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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 subcommunities 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

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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 or n.
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.
[a]Statistically significant between-group difference.