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Mapping Cortical Morphology in Youth with Velo-Cardio-Facial (22q11.2 Deletion) Syndrome

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Abstract

Objective—Velo-cardio-facial syndrome (VCFS; 22q11.2 deletion syndrome) represents one of the highest known risk factors for schizophrenia. Insofar as up to thirty percent of individuals with this genetic disorder develop schizophrenia, VCFS constitutes a unique, etiologically homogeneous model for understanding the pathogenesis of schizophrenia.

Method—Using a longitudinal, case-control design, we acquired anatomic magnetic resonance images to investigate both cross-sectional and longitudinal alterations in surface cortical morphology in a cohort of adolescents with VCFS and age-matched typical controls. All participants were scanned at two time points.

Results—Relative to controls, youth with VCFS exhibited alterations in inferior frontal, dorsal frontal, occipital, and cerebellar brain regions at both time points. We observed little change over time in surface morphology of either study group. However, within the VCFS group only, worsening psychosocial functioning over time was associated with Time 2 surface contractions in left middle and inferior temporal gyri. Further, prodromal symptoms at Time 2 were associated with surface contractions in left and right orbitofrontal, temporal and cerebellar regions, as well as surface protrusions of supramarginal gyrus.

Conclusions—These findings advance our understanding of cortical disturbances in VCFS that produce vulnerability for psychosis in this high risk population.

Keywords

velo-cardio-facial syndrome; 22q11.2 deletion syndrome; schizophrenia; prodromal; cortical morphology

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INTRODUCTION

Despite our improved understanding of the neuroanatomic correlates of schizophrenia, we still have not definitively identified the longitudinal trajectory of abnormalities in brain structure during adolescence that constitute vulnerability to psychosis. Recent longitudinal studies of adolescents at clinical or familial high risk for schizophrenia 1–3 suggest that youth displaying prodromal or psychotic symptoms show age-related gray matter loss in superior, and inferior temporal lobe, superior and inferior 1, 2 frontal lobe, and cingulate. However, the etiological heterogeneity of schizophrenia continues to challenge these efforts.

This challenge can be addressed, in part, by identifying neurobiological abnormalities in specific genetic syndromes that place individuals at an increased non-familial risk for schizophrenia. One such disorder is velo-cardio-facial syndrome (VCFS; 22q11.2 deletion syndrome). This syndrome confers the highest known risk for developing schizophrenia, with up to 25% of individuals developing schizophrenia in adulthood. VCFS therefore provides a unique, etiologically homogeneous model for understanding the neurobiological underpinnings of at least one form of schizophrenia. Here we report findings from a longitudinal study of cortical morphology and psychiatric functioning in a cohort of 44 youth with VCFS. Most cross-sectional investigations of brain morphology in VCFS have been limited to traditional volumetric analyses 3–6 7–11. More recently, studies have reported cortical thinning in parietal-occipital regions and inferior frontal gyrus 12 and reduced gyrification in the frontal, temporal, and parietal lobes 13 of individuals with VCFS.

One longitudinal study of brain development 14, 15 reported that VCFS-affected youth exhibited increased volumes of cranial and cerebellar white matter, increased caudate nucleus volumes, and reduced amygdala volumes. A recently published study of age-related changes in cortical thickness 16 reported cortical thinning in frontal, parietal, and occipital cortices over a three-year period in adolescents with VCFS. The current report complements these studies by examining longitudinal alterations (ie., surface contractions or protrusions) in cortical morphology and associations with psychatric symptoms. This knowledge contributes to the growing literature documenting specific anatomical abnormalities that produce cognitive and emotional disturbances in youth with VCFS 7, 9, 17, 18 and place them at elevated risk for psychosis as they reach adulthood.

Based on extant studies of individuals with VCFS and those with idiopathic schizophrenia, we hypothesized that relative to controls, youth with VCFS would exhibit (1) cross-sectional contractions in posterior cortical surfaces (e.g. parietal, temporal and occipital lobes, and the cerebellum) and protrusions in frontal cortical surfaces 3, 4, 6 ; and (2) more robust contractions of frontal, parietal and occipital cortices 16 over time. We further predicted that (3) contractions of frontal and temporal lobes 19, 20 at both Time 1 and Time 2 in youth with VCFS would be associated with more prodromal symptoms at Time 2.

METHOD

Sample

The sample (Table 1), drawn from a larger, longitudinal study of biomarkers for psychosis in VCFS9, 10, 21–28, consisted of 44 children with VCFS, 13 siblings of VCFS children, and 12 community controls. The sibling sample did not differ from the community sample in age (p = .92), gender distribution (p = .99) or full scale IQ (p = .15). Moreover, VCFS is a de novo dominant mutation that cannot confer carrier status on a sibling. Accordingly the two groups were combined into one control sample.

All participants were from 9 to 15 years of age at baseline. Families of children with cytogenetically-confirmed VCFS were recruited primarily from a VCFS Center at an urban medical center. Community controls were recruited through fliers distributed to local schools. Exclusion criteria for controls included seizure disorder, fetal exposure to alcohol or drugs, elevated lead levels, birthweight under 2500 grams (as reported by parents), paramagnetic implants, or orthodontic braces, and a previous diagnosis or family history of either schizophrenia or bipolar disorder. We did not screen, however, for the presence ADHD. Given the high incidence of ADHD in youth with VCFS, we did not screen for ADHD in controls, reasoning that controls with possible ADHD would provide a reasonable match to the higher-functioning VCFS participants, as well as control for potential alterations in cortical morphology that may be associated with ADHD 29. All participants and their parents provided informed assent or consent based on guidelines of our Institutional Review Board.

Participants were originally recruited and scanned at baseline (Time 1) between 2002 and 2005. Seventy-nine percent of participants recruited at Time 1 returned approximately three years later for follow-up (Time 2). Participants who did not return for follow-up did not differ significantly from returnees by age ($F = 1.57$; $p = 0.21$), IQ ($F = 0.5$; $p = 0.48$) or SES ($F = 0.00$; $p = 0.99$). The sample described here consists only of those participants for whom we have assessments at both Time 1 and Time 2.

MRI Acquisition and Processing

MRIs were acquired in the axial plane on a 1.5 T Philips Gyroscan scanner (Philips Medical Systems, Best, The Netherlands) utilizing the following T-1 weighted inversion recovery, turbo gradient echo (TFE) 3-D pulse sequence: echo time = 4.6; repetition time = 20; 2 repetitions; matrix size 256 × 154; field of view = 24 cm; multishot = 32; TFE pre-inversion recovery = 394 ms, 1.5 mm slice thickness.

Imaging data were transferred to local workstations via network connections. After isolating brain from nonbrain tissue using automated procedures30 images were transferred via FTP to Columbia University, where morphology of the brain surfaces (defined by all pixels in the interface of gray matter and CSF across the entire brain) was assessed. This procedure, summarized below, employed previously validated and automated algorithms. 31–33 First, brains at Time 2 were coregistered to an appropriately selected template brain at Time 2 32 using a similarity transformation, followed by a high-dimensional, nonrigid warping algorithm using the principles of fluid dynamics 34. Each brain was warped to the exact same size and shape as the template brain, thereby identifying corresponding points across the surface of each brain and the template brain. Second, each participant's brain at Time 1 was coregistered and warped to the same participant's brain at Time 2 to identify corresponding points on the brain surfaces at Times 1 and 2. We then applied the warping from the first step to the participant's brain at Time 1, determining precisely the corresponding points on the template surface and brain surface for each subject at Time 1. Approximately 85,000 points were identified on the surface of the template brain. Because each participant's brain at Time 1 well-matches that participant's brain at Time 2, coregistering and warping each Time 1 brain to its Time 2 counterpart minimizes errors in determining correspondences across the two surfaces. Our two-step procedure therefore precisely determines the correspondences between points on the template surface and those on the brain surfaces at Time 1. We then computed signed Euclidean distances between corresponding points across the cerebral surfaces for each participant from the template surface.

The signed Euclidean distances that we computed at each point at the cortical surface were statistically analyzed using multiple linear regression. We computed these test statistics for

the comparison of cortical morphology between study groups, and across time within study groups, while covarying for age and sex, having first ensured the absence of quadratic and cubic effects of age, and significant interactions among group, age, and sex. (On the basis of permutation analyses that tested the magnitude of association in Euclidean distances between VCFS subjects and both sibling and non-sibling controls, we determined that familial relatedness did not influence our results and, therefore, did not control for that factor.) We corrected for the multiple statistical comparisons performed at each point across the cerebral surface using the theory of Gaussian Random Fields (GRF). Type 1 error caused by multiple hypothesis testing could be minimized by applying the Bonferroni correction if the data on the neighboring voxels were statistically independent. However, the imaging data on the neighboring voxels are correlated and therefore Bonferroni correction is very conservative. To appropriately minimize the Type 1 error, we modeled the correlated imaging data across the brain surface as a Gaussian random field, and applied the theory of Guassian Random Fields on a 2-dimensional manifold 35 to compute p-values of significance that were corrected for these multiple comparisons.35 Thus, our GRF-corrected images display surface points that withstood a stringent statistical threshold for multiple comparisons. These methods have excellent sensitivity and specificity for detecting morphological abnormalities at the cortical surface31.

Assessment of Cognitive and Psychiatric Functioning

All participants, including children with VCFS and controls, were administered identical batteries assessing cognitive and psychiatric functioning.

The Wechsler Intelligence Scale for Children-Third Edition (WISC-III) was administered to all participants at Time 1. At Time 2, either the WISC-III or the Wechsler Adult Intelligence Scale-Third Edition was administered, depending on the age of the participant. Comparative studies between the Wechsler child and adult intelligence scales suggest that relative to WISC-III scores, WAIS-III scores are inflated between three and seven points. 36–38 Accordingly we subtracted five points from WAIS-III full-scale IQ scores.

The Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL) was administered by a child psychiatrist or psychologist (mean kappa inter-rater reliability across all diagnoses, .91) to the child and primary caregiver to assess the presence of child psychiatric diagnoses at both timepoints (Table 2). In the cases in which children had difficulty responding to interview questions due to cognitive deficits, final scores were based on the parent interview. 22, 27

We correlated the measures of psychiatric functioning described below with cortical morphology.

The Children's Global Assessment Scale (CGAS) 39 assesses global functioning. The CGAS was scored at Times 1 and 2 by doctoral-level clinicians within the context of administering the K-SADS-PL. We correlated Time 2 CGAS scores with cortical morphology at Times 1 and 2, and CGAS change scores (Time 2 minus Time 1) with cortical morphology at Time 2.

The Scale of Prodromal Symptoms (SOPS)40 was administered by a doctoral – level clinician during the structured psychiatric interview at Time 2 only. Inter-rater reliability, based on five SOPS interviews and assessed with the intraclass correlation coefficient, was 0.90. The SOPS consists of four domains, in which the clinician rates each participant and derives summary scores for positive prodromal symptoms, negative prodromal symptoms, disorganization, and general symptoms. As reported previously 27 we calculated a total

SOPS summary score from the Positive, Negative and Disorganization subscales of the SOPS (excluding the General subscale due to non-specificity).

Correlational Analyses

For the VCFS group only, multiple linear regression analyses were used to analyze the association between cortical surface morphology at Times 1 and 2 and scores on the Time 2 CGAS as well as CGAS change scores (Time 2 minus Time 1). Scores for the CGAS were regressed on the signed Euclidean distances that had been computed between corresponding points across the cerebral surfaces of each participant and the template surface. Associations between Time 1 and Time 2 Euclidean distances and Time 2 SOPS scores were assessed with the Zero-inflated Poisson regression analyses 41 due to the distribution of our SOPS data, which was a count of symptoms for which at least 50% of scores equaled zero (indicating the absence of any prodromal symptoms). 27 We covaried for age and sex in all regression analyses. Since FSIQ was correlated with CGAS scores, we also covaried for FSIQ in our CGAS analyses. All analyses were GRF-corrected for multiple comparisons. Due to restricted distribution of psychiatric function scores in the control group, analyses were conducted for the VCFS group only.

RESULTS

Group Differences at Time 1 and at Time 2

Figure 1 depicts differences in cortical surface morphology between study groups at Time 1 and Time 2. GRF-corrected analyses indicated that at both Time 1 and Time 2, youth with VCFS relative to controls exhibited significant reductions (ie., contractions of the cortical surface) bilaterally in inferior frontal cortex (BA 44, 45, and 47), anterolateral orbitofrontal cortex (OFC) (BA 11), inferior postcentral gyrus (BA 3), primary visual cortex (BA 17), inferior temporal gyrus (BA 20), and anterior cerebellum. In addition, youth with VCFS exhibited bilateral increases (ie., protrusions of the cortical surface) in the dorsal frontal cortices (BA 6, 8, and 9). The similarity of the maps at Times 1 and 2 demonstrates the remarkable test-retest reliability of these measures. In addition, Figure S1, available online, provides information on the effect sizes and variance of our findings, further supporting their validity.

Because IQ scores differed significantly between study groups, we conducted the same analyses as above, but entered IQ as a main effect and study group by IQ as an interaction term. Our findings indicated that the effect of IQ on cortical morphology did not differ appreciably between study groups (see Figure S2, available online).

Within-Group Changes from Time 1 to Time 2

We observed relatively little change in cortical morphology over the three-year period for either youth with VCFS or controls. Uncorrected images indicated that both typical youth and those with VCFS experienced local reductions in the anterior aspect of left middle and inferior frontal gyri (BA 9, 45, 46, 47), left middle temporal gyrus (BA 21), and bilateral cerebellum. VCFS youth also exhibited reductions in inferior parietal lobule (BA 40) and inferior occipital gyrus (BA 19) (not shown). However, reductions in most of those areas did not survive GRF correction. In addition, regression models in which we subtracted Time 1 distances from Time 2 distances, and then regressed age, sex and diagnostic status (VCFS vs. controls) onto the resulting net distances, did not yield significant results, indicating that age-related changes did not differ by study group.

Correlations of Cortical Morphology with Functional Impairment and Prodromal Symptoms

At our Time 2 assessment, 25% of our VCFS sample were experiencing intermittent symptoms of psychosis (primarily hallucinations) as assessed with the K-SADS-PL compared with 4% of our control sample (Table 2). Youth with VCFS who demonstrated transient, intermittent symptoms of psychosis showed significantly greater impairment than non-symptomatic (for psychosis) youth on both the CGAS ($F(1,42) = 8.5$; $p < .006$) and the SOPS ($F(1,42) = 35.6$; $p < 0.0001$). The images in Figure 2 depict associations between Time 1 and Time 2 cortical morphology, and Time 2 scores on the CGAS and the SOPS in the VCFS group. Figure 3 depicts scatterplots and graphs representing these associations. Figure 4 depicts a scatterplot representing the association between CGAS change scores and Time 2 cortical morphology. After GRF correction, we observed that at both Time 1 and Time 2, greater reductions in left superior and middle temporal gyri was significantly associated with greater functional impairment on the Time 2 CGAS, as were small reductions in left postcentral and precentral gyrus. Moreover, worsening CGAS scores over time were significantly associated with cortical contractions in left middle and inferior temporal gyri at Time 2. At both Time 1 and Time 2, cortical contractions in left and right (data not shown for right hemisphere) lateral orbitofrontal cortex, superior (to a small extent) and inferior temporal gyri, and cerebellum, and cortical protrusions in supramarginal gyrus were associated with higher Time 2 SOPS scores. Contractions in inferior frontal gyrus at Time 2 only were also associated with Time 2 prodromal symptoms. Interestingly, widespread contractions of left and right superior and middle temporal gyri at Time 1, but not at Time 2, were also associated with more prodromal symptoms at Time 2.

DISCUSSION

In sum, we observed that in cross-sectional analyses, at both Time 1 and Time 2, youth with VCFS relative to controls exhibited morphological alterations in inferior frontal, dorsal frontal, occipital, and cerebellar brain regions. Longitudinal analyses revealed little change in cortical morphology over time in either youth with VCFS or controls. However, we observed that Time 1 and Time 2 contractions in left and right orbitolateral frontal and inferior temporal gyri, and protrusions in parietal cortex, were robustly associated with more prodromal symptoms in the VCFS group at Time 2. In addition, Time 1 and Time 2 contractions over the left superior and middle temporal gyri were associated with lower CGAS scores in the VCFS group at Time 2.

Between-Group Comparisons at Each Time Point

At both Time 1 and Time 2 we detected in VCFS youth increases in dorsal and ventromedial prefrontal cortices, and contractions of Broca's region, ventrolateral prefrontal cortex, occipital cortex, and anterior cerebellum, Our findings of frontal enlargement are consistent with prior studies reporting increased overall frontal volumes relative to whole brain volumes in youth with VCFS, although reduced volumes have also been reported in specific frontal subregions. 25, 42. The superior frontal gyrus has been associated with motor planning, a capacity that is often impaired in children with VCFS 43. Contractions detected in more inferior prefrontal regions, in contrast, may underlie reported deficits in response inhibition in youth with VCFS 44.Whereas previous studies using ROI-based measures have reported significant decreases in volume of the cerebellum in VCFS, volume reductions in Broca's region have not been reported previously. Contractions in Broca's region (BA 44 and 45) and the anterior cerebellum could underlie the well-documented language deficits in VCFS 45. Primate studies demonstrate projections from superior cerebellum to inferior frontal cortex 46 supporting functional imaging findings of co-activation of cerebellum and inferior prefrontal cortex in language processing 47 and word generation 48. These findings suggest alterations in brain regions that compose cortico-cerebellar circuits in children with

VCFS. This circuit contains feed-forward46 and feed-backward 49, 50 pathways that link the cerebellum to the cerebral cortex. Primate studies 49 and human functional imaging studies suggest that cortico-cerebellar circuits support several cognitive functions, including executive functioning51, working memory47, temporal discrimination38, and language processes 52. Thus each of the cognitive functions attributed to the corticocerebellar pathway is known to be impaired in persons with VCFS53–59. We detected morphological abnormalities in each of the regions composing this circuit in children with VCFS.

Changes in Cortical Surface Over Time

Between Time 1 and Time 2, cortical surface morphology in both study groups was relatively consistent, suggesting little change in the overall contours of the cortical surface over a three-year period. Although several studies of age-related changes in gray matter density in typically developing youth 60, 61 have been published, relatively few studies have focused on changes in cortical surface morphology between childhood and adolescence. The method for mapping cortical surface morphology that is comparable to our method is the “distance from center” (DFC) method, included within the rubric of cortical pattern matching techniques developed at UCLA (see review by 62). Applying the DFC method to a cross-sectional sample of cortical morphology in youth and young adults, 63 few differences were observed between surface morphology of children and adolescents (comparable in age to our sample). In contrast, significant differences were observed in cortical surface (particularly dorsal frontal cortex and temporal cortex) between adolescents and adults. Based on these prior findings, we anticipate observing more robust changes in the cortical surface, at least in our control sample, when they are imaged at future time points.

Associations with Prodromal Symptoms and Psychosocial Functioning

We observed that a greater burden of prodromal / functional symptoms in the VCFS group at Time 2, and worsening in psychosocial functioning over time, were associated with cortical surface contractions in inferior frontal lobe, temporal lobe and cerebellum, and cortical protrusions in parietal cortex. Findings of frontal and temporal lobe contractions are consistent with longitudinal studies of adolescents at ultra high risk for schizophrenia that have reported neurodevelopmental abnormalities in superior temporal and frontal cortices during adolescence that predate the onset of overt psychosis 19, 20, 64. Parietal anomalies have also been reported in youth at genetic risk for schizophrenia 65 as well as those with psychosis 66. Although most studies have observed parietal reductions associated with psychosis, volumetric increases in parietal cortex 67 have also been reported. The presence of an association between Time 1, but not Time 2, superior temporal contractions and Time 2 prodromal symptoms may be a function of the developmental trajectory of superior temporal gyrus. Whereas frontal and parietal gray matter peak in early adolescence, temporal gray matter peaks between 14 and 16 years of age 68, 69, which coincides with the mean age of our participants at Time 2. At Time 1, therefore, superior temporal lobe contractions may have been specific to those youth who later developed prodromal symptoms. By Time 2, however, subtle cortical contractions in the superior temporal lobes of non-prodromal youth may have reduced the specificity of this association.

The results of this study must be viewed in the context of several limitations. Correlations of our psychosocial measures with cortical morphology were limited in their clinical relevance, because our sample has not yet reached the age of greatest risk for onset of psychosis.

In addition, the choice of appropriate comparison samples in studies of youth with genetically based impairments in cognitive and emotional functioning is controversial. Recruiting a sample of controls with idiopathic intellectual impairments can produce an

etiologically heterogeneous sample, potentially undermining the validity of data interpretation. The inclusion of a sample of typically developing controls, however, can contribute to findings that derive from nonspecific differences in intellectual capacities, rather than from the predisposition to develop psychotic illness per se.

Finally, as noted in Table 2, many of the youth in our sample are prescribed medications for current psychiatric disorders. Although we could not identify published studies that documented an effect of medication on cortical patterning, the potential effect of medication usage cannot be ruled out since our sample size was not large enough to control for medication usage.

Despite these limitations, our findings advance substantially the understanding of both the neural bases of VCFS and the alterations in brain development that contribute to functional psychiatric impairment in adolescents with VCFS. Moreover, because VCFS represents the highest known risk factor for schizophrenia apart from having an identical twin or two parents with this devastating psychiatric disorder, these findings contribute significantly to our understanding of anomalies in cortical surface morphology that may underlie the vulnerability to psychosis in non-VCFS adolescents who are at risk for schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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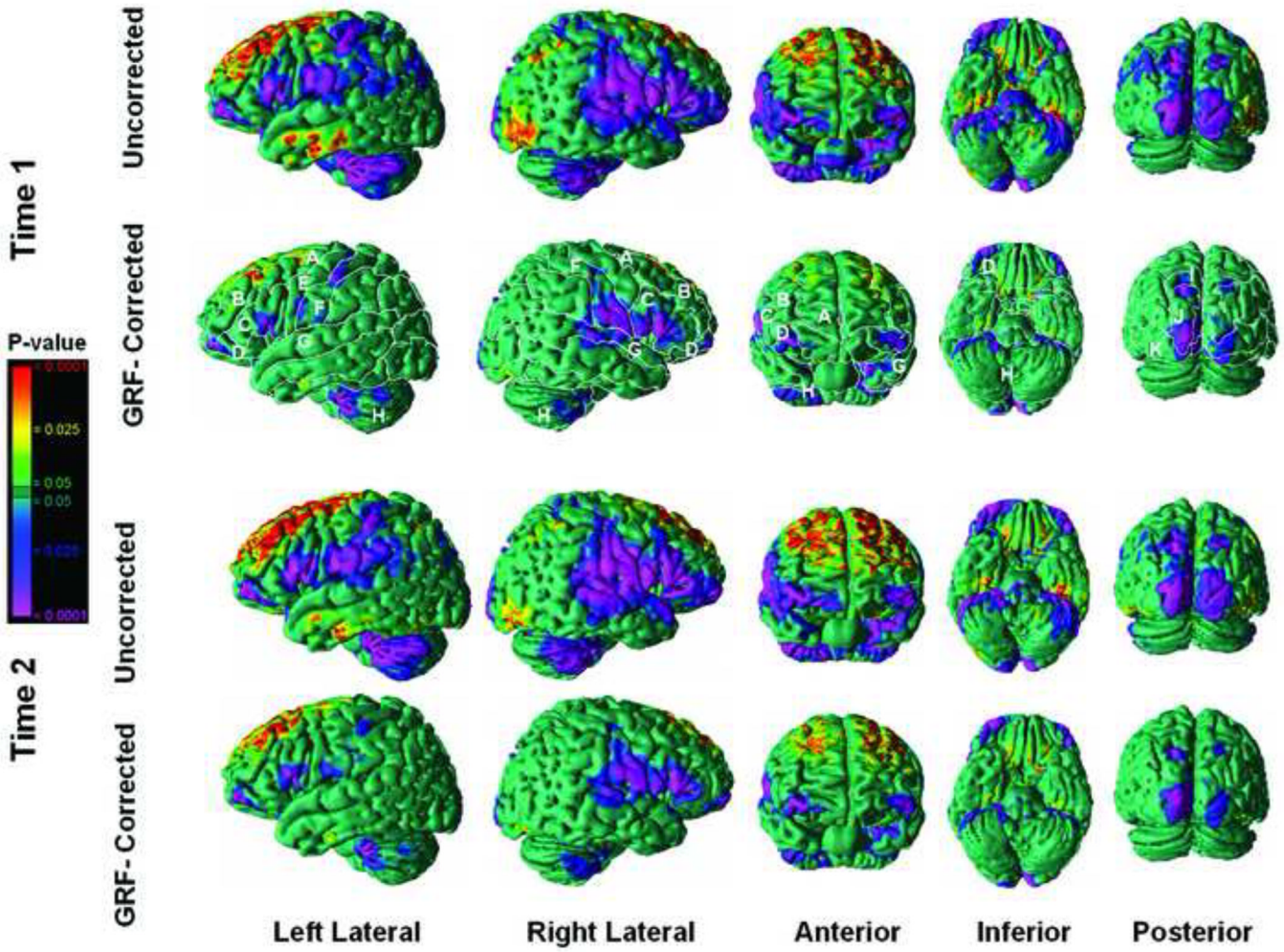

Figure 1. Group differences in morphological features of the cortical surface

Results are displayed for left lateral, right lateral, anterior, inferior and posterior views of the cortical surface at Time 1 and Time 2. The figure is based on a statistical model that includes study group (Velo-cardio-facial syndrome [VCFS] vs. control) as the main effect while covarying for age and sex. The color bar provides the color-coding for the main effects of study group. Warmer colors (red and yellow) indicate protruding surface (presumably representing larger underlying volumes) in youth with VCFS relative to controls, and the cooler colors (blue and purple) indicate indented, contracted surfaces (presumably representing smaller underlying volumes) in youth with VCFS relative to controls.

Maps display images both corrected and uncorrected for multiple comparisons using Gaussian Random Fields (GRF). The GRF-corrected images depict voxels surviving rigorous correction for multiple comparisons. Because the corrections are so rigorous, however, they may not fully represent the underlying spatial or anatomical configuration of the statistical effects we are modeling (as the anatomical location of the voxels identified in this sort of map are vulnerable to the effects of statistical thresholding that can cause them to shift in location). From the standpoint of accurately identifying anatomical subregions that carry the effect being modeled, GRF-uncorrected images are preferred; but from the standpoint of identifying voxels involved in the effect with the greatest statistical certainty, GRF-corrected images are preferred. Thus, GRF-corrected and –uncorrected images

together provide complementary information about the effect being modeled, each of which is important to the aims of the study.

The second row of the Time 1 images displays an overlay of cytoarchitectonic –based regions. Overlaid letters correspond to the following regions of interest: A: superior frontal gyrus; B: middle frontal gyrus; C: inferior frontal gyrus; D: lateral orbital frontal gyrus; E: precentral gyrus; F: postcentral gyrus; g: superior temporal gyrus; H: cerebellum; I: cuneus; J: superior occipital gyrus; K: inferior occipital gyrus. With kind permission of Paul M. Thompson, Laboratory of NeuroImaging, University of California at Los Angeles http://www.loni.ucla.edu/ICBM/Downloads/Downloads_ICBMtemplate.shtml.

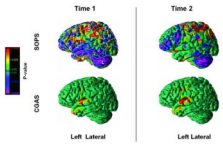

Figure 2. Correlations between cortical morphology and psychiatric function in the VCFS cohort

Images depict the association between cortical morphology at Time 1 and Time 2 scores on the Children's Global Assessment Scale (CGAS) and Scale of Prodromal Symptoms (SOPS). Warmer colors depict positive associations between psychiatric function scores and cortical morphology, and cooler colors depict negative associations between scores and cortical morphology. Higher scores on the the SOPS indicate poorer psychiatric function, whereas lower scores on the CGAS indicate poorer psychiatric function. Accordingly, the negative associations noted for the SOPS indicated that cortical contractions were associated with poorer functioning on that scale. Similarly, the positive association noted for the CGAS indicated that cortical contractions were also associated with poorer functioning. Regions in which associations were noted included: A: middle frontal gyrus; B: inferior frontal gyrus; C: lateral orbitofrontal gyrus; D: precentral gyrus; E: postcentral gyrus; F: superior parietal lobule; G: supramarginal gyrus; H: inferior parietal lobule; I: superior temporal gyrus; J: middle temporal gyrus; K:inferior temporal gyrus; L: cerebellum.

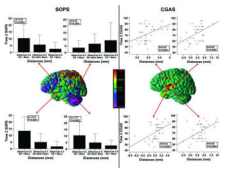

Figure 3. Box and scatterplots depicting associations between cortical distances and psychiatric function

This figure consists of box plots and scatterplots depicting the association between Time 2 cortical distances (in millimeters) and the Time 2 Scale of Prodromal Symptoms (SOPS) and Children's Global Assessment Scale (CGAS) scores, respectively. Each arrow locates the specific point for which its corresponding plot was generated. Points which reflected highly significant results were chosen for visualization with plots. The statistical association between distances and SOPS scores was calculated with the zero-inflated Poisson regression, which generates z-scores, provided in the upper left corner of each SOPS plot. The error bars in the box plots depict one standard deviation. Statistical associations between distances and CGAS scores were calculated with linear regressions: coefficients are provided in the lower right corner of each of those plots.

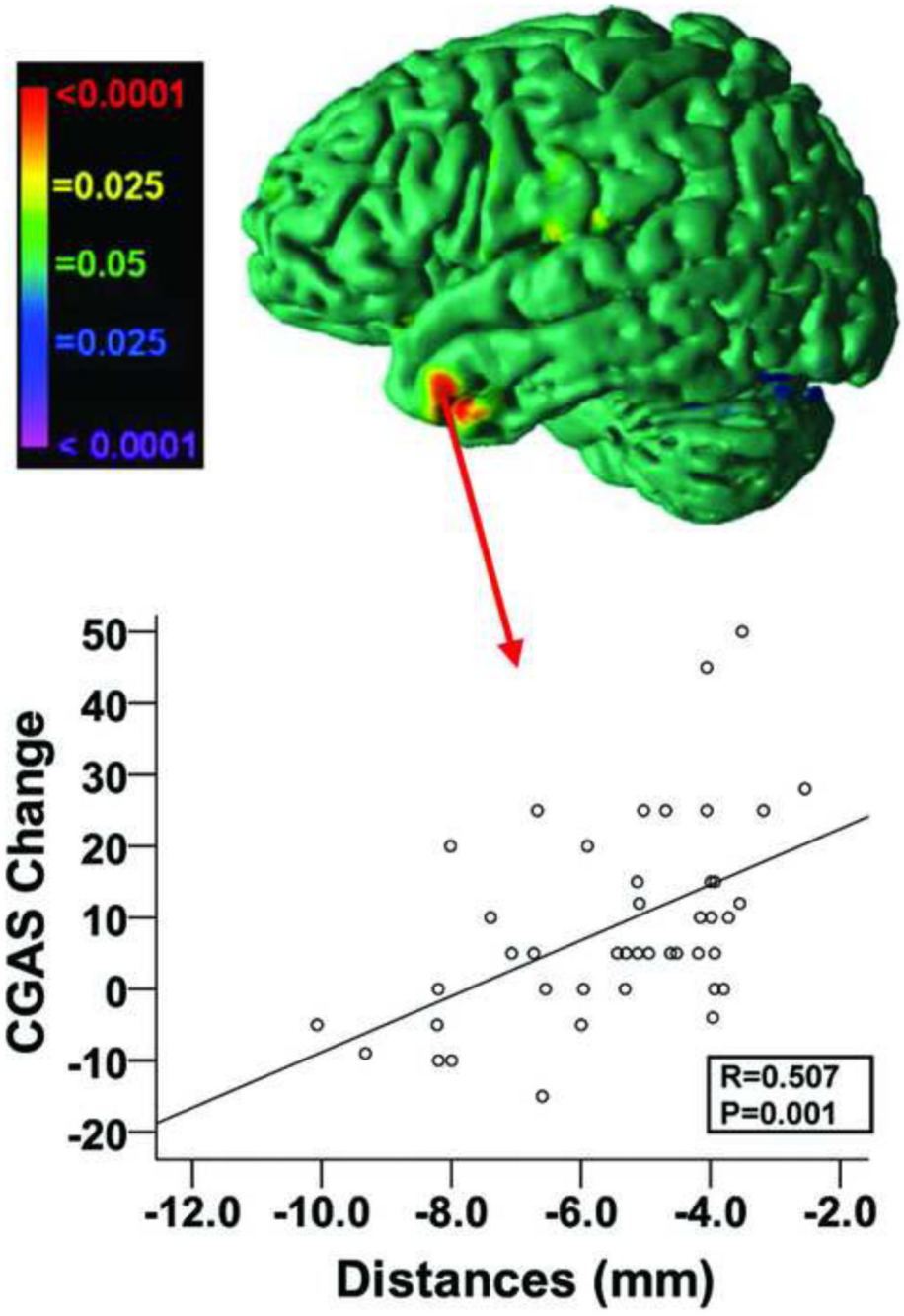

Figure 4. Scatterplots depicting associations between cortical distances and Children's Global Assessment Scale (CGAS) change scores

This figure consists of a scatterplot depicting the association between Time 2 cortical distances (in millimeters) and CGAS change (Time 2 minus Time 1) scores. The arrow locates the specific point for which the plot was generated. The statistical association between cortical distances and CGAS change scores was calculated with a linear regression: the coefficient is provided in the lower right corner of the plot. As in Figure 2, warmer colors depict positive associations between CGAS change scores and cortical morphology, such that cortical contractions were associated with negative change scores (indicating a worsening of psychosocial functioning).

Table 1

Participant Characteristics

	VCFS (N=44)	Controls (N=25)	ANOVA F-value (d.f.)	P-value
	Mean (S.D.)	Mean (S.D.)		
Age at Time 1	11.9 (2.2)	11.4 (1.9)	.82 (1, 67)	.37
Age at Time 2	15.1 (2.1)	14.5 (1.8)	1.3 (1, 67)	.31
Sex	25 F, 19 M	13 F, 12 M		.74
Years between Time 1 and Time 2	3.2 (.39)	3.2 (.51)	.11 (1, 67)	.19
Full Scale IQ / Time 1	72.7 (12.2)	98.8 (16.2)	57.9 (1, 67)	.0001
Full Scale IQ / Time 2	71.5 (12.6)	97.8 (14.5)	62.3 (1, 67)	.0001
CGAS Score / Time 1	63.3 (14.2)	78.7 (17.8)	15.4 (1,67)	.0002
CGAS Score / Time 2	72.6 (13.3)	86.3 (13.0)	17.1 (1, 67)	.0001
SOPS Score / Time 2	8.8 (11.5)	2.6 (5.0)	6.5 (1, 66)	.014

Note: ANOVA = analysis of variance; CGAS = Children's Global Assessment Scale; SOPS = Syndrome Scale of Prodromal Symptoms; VCFS = Velo-cardio-facial syndrome

Table 2

Medications and Psychiatric Diagnoses Based on the Time 2 K-SADS-PL

	VCFS (N=44)	Controls (N=25)
	Frequency (%)	Frequency (%)
Psychiatric Diagnoses		
Major Depressive Disorder	6 (13.6)	0
Bipolar Disorder, NOS	1 (2.2)	0
Anxiety Disorder (includes Separation, Overanxious, Generalized)	4 (9)	0
Obsessive Compulsive Disorder	2 (4.5)	1 (4)
Simple or Social Phobia	5 (11.4)	1 (4)
Attention Deficit Hyperactivity Disorder	13 (29.5)	3 (12)
History of Subthreshold Psychotic Symptoms	11 (25)	1 (4)
Medication Classes		
Total N Taking Psychotropic Medications	15 (34.1)	5 (20)
Stimulants / Straterra	10 (22.7)	4 (16)
Anti-depressants	4 (9)	1 (4)
Mood Stabilizers	4 (9)	0
Alpha 2 Agonists	1 (2.2)	0
Anti-psychotics	5 (11.4)	1 (4)
Other (Metyrosine)	1 (2.2)	0

Note: K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version; NOS = not otherwise specified; VCFS = Velo-cardio-facial Syndrome