($p = .03$). When compared with control subjects, PPs also showed increased modularity ($p = .0498$) and mean clustering coefficient ($p = .01$; see Figure 1). Differences in network architecture between PPs and NPPs were reduced to trend level ($p = .067$) when adding age² and age³ as additional covariates (Supplementary Table S12). Mean architectural

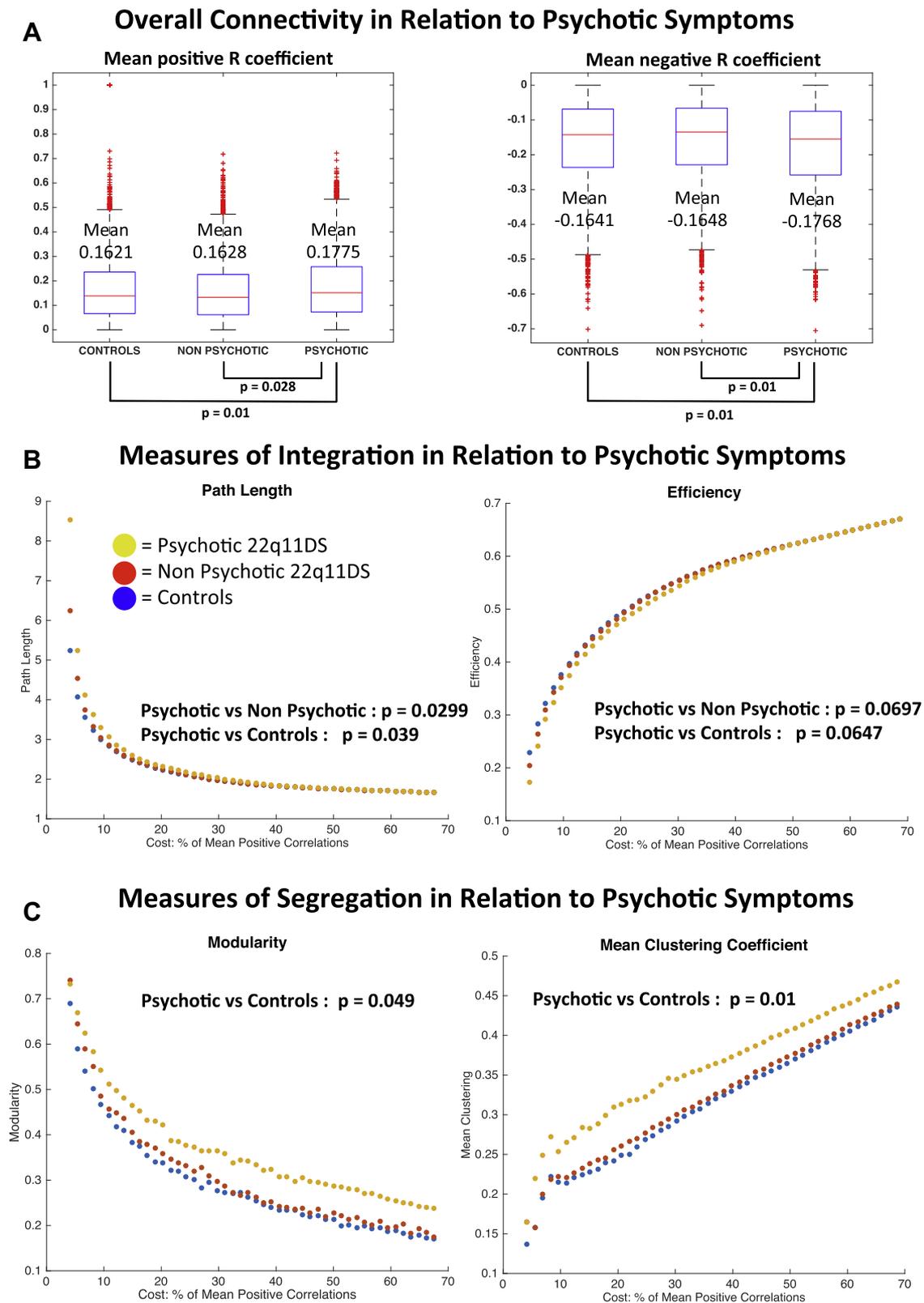


Figure 1. Alterations of mean overall connectivity and network architecture in relation to psychotic symptoms. **(A)** Alterations of mean overall connectivity for both positive and negative correlations in relation to psychotic symptoms. **(B)** Measures of network integration in relation to psychotic symptoms, plotted as a function of network sparsity. **(C)** Measures of network segregation in relation to psychotic symptoms, plotted as a function of network sparsity. 22q11DS, 22q11.2 deletion syndrome.

measures in NPPs were not significantly different from control subjects.

Local Graph Theoretical Measures. We observed increased centrality in PPs, compared with both control subjects and NPPs, in a cluster of regions (shown in Figure 2), represented by the right superior frontal gyrus and anterior and middle cingulate gyri. This pattern was conserved but did not survive FDR correction when regressing for age² and age³ (Supplementary Figure S9). Betweenness centrality was not different in NPPs compared with control subjects.

DISCUSSION

In the present study, we employed structural covariance of cortical thickness to investigate the connectivity patterns of a large population of patients with 22q11DS. We specifically explored the role of dysconnectivity in the pathophysiology of psychosis. We observed a pattern of increased mean overall connectivity coupled with decreased architectural integration and increased segregation that was specific for patients with at least attenuated psychotic symptoms (PPs). PPs also presented increased centrality for right dorsomedial prefrontal and anterior cingulate regions. These results confirm the importance of cortical dysconnectivity in the pathophysiology of psychosis.

Differences in Mean Correlation Strength

Patients with 22q11DS presented an increase in mean correlation strength compared with control subjects. This difference was selectively driven by PPs whose mean correlation strength was increased compared with both control subjects and NPPs.

Our results are in line with several previous studies examining structural covariance in the field of psychosis. Indeed increased covariance was found among the frontotemporal (58–63), fronto-occipital (64), and frontoparietal regions (65) as well as between the anterior cingulate and prefrontal regions (59). Furthermore, increased mean correlation strength was found in a population suffering from first-episode psychosis (66). However, the previous literature also reports several inconsistencies, with various accounts of decreased connectivity (67–69) particularly in cohorts composed of chronic patients [for a review, see (26)].

Nonetheless, several non-mutually exclusive interpretations can be given to explain the increased mean correlation strength that we report in PPs. First, psychosis has consistently been shown to impact cortical morphology with reductions of both cortical volume and cortical thickness (19–23) both in nonsyndromic psychosis and in 22q11DS (39–43). It has been proposed that a common vulnerability to an insult affecting a subset of regions could determine the presence of an increased covariance among these regions (59). Therefore, two regions that are morphologically independent from one another in control subjects and in NPPs could be correlated in PPs, because both regions are similarly affected by the disease. The network approach offered by structural covariance provides additional insight compared with classical morphological studies. Indeed it was proposed by Friston (9) that morphological alterations are the consequence of alterations involving the connectivity between regions, rather than of insults affecting different regions separately. Our results lend support to this hypothesis, considering that architectural alterations that we found in PPs, and that we discuss in the following section, were consistent with those reported in tractography-based studies of psychosis. The preferential

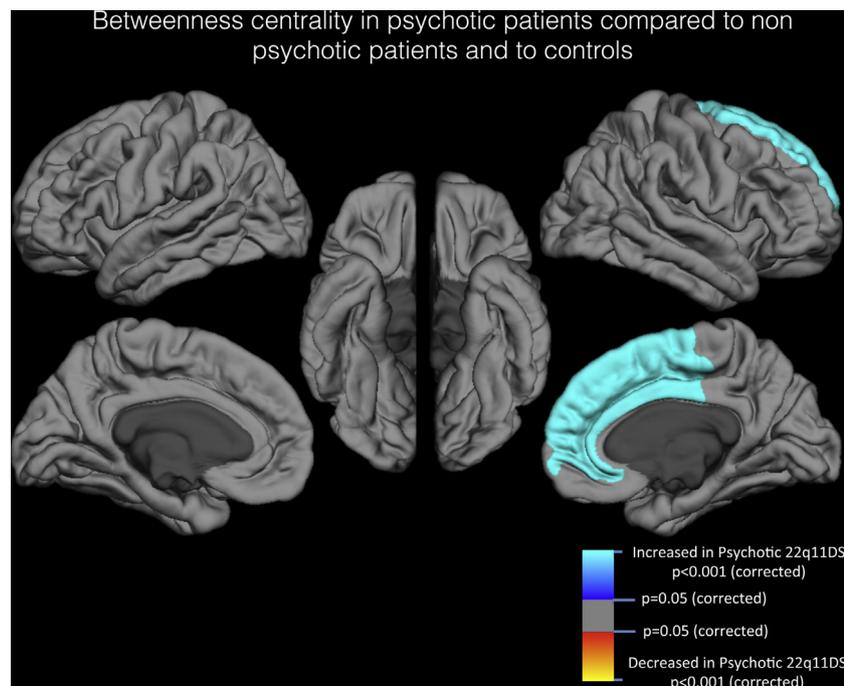


Figure 2. Alterations in betweenness centrality in psychotic patients compared with both nonpsychotic patients and control subjects. 22q11DS, 22q11.2 deletion syndrome.

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increase in local intralobar as opposed to extralobar correlations is also consistent with previous reports of white matter dysconnectivity in 22q11DS (70). These parallelisms could suggest that aberrant connectivity may play a role in shaping the morphological alterations characterizing 22q11DS and psychosis, possibly through alterations in the mutually trophic effect of axonal connections.

The relationship between local network architecture and alterations in mean cortical thickness (displayed in Supplemental Figure S8) appears nonetheless complex and should be addressed by future longitudinal investigations.

Second, an alternative non-mutually exclusive interpretation is that the increased morphological correlation reflects an abnormally increased functional coupling. Functional coactivation has been shown to significantly overlap with structural covariance (27,71–73), possibly due to coordinated effects of activity-induced plasticity (26,74–77). Indeed although tractography-based connectivity studies of psychosis have generally reported reductions of connectivity, functional connectivity studies have been less consistent (17). Several studies have reported an increased functional coupling (78–81), in some case correlated with the intensity of symptoms (78,81).

Differences in Network Architecture

We did not confirm our hypothesis that patients with 22q11DS would present alterations in global network architecture compared with control subjects, contrary to reports of white matter dysconnectivity in this syndrome (36,37). Covariance architectural alterations, however, were specific for PPs that presented reduced integration, compared with both control subjects and NPPs, and increased segregation, compared with control subjects. It would therefore appear that white matter network alterations are a feature of this syndrome, possibly representing a risk factor for psychosis, while structural covariance dysconnectivity only develops in those patients who manifest an attenuated psychosis phenotype.

The same architectural features of decreased integration and increased segregation have been previously reported in structural covariance studies of schizophrenia (35) and in subjects at high genetic risk for schizophrenia (34). A reduction of the global efficiency has also been highly replicated in structural connectomics studies in schizophrenia (82–85). In schizophrenia, reduced efficiency has been furthermore correlated to the intensity of positive and negative symptoms (84).

Our results, therefore, confirm the notion that a loss of global integration mirrored by an increase in local segregation of brain connectivity networks is a central element in the physiopathology of psychosis. This could lead to an altered dynamic of information processing, with a deficient integration of signals originating from functionally specialized sub-networks. This could in turn predispose to the emergence of psychosis.

Local Betweenness Centrality

Similarly to differences in global architectural parameters, also at the local level, differences in betweenness centrality were specific to the subgroup of patients suffering from psychotic symptoms.

Indeed, we observed that PPs selectively presented increased centrality for a cluster of four regions encompassing the dorsomedial prefrontal cortex and dorsal anterior cingulate cortex compared with both control subjects and NPPs. These regions have been shown to functionally anchor the salience network (SN) together with the insula (86,87). This network is thought to be responsible for the attribution of salience to both internally and externally generated events (88). Aberrant activation and connectivity of the SN has been proposed to be central to the development of several psychotic symptoms, whose common denominator can be found in the misattribution of salience to internally generated events (88,89).

Recent functional findings in 22q11DS have corroborated this hypothesis (90–92). Indeed, patients with 22q11DS presented an overrepresentation of the electroencephalogram microstate C (91), whose activation had been previously related to that of the SN (93). This overrepresentation correlated with the intensity of hallucinations (91) and has been highly replicated in populations of patients with idiopathic schizophrenia (92,94). Furthermore functional magnetic resonance imaging studies in 22q11DS have confirmed the role of aberrant anterior cingulate cortex activation and connectivity in the development of psychotic symptoms (50,95). In this perspective, our finding of increased centrality for regions anchoring the SN, selectively for PPs, could reflect a functional overrepresentation and hypercentrality of this network. The resulting misattribution of salience could in turn provide a parsimonious account of several key elements of the psychosis phenotype (88,89).

Conclusions and Limitations

The results of this study confirm the importance of dysconnectivity in the physiopathology of psychosis, particularly involving the SN.

This study nonetheless comes with some limitations. First, the two subgroups of patients differed in terms of their comorbidity profile, such as the frequency of mood and anxiety disorders. The limited size of our subgroups did not allow us to disentangle the effects of comorbidities as a potential confounding factor. Second, adding age² and age³ as additional covariates influenced some of the reported findings, suggesting that a differential nonlinear effect of age contributed to the observed results. This should nonetheless be explicitly tested by future longitudinal investigations.

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