ABSTRACT

BACKGROUND: There is increased risk of developing psychosis in 22q11.2 deletion syndrome (22q11DS). Although this condition is associated with morphologic brain abnormalities, simultaneous examination of multiple high-resolution measures of cortical structure has not been performed.

METHODS: Fifty-three patients with 22q11DS, 30 with psychotic symptoms, were compared with demographically matched nondeleted youths: 53 typically developing and 53 with psychotic symptoms. High-resolution magnetic resonance imaging measures of cerebral volume, cortical thickness, surface area, and an index of local gyrification were obtained and compared between groups.

RESULTS: Patients with 22q11DS demonstrated global increases in cortical thickness associated with reductions in surface area, reduced index of local gyrification, and lower cerebral volumes relative to typically developing controls. Findings were principally in the frontal lobe, superior parietal lobes, and in the paramedian cerebral cortex. Focally decreased thickness was seen in the superior temporal gyrus and posterior cingulate cortex in 22q11DS relative to nondeleted groups. Patterns between nondeleted participants with psychotic symptoms and 22q11DS were similar but with important differences in several regions implicated in schizophrenia. Post hoc analysis suggested that like the 22q11DS group, cortical thickness in nondeleted individuals with psychotic symptoms differed from typically developing controls in the superior frontal gyrus and superior temporal gyrus, regions previously linked to schizophrenia.

CONCLUSIONS: Simultaneous examination of multiple measures of cerebral architecture demonstrates that differences in 22q11DS localize to regions of the frontal, superior parietal, superior temporal, and paramidline cerebral cortex. The overlapping patterns between nondeleted participants with psychotic symptoms and 22q11DS suggest partially shared neuroanatomic substrates.

Keywords: 22q11 Deletion syndrome, Cortical thickness, Genetics, Gyriﬁcation index, MRI, Psychosis
22q11DS and nondeleted (ND) patients with psychotic symptoms using anatomic MRI. It also represents one of the largest studies of brain morphometry to date.

METHODS AND MATERIALS

Sample

The 22q11DS sample was drawn from a prospective study, Brain-Behavior and Genetic Studies of the 22q11DS, at the University of Pennsylvania and Children’s Hospital of Philadelphia (CHOP). Subjects were recruited from the 22q and You Center at CHOP and through social media. Inclusion criteria were age ≥ 8, English proficiency, estimated IQ > 70 by clinical testing and the Wide Range Achievement Test 4 (20), and stable medical status. Exclusion criteria were pervasive developmental disorder or IQ < 70 and medical disorders that may affect brain function (e.g., uncontrolled seizures, head trauma, central nervous system tumor and infection) or visual performance (e.g., blindness). Subjects 12 years or older were eligible for MRI scanning.

Psychopathology was assessed with the Kiddie-Schedule for Affective Disorders and Schizophrenia (21), Structured Interview for Prodromal Syndromes (22), and the psychotic and mood differential diagnoses modules of the Structured Clinical Interview for DSM-IV (modules C and D) (23). As detailed previously (20), positive, negative, and disorganized symptoms were rated on the 7-point Scale of Prodromal Symptoms from the Structured Interview for Prodromal Syndromes (22) (0 = absent, 1 = questionable present, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe but not psychotic, and 6 = severe and psychotic). A prodrome diagnosis was given if a patient had one positive symptom rated ≥3 or at least two negative and/or disorganized symptoms rated ≥3 within the past 6 months. The 22q11DS psychosis spectrum group included those with the prodrome diagnoses and psychiatric disorders with psychotic symptoms (schizophrenia, psychosis not otherwise specified, major depression with psychotic features, schizoaffective disorder, and delusional disorder).

Deletion status was confirmed using multiplex ligation-dependent probe amplification (24). University of Pennsylvania and CHOP institutional review boards approved all procedures. Informed consent/assent was obtained from each participant and accompanying parent for those younger than 18 at the time of initial evaluation.

Control groups were obtained from the Philadelphia Neurodevelopmental Cohort (PNC), a prospective neuroimaging sample of 1400 youths aged 8 to 21 years (25–27). An automated optimal matching algorithm developed by Kosanke and Bergstrahl (28) (GREEDY) written in SAS (SAS Institute, Cary, North Carolina) generated a 1:1 typically developing (ND–TD) subsample from this population matched to the 22q11DS sample based on age, race, and gender (28). A second subsample of subjects from the PNC with psychosis spectrum symptoms (PS) (ND–PS) was obtained and similarly matched using an automated algorithm. Psychosis spectrum symptoms were assessed using an abbreviated Kiddie-Schedule for Affective Disorders and Schizophrenia and scales for measuring subthreshold psychotic symptoms, including the PRIME Screen-Revised and selected Scale of Prodromal Symptoms scales (21,26,27). Summary group statistics are provided in Table 1.

Image Acquisition

High-resolution axial T1-weighted magnetization prepared rapid acquisition gradient-echo was acquired, with the following parameters; repetition time/echo time 1810/3.51 milliseconds; inversion time 1100 milliseconds; field of view 180 × 240 mm; effective resolution 1 mm³. Subjects were scanned by a board certified technologist on the same 3T MRI scanner (TIM Trio; Siemens, Erlangen, Germany) using a 32-channel head coil.

Image Processing

Digital imaging and communications in medicine images were imported into FreeSurfer version 5.0, a freeware image-processing program (MGH, Harvard, Cambridge, Massachusetts; http://surfer.mgh.harvard.edu). FreeSurfer’s surface-based image processing pipeline has been described (29–32). Briefly, for each subject, image intensity was normalized to account for magnetic field inhomogeneity. The skull and other nonbrain tissues were removed (33). Preliminary segmentation was then performed using a connected components algorithm. The surface boundary was then covered with a polygonal tessellation and smoothed, resulting in high-resolution vertices over both cerebral hemispheres. A deformable surface algorithm was then employed to identify the pial surface. For all subjects, the cortical surface model was manually reviewed and edited if necessary.

CV, cortical thickness (CT), surface area (SA), and local gyriﬁcation index (IGI) were subsequently calculated at high resolution. Cortical thickness is estimated as the distance between the pial surface and the gray-white matter junction (31). Surface area was calculated by measuring the average triangular size surrounding the tessellated cortical vertices, following deformation of individual subject vertices (32,34). Maps of CV could then be generated by calculating the product of SA and CT at each vertex.

Gyriﬁcation index was determined using a method originally described by Schae et al. (19) for evaluating gyral complexity in 22q11DS and subsequently integrated into FreeSurfer. Briefly, this method creates a smoothed outer surface surrounding the more convoluted pial surface at every vertex. The

<table>
<thead>
<tr>
<th>Table 1. Demographic Characteristics of the Samples</th>
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<tbody>
<tr>
<td>22q11DS</td>
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<tr>
<td>--------</td>
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<tr>
<td><strong>n</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td>20.3 (4.5)</td>
</tr>
<tr>
<td>14.6–29.7</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td>27 M (51%)</td>
</tr>
<tr>
<td>26 F (49%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
</tr>
<tr>
<td>43 White (81%)</td>
</tr>
<tr>
<td>7 AA (13%)</td>
</tr>
<tr>
<td>3 Other (6%)</td>
</tr>
</tbody>
</table>

*p values are based on analysis of variance for age and chi-square test for categorical variables.

22q11DS, 22q11 deletion syndrome; AA, African American; ND, nondeleted; PS, psychotic symptoms; TD, typically developing.
algorithm then calculates the ratio of the inner and outer surfaces for \( j \) faces in the three-dimensional mesh

\[
GL_{3D} = \frac{\sum M_f \cdot A_D^f}{\sum M_D \cdot A_P^j}
\]

where \( A_D^f \) and \( A_P^j \) represent the pial and outer (smoothed) surfaces, respectively, and \( M_D \) and \( M_P \) represent the total number of faces in the pial and outer mesh.

### Statistical Analyses

Measures of total cortical volume, total surface area, mean cortical thickness, and mean IGI were calculated to identify global group differences in cerebral morphology. Analysis of variance (ANOVA) was performed with diagnostic group as an independent factor controlling for linear and nonlinear effects of age, sex, and race. Post hoc Tukey-Kramer tests were employed to identify which groups drove global differences.

Three group ANOVAs were then performed at each vertex for CT to identify significant group differences, controlling for linear and nonlinear effects of age, sex, and race. Control for multiple testing was performed using false discovery rate (FDR), with a threshold of \( q = .05 \) \( (35) \). Univariate ANOVA probability maps were similarly constructed for measures of SA, CV, and IGI. Post hoc pairwise tests were performed to identify which group contrasts were driving the observed differences in brain measures. Control of multiple testing was performed via FDR.

To explore the relationships between 22q11DS and psychosis, we performed subgroup analyses comparing the 30 22q11DS subjects with psychosis spectrum symptoms with their matches from the ND–TD and ND–PS groups \( (Table \text{ S1 in Supplement} \text{ 1}) \). Post hoc pairwise tests were similarly performed on the full group models. We similarly contrasted cerebral measures between the 22q11DS subjects with and without psychosis spectrum symptoms \( (Table \text{ S2 in Supplement} \text{ 1}) \).

To increase sensitivity for subtle group differences (particularly between the two nondeleted groups), we reanalyzed the data using cluster threshold permutation methods rather than FDR to control for multiple testing \( (33–35) \). These methods, adapted for surface-based anatomical analysis from methods originally designed for functional MRI data, are built into the FreeSurfer environment. They use permutation to estimate maximum cluster size assuming that false-positive vertices are less likely to be near each other; thus, unlike FDR, cluster thresholding takes advantage of spatial information inherent to imaging data. The cluster thresholding approach does sacrifice spatial specificity relative to FDR in return for an increased sensitivity for small but more regional group differences. For these analyses, a full-width at half maximum of 20 with 5000 permutations and global \( p \) value threshold of .05 were used to identify significant clusters. Post hoc statistical testing of pairwise group differences was then performed, with control of multiple testing via the Tukey-Kramer test.

### RESULTS

#### Global Measures

Patients with 22q11DS had significantly reduced total cortical volumes relative to nondeleted control subjects \( (Table \text{ 2}) \).

These reductions were driven by global reductions in total brain area rather than reductions in cortical thickness. Indeed, global measures of thickness were significantly increased in 22q11DS relative to control subjects. Mean IGI was decreased in the 22q11DS group. Statistically significant group differences were identified for all four global measures, with \( p \) values < .0009. Global differences were primarily driven by differences in deletion status; there were no significant differences between the TD and PS groups. Vertex level ANOVA demonstrated that significant differences in all measures were heterogeneous throughout the cerebrum \( (Figure \text{ 1}) \), with the midline cortex and frontal and superior parietal lobes particularly affected.

#### Cerebral Volume

Subjects with 22q11DS had multiple foci of significantly lower CV relative to ND–TD \( (Figure \text{ 2}) \); differences were centered on the rostral lateral frontal lobe, superior parietal lobe, medial occipital lobe, and temporal pole. Relative volumetric increases were observed in the insular cortex bilaterally in 22q11DS relative to ND–TD. Similar but less extensive differences were seen when comparing 22q11DS and ND–PS groups. An exception was a focal region of bilaterally decreased volume in the caudal frontal lobe in ND–PS relative to 22q11DS. There were no significant differences between 22q11DS subjects with and without psychosis spectrum

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**Table 2. Mean (SD) Global Measures by Group**

<table>
<thead>
<tr>
<th></th>
<th>Cortical Volume (mm³)</th>
<th>Cortical Thickness (mm)</th>
<th>Surface Area (mm²)</th>
<th>IGI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND–TD</td>
<td>525788 (68511)</td>
<td>2.69 (.09)</td>
<td>176346 (19263)</td>
<td>3.01</td>
</tr>
<tr>
<td>ND–PS</td>
<td>543620 (60455)</td>
<td>2.68 (.11)</td>
<td>171569 (19353)</td>
<td>3.01</td>
</tr>
<tr>
<td>22q11DS</td>
<td>495180 (56334)</td>
<td>2.75 (.10)</td>
<td>157533 (19192)</td>
<td>2.88</td>
</tr>
</tbody>
</table>

\( p \) Value .0009 .0004 <.0001 .0001

22q11DS, 22q11 deletion syndrome; IGI, local gyriﬁcation index; ND, nondeleted; PS, psychotic symptoms; TD, typically developing.

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**Figure 1.** Probability maps from four-group analysis of variance showing regional differences in cerebral volume, cortical thickness, surface area, and local gyriﬁcation index. Statistical maps for each hemisphere are first masked at \( p_{\text{voxel}} = .05 \) and then displayed at an uncorrected threshold of \( 1.3 < -\log(p) < 4 \) for consistency. FDR, false discovery rate.

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Biological Psychiatry July 15, 2015; 78:135–143 www.sobp.org/journal 137

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Cortical Morphometry in 22q11.2DS
symptoms or between the ND–TD and ND–PS groups after adjusting for multiple testing.

**Cortical Thickness**

Thicker cortex was seen in 22q11DS relative to the ND–TD group in frontal lobes bilaterally, orbitofrontal cortex bilaterally extending into anterior insula and operculum, inferior parietal lobe and paracentral lobule, fusiform gyrus, cuneus, and paracalcarine cortex (Figure 2). In contrast, significantly lower cortical thickness in 22q11DS was observed in anterior and middle superior temporal gyrus and mid to posterior cingulate gyrus bilaterally. Similar patterns were seen for the 22q11DS compared with ND–PS. However, we observed additional foci of significantly greater thickness in 22q11DS in left dorso-lateral prefrontal cortex and right insula and less pronounced decreases in superior temporal cortex and medial frontal lobes. Direct comparison between ND–TD and ND–PS groups did not demonstrate significant findings at vertex level. Similarly, no significant differences in cortical thickness were seen between 22q11DS subjects with and without psychosis spectrum after controlling for multiple testing with FDR.

Clusterwise correction identified 10 significant clusters (Figure 3). For clusters in the parietal and occipital lobes, group differences were driven by significantly thicker cortex in 22q11DS compared with the two control groups. In contrast, a cluster including portions of the left superior frontal gyrus, anterior cingulate, and medial orbitofrontal cortex was more complex, with significant differences between all groups and with the ND–PS intermediate in thickness between the other two groups. A similar pattern was seen in left superior temporal lobe (STG). In right STG, there were significant group decreases in the ND–PS group relative to ND–TD ($p = .001$). The results from cluster analyses for CV, surface area, and local gyri-ration index are presented in Figure 2S in Supplement 1.

**Surface Area**

Analysis of cerebral surface area identified multiple areas that were significantly smaller in 22q11DS relative to TD (Figure 2). On the lateral surface, rostral frontal lobes, superior parietal lobe, and lingual gyrus were particularly affected bilaterally. Midline areal differences were more extensive than those of cortical thickness, with large portions of the medial superior frontal gyrus, anterior cingulate cortex, and midline occipital lobe affected bilaterally. Similar findings were seen comparing 22q11DS with the ND–PS group at the vertex level, with less extensive differences in the lateral temporal lobe relative to the 22q11DS compared with ND–TD contrast. There were no significant differences between ND–TD and ND–PS groups or between 22q11DS subjects with and without psychosis spectrum. Cluster models produced similar patterns; group differences were entirely driven by areal decreases in 22q11DS relative to ND–TD; there were no significant differences between ND–PS and 22q11DS.

**Local Gyri-ration Index**

Analysis of IGI demonstrated group differences in gyral complexity (Figure 2). Smaller IGIs were noted in 22q11DS.
throughout anterior and posterior midline cerebral cortex, in orbitofrontal cortex and frontal pole, centered over angular gyrus and extending into the remainder of the inferior parietal lobe, and mid precentral and postcentral gyrus. Similar to surface area, group differences were principally explained by deletion status. Cluster threshold models produced similar findings, with significant decreases in mean lGI ($p < .0001$) between 22q11DS and other groups in all cases.

**DISCUSSION**

Although schizophrenia is a devastating condition with significant morbidity and mortality, the underlying biological manifestations remain elusive. Twin and family studies have demonstrated a strong genetic influence on liability to develop schizophrenia (10) and large-scale genetic studies have begun to identify putative genes, most with very small effect sizes (36). Understanding the neural substrates of this genetic variation remains an area of active research. 22q11DS represents the genetic variant of the largest effect on liability to schizophrenia and thus warrants investigation.

Our study provides a comprehensive examination of morphological characteristics of 22q11DS in a relatively large sample at high resolution and high field strength. Our findings replicate observed patterns of volumetric reductions in parieto-occipital cortex, dorsolateral prefrontal cortex, and midline structures, with relative increases in insular volumes compared with the ND–TD (12,15,16,37,38). In 22q11DS, we additionally identified significantly thicker cortex in the frontal lobes, inferior parietal lobes, lingual gyrus, and medial occipital lobes. Higher cortical thickness in these regions was associated with corresponding smaller mean surface area. The observed patterns of areal reduction in 22q11DS were similar to, but more extensive than, the observed increases in cortical thickness. We also observed extensive midline, frontal, and parietal reductions in cortical gyral complexity relative to ND–TD control subjects.

A similar approach by Jalbrzikowski et al. (16) simultaneously examined differences in cortical thickness, surface area, and volume in a sample of 31 individuals with 22q11DS (mean age 16.4 years) and 34 matched ND–TD control subjects, also at 3T. FreeSurfer analysis of 60 cortical regions of interest identified volumetric reductions in frontal lobes, anterior cingulate, cuneus, precuneus, superior parietal, and temporal cortex. Like the current study, the volumetric differences were primarily driven by decreases in cortical surface area. Also similar to the current study, they observed relatively thickened cortex in 22q11DS, most pronounced in frontal lobes. Thus, higher cortical thickness may explain why early volumetric studies observed relative preservation of the frontal lobe (12) despite the observed large reductions in area. Schaer et al. (14) similarly reported increased cortical thickness in frontal regions in a large sample of children and adolescents with 22q11DS. However, in this longitudinal study, deviant trajectories of cortical thickness were observed in 22q11DS compared with ND–TD; while dorsal frontal regions were thicker in
22q11DS during late childhood and adolescence, thickness in these regions by adulthood was comparable with ND–TD (group by age interaction). Schaer et al. (14) also observed this interaction in left superior temporal gyrus; although there were no significant group differences in younger subjects, relative decreases in this region manifested by adulthood in 22q11DS.

Unlike elsewhere in the brain, we also observed significant reductions in cortical thickness within superior temporal lobes and in mid cingulate gyrus bilaterally in 22q11DS. Several prior studies on 22q11DS suggested morphological deficits in superior temporal gyrus. Jalbrzikowski et al. (16) observed reductions in superior temporal lobes in their region of interest analysis, although the findings did not reach statistical significance. Eliez et al. (39) identified significant reductions in hand-drawn superior temporal gyrus volumes in 23 children and adolescents with 22q11DS compared with matched ND–TD; these differences were not significant after adjusting for global brain volume. Abrant morphology of STG has long been associated with schizophrenia (40), with recent studies showing reductions in both gray matter density and cortical thickness (41,42). A large study by Chow et al. (43) on subjects with 22q11DS demonstrated significant reductions in STG gray matter density in the group with schizophrenia, a finding particularly interesting given that STG morphological abnormalities have been associated with idiopathic schizophrenia.

To further characterize the neurodevelopmental patterns in 22q11DS, we examined differences in gyral complexity using the local gyrification index. We identified smaller IGI in 22q11DS, primarily in the paramidline cerebral cortex and extending to the superior and lateral parietal cortices. Decreases in gyrification in frontal and parietal lobes have been reported in several studies at lower levels of resolution (18,44). Prior studies of gyral complexity at vertex level are limited. For example, Schaer et al. (45) examined IGI in 44 young individuals with 22q11DS (mean age 9.1 years) and also identified significantly smaller IGLs in orbitofrontal cortex, superior parietal lobes extending into the angular gyri, and midline structure including the cingulate cortex and midline parietal and occipital lobes. Likewise, Srivastava et al. (46) examined IGI in 49 children with 22qDS (mean age 10.74 years) and found lower measures of gyral complexity in midline structures and within the parietal lobes and orbitofrontal cortices. Although our findings suggest more extensive changes in the midline frontal lobes, the overall pattern of findings is strikingly similar to these prior reports.

Considered together, the overlapping patterns of generally thicker cortex, smaller surface area, and reduced gyral complexity are suggestive of aberrant neural organization and migration in 22q11DS, most pronounced in the frontal and parietal lobes and midline occipital lobe. Thickened cortex compared with ND–TD control subjects is an unusual finding in the literature, although it has been reported with other neurodevelopmental conditions including Williams syndrome (47), autism (48,49), and both idiopathic polymicrogyria and lissencephaly (50,51). Notably, neuropathologic correlation in 22q11DS is limited, with a single case series demonstrating extensive microscopic gray matter heterotopia in one of three specimens (52). Qualitative MRI studies have reported pachygyria and polymicrogyria (abnormalities of migrational and postmigrational neuronal development, respectively) in 22q11DS (53,54), findings that may relate to the quantitative reductions in IGI found in the current study. Although qualitative reports of polymicrogyria have not noted as extensive or consistent findings compared with newer quantitative measures, differences are likely due to increased sensitivity of these new measures to detect more subtle abnormalities.

The potential etiologies of polymicrogyria are myriad and include genetic, metabolic, infectious, and traumatic causes (55). However, it is hypothesized that most are ultimately caused by vascular injury resulting in disruption of cellular interactions at the glial-pial barrier (51). A putative vascular cause of neuromigrational abnormalities is a particularly intriguing hypothesis in 22q11DS, given the spectrum of cardiovascular features associated with the condition (1). Schaer et al. (56) have described an association between congenital heart disease and gyrification at the parieto-temporal-occipital junction, although the reason for this association is incompletely understood. Ongoing genetically mediated cerebrovascular insult could potentially explain both the observed congenital neuroanatomic abnormalities and the aberrant neurodevelopmental trajectories observed later in life (14,16,46). 22q11DS is associated with diffuse white matter abnormalities reminiscent of small vessel ischemic changes, findings often seen in healthy people following middle age (57–59). Limited pathological examination of individuals with 22q11DS has demonstrated astrocytic gliosis and hemosiderin-laden macrophages in cerebral white matter, suggestive of diffuse cerebrovascular injury consistent with small vessel ischemia (52) in two out of three specimens examined.

**Morphometric Relationships to Psychosis Spectrum Symptoms**

Our purely vertex-level analysis did not identify any direct differences between subgroups with and without psychosis spectrum symptoms after controlling for multiple testing. This may be due to our relatively small sample and possibly the relatively broad definition of the psychosis spectrum in our ND–PS group. The broad definition permitted power to establish differences between individuals with psychotic symptoms and those without psychotic symptoms across deletion groups. As our 22q11DS sample grows, we will be able to examine whether individuals with more severe psychotic symptoms have more specific patterns of abnormalities. It is important to note that in our efforts to control for type I error, we are at risk for committing a type II error and therefore should await the availability of larger samples before concluding that such differences do not exist.

We did observe indirect vertex-level differences between our ND–TD and ND–PS groups, as there were significant differences in their probability maps when each was compared with the 22q11DS group. In particular, the ND–PS group had more extensive cortical thickness reductions in the dorsolateral prefrontal cortex relative to 22q11DS but less extensive thickness differences elsewhere in the brain including the superior temporal gyrus and superior frontal lobe. Post hoc cluster threshold models did identify significant reductions in right STG in ND–TD relative to ND–PS and superior frontal cortex.
gyrus thickness intermediate between 22q11DS and ND–TD groups, suggesting a partially shared neural etiology for psychosis. The ND–PS group also tended toward less extensive differences in area compared with 22q11DS, particularly in the temporal lobes.

The literature on anatomic differences in schizophrenia is variable, but volume and cortical thickness reductions in dorsolateral prefrontal cortex, limbic and midline structures, and mesial temporal structures are most commonly reported (42,60–65). Unlike the prior literature on schizophrenia, the current study focuses on subthreshold psychotic symptoms, which may explain the more subtle findings we observed relative to the schizophrenia literature. There is mounting evidence that neurodegeneration during late childhood and adolescence is evident at the onset of schizophrenia in susceptible individuals; patients with schizophrenia experience loss of cortical thickness and volume over time when examined longitudinally (66). It is possible that our ND–PS subjects represent individuals experiencing early neurodegenerative changes that are difficult to detect when compared with typically developing control subjects directly. Subtle differences in ND–PS groups (for example in dorsolateral prefrontal cortex and superior temporal gyrus) may become more apparent when the 22q11DS contrast is added. Although our findings are preliminary, the approach of group triangulation may ultimately help to disentangle what portions of the 22q11DS endophenotype are shared with idiopathic schizophrenia. Longitudinal studies using this multiple group approach may prove particularly fruitful for identifying putative biomarkers present before the manifestation of florid psychosis.

Although the current study supports several prior findings on 22q11DS in a relatively large sample, there are several limitations of the study that must be noted. First, our subject ascertainment procedures selected for higher functioning patients. Thus, the study may underestimate morphological differences between the 22q11DS and the nondeleted groups. Similarly, our study excluded patients with neurological diagnoses, including seizure disorders. Considering that seizures are associated with neurodevelopmental abnormalities, this selection criteria again may underestimate true group differences as compared with an unscreened sample (55). Second, although ND–TD and 22q11DS were matched for age, gender, and race, the 22q11DS groups were still significantly older. Age, along with race and gender, was partially controlled statistically in our analyses. Third, our PNC screening procedure for psychotic symptomology is less comprehensive as compared with the 22q11DS group. Finally, there were differences in the prevalence of mood disorders between 22q11DS subjects with and without psychosis spectrum symptoms, which could potentially affect the contrast between these subgroups.

Conclusions
Comprehensive analysis of multiple complementary measures of cerebral architecture in 22q11DS demonstrate overlapping abnormalities in cortical thickness, surface area, and grey matter, most notably in the frontal, superior parietal, and paramidline cerebral cortex. Findings suggest a neurodevelopmental origin of many of the neuroanatomic manifestations of 22q11DS. Several affected regions are associated with idiopathic schizophrenia in the literature, most strikingly in the superior temporal gyrus and prefrontal cortex, with our study providing preliminary evidence that subjects with idiopathic psychotic symptoms may have somewhat different morphological patterns than ND–TD control subjects when compared with 22q11DS. By identifying the neuroanatomic fingerprint of a deletion, we can elucidate the contribution of specific genetic effects to the phenotypic manifestations of psychosis. This paradigm can extend to other populations with genetic alterations associated with increased risk for psychosis, thereby establishing both shared and unique biomarkers for at-risk populations.

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Cortical Morphometry in 22q11.2DS


