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Neuroanatomic Predictors to Prodromal Psychosis in Velocardiofacial Syndrome (22q11.2 Deletion Syndrome): A Longitudinal Study

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Abstract

Background—Up to 30% of young adults with velocardiofacial syndrome (VCFS; 22q11.2 deletion syndrome) develop schizophrenia or psychosis. Identifying the neuroanatomic trajectories that increase risk for psychosis in youth with this genetic disorder is of great interest.

Methods—We acquired high-resolution anatomic MR images and measures of psychiatric function on 72 youth with VCFS, 26 unaffected siblings and 24 age-matched community controls at two timepoints, between late childhood (mean age, 11.9 years) and mid-adolescence (mean age, 15.1 years).

Results—With the exception of cranial gray matter and orbitofrontal prefrontal cortex, neuroanatomic trajectories in youth with VCFS were comparable to unaffected siblings and community controls during this developmental window. However, in youth with VCFS, longitudinal decreases in the volumes of cranial gray and white matter, prefrontal cortex, mesial temporal lobe, and cerebellum were associated with increased combined prodromal symptoms at Time 2. In contrast, only decreases in temporal lobe gray matter volumes ($p < .002$) and verbal IQ ($p < .002$) predicted specifically to positive prodromal symptoms of psychosis at Time 2.

Conclusions—These findings are in line with studies of non-VCFS individuals at risk for schizophrenia, and suggest that early decrements in temporal lobe gray matter may be predictive of increased risk of prodromal psychotic symptoms in youth with VCFS.

Keywords

22q11.2 deletion syndrome; brain development; MRI; longitudinal; temporal lobe; prodromal; psychosis; schizophrenia

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INTRODUCTION

Velo-cardio-facial syndrome (VCFS), also known as 22q11.2 deletion syndrome and DiGeorge syndrome, is caused by an interstitial deletion of approximately 40 genes at the q11.2 locus of chromosome 22 (1). Children with VCFS have physical anomalies, intellectual deficits and psychiatric disorders. Common childhood disorders include attention deficit hyperactivity disorder, phobias, generalized anxiety disorder and major depression (3,4). As youth with VCFS reach adulthood, up to 32% develop psychotic disorders, including schizophrenia and schizo-affective disorder (2,5–8). Accordingly, VCFS is the highest known genetic risk factor for schizophrenia next to having two parents with the illness (9). The onset of psychosis in young adults with VCFS is accompanied by a decline in verbal IQ (2).

The high co-occurrence of schizophrenia and VCFS has increased interest in identifying biological risk factors for psychosis in VCFS individuals. Since neuroanatomic anomalies in the non-VCFS population have been reported [albeit inconsistently, see review by Pantelis (10)] in youth at familial (11–14) and clinical (15) high risk for schizophrenia, and in first episode patients with schizophrenia (16,17), several studies have focused on the brain structure of individuals with VCFS. Like youth at risk for schizophrenia, youth with VCFS display reductions in volumes of the hippocampus (18), inferior frontal lobe (19) and anterior cingulate gyrus (20). In addition, associations have been reported between volumes of temporo-occipital cortex and corpus striatum, and schizotypy in VCFS (21). However without longitudinal data, it is not clear whether these neuroanatomic anomalies are early markers for psychosis or characteristics of VCFS.

Only one longitudinal study of volumetric alterations (22) and another of cortical thickness (23) in youth with VCFS have been published. Gothelf and colleagues (22) examined neuroanatomic trajectories in nineteen individuals with VCFS and eighteen controls. Youth with VCFS displayed significant longitudinal reductions in amygdala volumes, and longitudinal increases in superior temporal gyrus gray matter, cranial white matter and cerebellar white matter. Although longitudinal decline in verbal IQ was associated with psychotic disorder at Time 2, longitudinal alterations in neuroanatomic regions of interest were not. Similarly, Schaer and colleagues (23) did not observe an association between longitudinal alterations in cortical thickness and psychosis, although they observed cortical thickness reductions in superior and inferior temporal gyri in a cross-sectional sample of adults with VCFS and psychosis relative to VCFS-affected adults without psychosis.

Herein, we report a longitudinal study of youth with VCFS, their unaffected siblings and community controls. Based on the literatures cited above, we measured several neuroanatomic regions of interest including lobar gray and white matter (22,24), frontal lobe subregions ((25,26), amygdala (27),hippocampus (12,27), superior temporal gyrus (24,27,28), and cerebellum (24). By recruiting over 70 youth with VCFS and administering dimensional and categorical measures of psychosis, we address limitations of previous longitudinal studies of VCFS, which were underpowered to detect associations between neuroanatomic trajectories and psychosis.

We hypothesized: 1) relative to controls, volumetric changes between Time 1 and Time 2 would be observed in amygdala, superior temporal gyrus, cranial white matter and cerebellum; 2) associations would be observed between a decline in verbal IQ score and prodromal symptoms; and 3) volumetric changes between Time 1 and Time 2 in hippocampus, temporal gray matter, and inferior frontal lobe would predict to prodromal symptoms.

METHODS

Participants

156 participants were enrolled in the longitudinal study of risk factors for psychosis in VCFS. Recruitment methods were described previously (29). Families of children with cytogenetically-confirmed VCFS were recruited from the VCFS International Center at SUNY Upstate Medical University. Unaffected siblings of VCFS participants were included as a separate study group to account for potential familial effects on development. Community controls were recruited through fliers at local schools. Exclusion criteria for all participants were seizure disorder, fetal exposure to alcohol or drugs, parent-reported elevated lead levels or birthweight under 2500 grams, loss of consciousness lasting longer than 15 minutes, paramagnetic implants, or orthodontic braces. Potential controls with a personal or family history of schizophrenia or bipolar disorder were excluded.

MRI Acquisition and Processing

MRIs were acquired at both time points in the axial plane on a 1.5 T Philips Gyroscan scanner (Philips Medical Systems, Best, The Netherlands) utilizing the following T1-weighted inversion recovery, turbo gradient echo (TFE) 3-D pulse sequence: echo time = 4.6 ms; repetition time = 20 ms; 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 imported into the image processing program, *BrainImage*. A previously published (30–33) semi-automated procedure was implemented to measures volumes of gray and white tissue compartments of lobar regions of the brain. In addition, previously published, reliable protocols were implemented to generate manually-traced measurements for subregions of the frontal lobe (34–36), amygdala (29,37), hippocampus (35,37), superior temporal gyrus (38), cerebellum (unpublished) and ventricles (39). Intraclass correlation coefficients (ICC), calculated to determine inter-rater reliability for each of these measures, ranged from .96 to .99 for the segmentation procedure, and .91 to .99 for manually-traced measures.

Psychological and Psychiatric Assessment Tools

At both timepoints, intellectual function was assessed with the Wechsler scales (40) and psychiatric status was assessed with the K-SADS-PL. The K-SADS-PL was administered at each timepoint by one of two investigators (K.A. and W.F.). The mean kappa coefficient across all diagnoses was .91.

The Scale of Prodromal Symptoms (SOPS)(41) was administered to all participants by a doctoral – level clinician during the structured psychiatric interview at Time 2. Inter-rater reliability, based on ratings of five consecutive, audio-taped SOPS interviews by the two clinicians noted above, and assessed with the ICC, was 0.90. The SOPS comprises four clinician-rated domains: positive prodromal symptoms, negative prodromal symptoms, disorganization and general symptoms. Since many of the children in our study had difficulty responding to a psychiatric interview, we slightly reworded the questions to permit administration to the child's parent (42). Ratings were based on a Likert-type scale. Summary scores for the four symptom domains were calculated.

We calculated two scores from the SOPS as outcome measures: 1) total SOPS summary score (SOPS Total) from Positive, Negative and Disorganization subscales of the SOPS (thus excluding the relatively non-specific General subscale); and 2) summed scores from the SOPS Positive symptom scale (SOPS Positive Symptoms), since positive symptoms are the most specific to psychosis.

Data Analyses

Multivariate analyses of co-variance (MANCOVAs) compared the neuroanatomic volumes between study groups at Time 1 and Time 2. Whole brain volume was entered as a covariate for tissue or CSF measures, including prefrontal subregions, amygdala, hippocampus, cerebellum and ventricles. Analyses of lobar gray matter (frontal, parietal, temporal, occipital) and superior temporal gyrus gray matter were adjusted for cranial gray volumes, and analyses of lobar white matter regions and STG white matter were adjusted for cranial white matter volumes. All MANCOVAs yielded significant Wilk's Lambda scores, and were followed up with planned, univariate comparisons.

Repeated-measures multivariate analyses of variance models tested for longitudinal effects, with diagnostic group as the main effect, and neuroanatomic volumes and time as repeated factors. Group and time effects and group-by-time interaction were examined.

To test the association between SOPS Total scores, SOPS Positive Symptoms and neuroanatomic variables, we calculated neuroanatomic change scores for each region of interest, using the following equation (22): ((T2 volume−T1 volume)×100)/(T1 volume×interval between scans in years). Associations between change scores and the SOPS were assessed with the Zero-inflated Poisson (ZIP) regression analyses (43) 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). We performed the Vuong test to determine if the proportion of scores equaling zero warranted traditional Poisson regression or ZIP regression. Based on the results of the Vuong test, we conducted the ZIP analysis for all variables (42).

In an effort to replicate previous longitudinal findings (22), we used Poisson regression to investigate the association between longitudinal changes in full-scale and verbal IQ scores and prodromal symptoms at Time 2.

For each set of analyses (MANCOVA, repeated measures, and ZIP regressions), comparisons were Bonferroni-corrected, resulting in a significance threshold of $p \leq .006$. P-values greater than .006 and less than or equal to .01 were considered trends.

We used Receiver Operating Characteristic (ROC) curve analysis to determine the potential for making accurate predictions of prodromal symptom status from brain regions significantly associated with SOPs scores. ROC analysis assesses the accuracy of diagnostic tests (44) (45–48).

We defined prodromal symptom status as positive if the SOPS Total score was 0.5 standard deviations above the VCFS mean. We then used logistic regression to predict this binary prodromal symptoms status variable from the brain regions associated with SOPS Total scores. For each subject, we computed the predicted values, or logits, from logistic regression. For each successive point on the logit scale we computed a sensitivity and specificity of the logit as a predictor of prodromal status by predicting those higher than the cut-point to be prodromal and others not to be prodromal. The sensitivities and specificities at each cut-point were used to draw the ROC curve. On the ROC graph, the sensitivity of different logit cut-points are graphed on the Y axis along with 1 minus the specificity on the X axis. The higher the graph extends toward the upper left corner of the graph, the higher the discriminatory power of the logit.

ROC analysis summarizes diagnostic efficiency with the area under the curve (AUC) statistic, which ranges from 0.5 (for a diagnostically useless predictor) to 1.0 (for a perfect predictor). The AUC is equivalent to the Mann-Whitney U-statistic computed from a

comparison of a continuous score between two groups (49) and it equals the probability that a randomly selected prodromal case will have a more extreme logit score than a randomly selected non-prodromal subject (49,50).

RESULTS

Sample characteristics

At Time 1, 86 youth with VCFS (Mean age = 11.9 years, SD = 2.1), 33 siblings of youth with VCFS (sibling control; Mean age = 12.3 years, SD = 2.0) and an age- and gender-matched group of 37 community controls (Mean age = 12.1 years, SD = 1.8) participated. No age [F (2, 155) = 0.55, p = .575, η^2 = .007] or gender [χ^2 (df = 2) = 2.78, p = .25] differences existed between the groups at Time 1.

A total of 122 youth returned for Time 2 follow-up. Time 2 participants included 72 youth with VCFS (Mean age = 15.1 years, SD = 2.1), 26 siblings of youth with VCFS (Mean age = 15.2 years, SD = 2.0) and 24 community controls (Mean age = 15.0 years, SD = 1.9). No age [F (2, 121) = 0.05, p = .95, η^2 = .001] or gender differences [χ^2 (df = 2) = 0.9, p = .64] existed between the groups at Time 2. The mean number of days between Time 1 and Time 2 visits was 1161.8 (S.D. = 179.3), and did not differ between study groups (F (2, 121) = 0.352, p = .70, η^2 = .006). A comparison (within each study group) between participants lost to follow-up and Time 2 returnees indicated no differences on (Time 1) sociodemographic measures including age, gender, and socioeconomic status. Accordingly, participants who completed Time 2 assessments represented the broader Time 1 sample. Table S1 (see Supplement) provides complete participant information. Longitudinal cognitive and psychiatric alterations in this cohort are described elsewhere (37).

Brain Volumes at Time 1

Table 1 reports volumes of neuroanatomic regions of interest at Time 1. Group differences in brain volumes at Time 1 were consistent with previous reports from our group on a subset of the current sample (29,34). Whole brain volume was decreased in VCFS participants relative to siblings ($p < .024$) (but not controls), however this difference did not survive Bonferroni correction. Differences in cranial gray matter volumes between the VCFS and sibling groups approached significance ($p < .008$) following Bonferroni correction. No group differences were detected in total cranial white matter. Multiple analyses of covariance models were significant for regions comprised of total tissue, gray matter and white matter. Follow-up, univariate analyses of variance indicated that relative to both siblings and controls, adjusted volumes of amygdala tissue, frontal lobe gray, and white matter, and lateral ventricles were significantly increased in participants with VCFS. Cerebellar tissue, occipital gray and occipital white matter (relative to controls only) volumes were significantly decreased in VCFS. No group differences at Time 1 were found for prefrontal subregions, hippocampus (although differences reached trend level), and superior temporal gyrus volumes. P-values ranges for these analyses are reported in Table 1.

Volumetric trajectories from Time 1 to Time 2

As described in Table 2 and Figure 1, we found nominally significant group differences in the trajectories of orbitolateral prefrontal (OLPFC) and cranial gray matter volumes between Time 1 and Time 2. The time by group interaction for the OLPFC was driven by a 14% increase in OLPFC volumes in controls relative to a 4% increase in siblings and no change in youth with VCFS. The time by group interaction for cranial gray matter was driven by a 2.7% volumetric decrease in siblings, relative to a 0.2% decrease in controls and a 0.6% decrease in youth with VCFS.

In all three study groups, we observed volumetric decreases over time in dorsomedial prefrontal tissue (between group mean: 8.4%), and frontal (2.8%), parietal (4.3%) and superior temporal gray matter (6.6%), and volumetric increases in cerebellar tissue (3.3%) and superior temporal white matter (8.8%). Although the effect of time was also significant for the overall model of parietal white matter, and approached significance for cranial, temporal and occipital white matter, post-hoc t-tests indicated that these effects were driven primarily by significant volumetric white matter increases in the group of participants with VCFS. In youth with VCFS, cranial white matter volumes increased by 2.9%, parietal by 3.3%, temporal by 7.3% and occipital by 12.4%. With the exception of parietal white matter volumes in siblings (+3.5%), age-related change in these white matter regions did not reach significance for non-VCFS participants.

Association Between Neuroanatomic Trajectories and Prodromal Symptoms in VCFS

As noted above, associations between neuroanatomic trajectories and both the SOPS (3-category) Total score and the SOPS Positive Symptom scores were investigated. Since very few siblings or controls obtained scores above zero on the SOPS, these analyses were conducted on participants with VCFS only. Over the three-year time period, volumetric decreases in multiple brain regions (see Table 3) were associated with SOPS Total scores at Time 2. In contrast, only decreases in temporal lobe gray matter volumes ($p < .002$) predicted to positive prodromal symptoms of psychosis at Time 2 (See Figure 2).

Longitudinal decreases in full-scale IQ predicted to SOPS Total scores ($p < .0001$), but not to SOPS Positive Symptoms scores at Time 2. In contrast, longitudinal decreases in verbal IQ scores predicted to SOPS Positive Symptom scores ($p < .002$), but not to SOPS Total scores at Time 2.

We used Receiver Operating Characteristic (ROC) curve analysis to determine the potential for making accurate predictions of SOPS Summary score diagnostic status at Time 2 from the significant association seen in Table 3. Figure S1 (see Supplement) plots the ROC curve. The area under the curve (AUC) statistic was 0.864, which means that, with a probability of 86.4%, a randomly selected prodromal case is likely to have a more extreme logit score than a randomly selected member of the non-prodromal group.

DISCUSSION

In this longitudinal study, we observed that at Time 1, adjusted volumes of frontal gray and white matter, amygdala and lateral ventricles were increased in participants with VCFS relative to siblings and controls, whereas adjusted volumes of occipital gray and white matter, and cerebellum, were decreased. Neuroanatomic trajectories between Times 1 and 2 were comparable among groups for most regions of interest, except cranial gray matter, which decreased in siblings but not controls or VCFS youth, and orbitofrontal cortex, which increased in controls, but not siblings or VCFS youth with. However, the overall significant effect of time for white matter volumes in several lobar regions was driven primarily by the group of youth with VCFS, in whom white matter volumes in several posterior lobar regions of the brain increased significantly. Finally, we observed that in youth with VCFS, longitudinal alterations in multiple brain regions predicted to total prodromal symptoms, whereas longitudinal decreases in temporal lobe gray matter volumes and in verbal IQ predicted specifically to positive prodromal symptoms of psychosis at Time 2.

Cross – Sectional Findings

Group differences observed at Time 1 between youth with VCFS, siblings and community controls are in line with previous cross-sectional studies of neuroanatomy (32,33)

demonstrating that frontal lobe (as a whole) is relatively enlarged in children with VCFS, and that posterior regions of the brain are relatively reduced in volume. The mechanism for this has not been established, although it is consistent with disruption of early neural crest development that has been previously described in individuals with this disorder (51). Interestingly, tissue redistribution involving relative enlargement of anterior brain regions and relative reduction in posterior brain regions have also been observed in individuals with non-syndromic clefts (52), suggesting that genetic and molecular factors in early embryological development may be influencing craniofacial and brain morphology in a parallel manner (52).

Our findings of enlarged amygdala volumes in youth with VCFS are consistent with our previously published study (29) conducted on a subset of the current sample. Enlarged amygdala volumes in VCFS have also been reported by Gothelf and colleagues (22), although group differences in amygdala volumes did not reach significance in their sample, which was considerably smaller than the current sample. Previously we reported that enlarged amygdala volumes in VCFS were associated with higher parent ratings of child anxiety and aggression (29). A recent report of typically - developing girls (53) supports this association and suggests, if replicated, that the amygdala may play a role in the clinical manifestation of anxiety that is frequently reported in VCFS.

Longitudinal Trajectories of Brain Structures

The longitudinal trajectories of most brain regions in VCFS were comparable in direction, although not necessarily magnitude, to unaffected siblings and community controls. The lobar trajectories for all study groups are consistent with a substantial literature that demonstrates a dynamic relationship between gray and white matter in which cerebral gray matter volumes generally peak and then decrease during adolescence while cerebral white matter volumes increase (54–58). Moreover, within frontal lobe, the dorsolateral PFC usually matures relatively later than other frontal lobe subregions (55), potentially explaining longitudinal changes observed across all study groups in dorso- and orbitomedial PFC, but not in dorsolateral PFC. Consistent with the study by Gothelf et al.(22), hippocampal volumes increased significantly across all study groups as well. The only significant time by group effect was for the orbitolateral cortex, which increased significantly in controls but not in VCFS participants or their siblings. This suggests that the developmental trajectories we observed in that region may be due to familial/genetic effects rather than the 22q11.2 deletion per se.

Our study did not replicate the group differences in brain trajectories that Gothelf and colleagues (22) reported in STG gray matter or amygdala volumes. Although our observations of accelerated increases in cranial (and lobar) white matter in youth with VCFS relative to controls were consistent with the findings of Gothelf et al., we did not observe a significant interaction between time and diagnosis for those brain regions. This is likely due to the fact that whereas Gothelf and colleagues compared their VCFS cohort to a single control group, we compared our cohort to both siblings and controls, potentially reducing power in our time by diagnosis statistical analyses.

Several cross-sectional studies have observed relative reductions in both frontal and posterior lobar white matter regions (21,33,59) in children with VCFS. The longitudinal increases in posterior white matter volumes that we found, and the increases in total cranial white matter that Gothelf et al. also observed in patients with VCFS are intriguing. However, as Gothelf and colleagues note, these alterations could reflect a pathological process, in which lobar white matter volumes continue to increase, or a “catch-up” process in adolescent youth with this syndrome, by which volumes will stabilize to the point at which they are comparable to siblings and controls.

Prediction to Symptoms of Psychosis

Although we found that in VCFS, volumetric decrements over time in cranial gray and white matter, prefrontal cortex, mesial temporal lobe, and cerebellum were predictive of prodromal symptoms, only decrements in temporal lobe gray matter predicted to prodromal positive symptoms of psychosis at Time 2. These changes could represent accelerated synaptic pruning, biochemical cascades that ultimately influence alteration in brain tissue, or other, unknown, pathophysiological mechanisms. Interestingly, this finding is consistent with several longitudinal neuroimaging studies of adolescents at clinical and familial high risk for schizophrenia, in which youth who either display prodromal symptoms (14) or transition to psychosis demonstrate gray matter loss over time in superior (60) and inferior temporal lobe (25), as well as superior (60) and inferior (25,61) frontal lobe, and cingulate (25). Importantly, however, none of our participants had developed frank psychosis or received a diagnosis of schizophrenia by Time 2 (although several were experiencing transient hallucinations). Moreover, the age range of our participants is characterized by continuing dynamic alterations in the structure of the brain, due to ongoing myelination and synaptic pruning (10). Accordingly, decrements in temporal lobe gray matter during this transitional window in time may not necessarily reflect a stable marker of psychosis in youth with VCFS (10).

Our finding that decline in verbal IQ scores were predictive of positive symptoms of psychosis is consistent with that of Gothelf and colleagues (22), and with several studies demonstrating a decline in verbal skills in the years preceding the onset of schizophrenia (62,63). Accordingly, in combination with Time 1 neuropsychological markers that we have previously identified in this cohort (42), longitudinal decline in verbal IQ can be considered a risk factor for severe psychiatric disorder in youth with VCFS.

Our ROC analysis suggests that, in addition to being statistically significant, our finding that multiple brain regions predict prodromal symptoms may have substantial predictive accuracy. This is seen by the high AUC statistic of 0.8636 and also by inspection of Figure S1 (see Supplement). By following the ROC curve from the lower left corner to upper right corner, we can see how changes in the predictor score cutpoint affect the tradeoff between sensitivity and specificity. For example, the 12^{th} point on the graph indicates that our logit score predictor can achieve a sensitivity of 70% and a specificity of 90%, which would be reasonable for a screening tool meant to identify VCFS children at risk for prodromal psychosis. Further research is needed because the screening accuracy would likely decrease somewhat with cross-validation and studies of non-VCFS samples would be needed to assess generalization.

This study must be considered within the context of its limitations. Although our published protocol to parcellate subregions of the frontal lobe is highly reliable, it does not correspond precisely to gyral/sulcal boundaries of frontal subregions, potentially undermining the construct validity of the measures. Nonetheless, the predictive validity of these measures has been demonstrated in studies of schizophrenia (36). In addition, our sample was not large enough to control for the possible effects of medication on neuroanatomic change. Moreover, as noted above, our sample is just reaching the age at which the risk for schizophrenia increases. Although several participants in our sample were already exhibiting prodromal symptoms of psychosis at the second timepoint that were related to temporal lobe volume loss, we are unable to make more definitive statements about the association between decrements in brain volume and onset of schizophrenia. Even with these limitations, our observations are consistent with the findings of studies of non-VCFS adolescents at risk for schizophrenia, and contribute to our identification of specific, longitudinal neuroanatomic alterations in VCFS youth that may be predictive of increased risk for psychosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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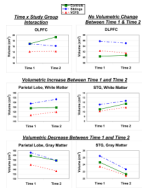

Figure 1.

This figure depicts variability in neuroanatomic trajectories across brain regions, by study group. With the exception of the plot depicting Time × Study Group Interaction for the orbitolateral prefrontal cortex (OLPFC), the plots are exemplary of the patterns of neuroanatomic development we observed for several brain regions. The plot for the dorsolateral prefrontal cortex (DLPFC) exemplifies the brain regions for which we found *no significant effect of time* in any study group. The plots for parietal and superior temporal gyral (STG) white matter exemplify the brain regions for which we observed a significant effect of time, indicating *volumetric increases* in all study groups. The plots for parietal and STG gray matter exemplify brain regions for which we observed a significant effect of time, indicating *decreases* in all study groups.

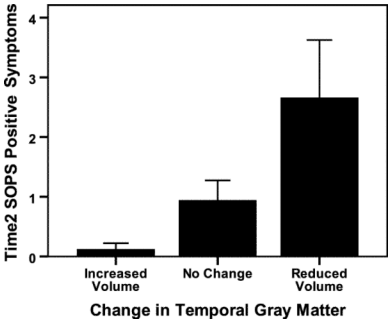

Figure 2.

This figure represents the significant association between longitudinal change in the volumes of temporal lobe gray matter and Time 2 SOPS scores on the Positive Symptom Scale. The distribution of SOPS Positive Symptom scores prevented us from using a regression plot. Instead, degree of temporal lobe gray matter change in youth with VCFS was represented with three categories: 1) no change = mean change score + / − 0.5 standard deviations; 2) volumetric decrease < 0.5 standard deviations below mean change score; 3) volumetric increase > 0.5 standard deviations above mean change score.

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Table 1

MANCOVA Results Comparing Study Groups For Time 1 and Time 2 Volumes (Mean, Standard Deviation) of Brain Regions of Interest

Brain Regions	Time 1			Time 2		
	Controls	Siblings	VCFS	Controls	Siblings	VCFS
Total Tissue €						
WBV	1364.4 (130.5)	1425.8 (169.8)	1335.1 (120.0)	1362.8 (111.4)	1424.0 (161.9)	1336.9 (126.4)
DLPFC	60.3 (12.9)	65.7 (12.8)	62.3 (10.2)	60.7 (13.9)	65.0 (12.7)	61.5 (9.8)
DMPFC	62.9 (9.2)	66.8 (11.4)	64.5 (9.8)	56.9 (7.6)	61.3 (9.0)	59.6 (9.3)
OLPFC	16.9 (5.6)	16.8 (7.5)	14.1 (6.1)	19.3 (6.9)**	16.1 (4.8)	14.2 (6.1)
OMPFC	25.5 (6.9)	25.2 (7.4)	24.8 (7.1)	24.5 (5.0)	23.2 (5.2)	23.1 (6.4)
Amygdala	4.0 (0.9)**	4.2 (0.6)**	4.5 (0.8)	4.1 (1.1)	4.2 (0.9)	4.4 (0.9)
Hippocampus	6.1 (0.6)	6.1 (0.6)	5.6 (0.8)	6.3 (1.0)	6.5 (1.1)	6.0 (1.0)
Cerebellum	138.2 (12.6)**	143.6 (18.8)**	126.2 (13.5)	141.8 (10.6)**	151.5 (17.0)**	130.6 (12.8)
Gray Matter £						
Cranial Gray	732.0 (76.1)	766.6 (104.2)**	707.5 (63.2)	730.5 (69.6)	745.8 (85.6)	703.5 (72.2)
Frontal	228.6 (25.2)**	238.4 (32.4)**	230.7 (20.5)	223.5 (31.0)	231.0 (28.2)	223.3 (23.1)
Parietal	154.4 (15.4)	157.7 (24.7)	144.9 (15.2)	149.5 (14.8)	149.4 (21.7)	138.3 (16.7)
Temporal	138.8 (18.4)	147.6 (22.4)	135.4 (14.4)	136.9 (25.4)	144.4 (17.8)	137.8 (17.8)
Occipital	73.8 (11.5)**	77.1 (14.6)	66.6 (8.2)	77.7 (18.0)	73.6 (11.2)	70.0 (18.9)
STG Gray	24.3 (2.7)	25.2 (3.4)	23.7 (3.0)	22.6 (3.1)	23.3 (2.6)	22.4 (3.0)
White Matte ℓ						
Cranial White	511.2 (74.6)	537.4 (74.4)	497.4 (64.5)	523.3 (75.6)	550.9 (76.6)	514.0 (73.6)
Frontal	166.0 (24.8)**	173.6 (27.2)**	174.5 (21.8)	165.4 (26.8)**	175.2 (27.8)**	174.6 (24.4)
DLPFC	7.8 (3.4)	9.9 (4.4)	8.6 (3.4)	9.1 (5.0)	9.7 (3.8)	8.3 (2.9)
Parietal	123.8 (17.0)	128.6 (19.4)	116.5 (15.9)	124.5 (15.7)	133.1 (20.2)	119.9 (16.5)
Temporal	69.0 (12.5)	75.0 (14.2)*	65.9 (9.1)	69.7 (20.0)	76.8 (12.7)	70.7 (14.6)
Occipital	52.9 (10.0)**	54.5 (10.1)	47.5 (7.7)	58.5 (18.6)	57.0 (8.6)	53.4 (18.8)
STG White	10.5 (1.9)	11.5 (1.7)	10.1 (1.8)	11.7 (1.9)	12.3 (2.2)*	10.9 (1.7)
Cerebral Spinal Fluid						

Brain Regions	Time 1			Time 2		
	Controls	Siblings	VCFS	Controls	Siblings	VCFS
Lateral Ventricles	3.8 (4.8)	3.6 (2.6)	8.4 (7.7)	3.7 (4.4)	3.4 (2.3)	7.7 (7.5)

all p - values are reported in relation to the VCFS sample

Abbreviations: WBV: Whole Brain Volume; DLPFC: Dorsolateral Prefrontal Cortex; DMPFC: Dorsomedial Prefrontal Cortex; OLPFC: Orbitolateral Prefrontal Cortex; OMPFC: Orbitomedial Prefrontal Cortex; STG: Superior Temporal Gyrus

** $p \leq .006$;

* $0061 < p \leq .01$;

€ MANCOVA conducted for these variables (whole brain volume entered as covariate). Time 1 Wilks Lambda [df: 1,2,107] = .52; $p < .001$; et = .28; Time 2 Wilks Lamda [df: 1,2,107] = .50; $p < .001$; eta2 = .29.

£ MANCOVA conducted for these variables (cranial gray matter entered as covariate). Time 1 Wilks Lambda [df: 1,2,103] = .70; $p < .001$; eta2=.17; Time 2 Wilks Lamda [df: 1,2,102] = .71; p = < .001; eta2 = .16.

ℓ MANCOVA conducted for these variables (cranial white matter entered as covariate). Time 1 Wilks Lambda [df: 1,2,103] = .52; $p < .001$; eta2 = .28; Time 2 Wilks Lamda [df: 1,2,102] = .62; $p < .001$; eta2 = .22.

Table 2

Repeated Measures Analyses of Trajectories of Brain regions of Interest Between Timepoints

Neuroanatomic Region	Time			Time X Diagnosis			Percent Change in Volume (p)		
	F (df)	p	eta^2	F(df)	p	eta^2	Controls	Siblings	VCFS
Total Tissue									
DLPFC	0.0 (1,94)	.91	.00	0.1 (2,94)	.91	.00	+0.7 (.83)	−1.1 (.79)	−1.3 (.73)
DMPFC	73.6 (1,94)	.0001	.44	0.9 (2,94)	.41	.02	−9.5 (.001)	−8.2 (.001)	−5.4 (.001)
OLPFC	3.9 (1,94)	.02	.06	3.9 (2,94)	.02	.08	+14.2 (.002)	−4.2 (.91)	+0.7 (.84)
OMPFC	3.7 (1,94)	.06	.04	1.4 (2,94)	.26	.03	−3.9 (.80)	−7.9 (.11)	−6.9 (.004)
Amygdala	1.6 (1,87)	.21	.02	0.2 (2,87)	.84	.00	+2.5 (.34)	+0.0 (.82)	−2.2 (.21)
Hippocampus	7.5 (1,80)	.008	.09	0.1 (2,80)	.90	.00	+3.3 (.20)	+6.6 (.21)	+7.1 (.004)
Cerebellum	20.8 (1,92)	.0001	.18	1.2 (2,80)	.31	.03	+2.6 (.05)	+5.5 (.001)	+3.5 (.006)
Gray Matter									
Cranial Gray	1.6 (1,95)	.21	.02	3.3 (2,95)	.04	.07	−0.2 (.35)	−2.7 (.009)	−0.6 (.54)
Frontal	16.7 (1,95)	.0001	.15	1.5 (2,95)	.22	.03	−2.2 (.51)	−3.1 (.002)	−3.2(.0001)
Parietal	33.5 (1,95)	.0001	.26	1.9 (2,95)	.15	.04	−3.2 (.18)	−5.2 (.0001)	−4.5 (.0001)
Temporal	0.0 (1,95)	.98	.00	1.4 (2,95)	.24	.03	−1.4 (.67)	−2.2 (.23)	+1.8 (.20)
Occipital	0.6 (1,95)	.44	.01	1.8 (2,95)	.17	.04	+5.3 (.28)	−4.5 (.30)	+5.1 (.08)
STG Gray	51.2 (1,93)	.0001	.36	0.7 (2,93)	.50	.02	−7.0 (.005)	−7.5 (.0001)	−5.5 (.0001)
White Matter									
Cranial White	6.8 (1,95)	.01	.07	0.1 (2,95)	.90	.00	+2.4 (.14)	+2.5 (.31)	+3.3 (.01)
Frontal	0.3 (1,95)	.58	.10	0.0 (2,95)	.97	.00	−0.4 (.92)	+0.9 (.79)	+0.1 (.22)
DLPFC White	1.0 (1,93)	.32	.01	1.8 (2,93)	.16	.03	+16.7 (.06)	−2.0 (.77)	−3.5 (.73)
Parietal	15.5 (1,95)	.0001	.14	1.2 (2,95)	.29	.03	+0.6 (.45)	+3.5 (.003)	+2.9 (.0001)
Temporal	3.6 (1,95)	.06	.04	0.7 (2,95)	.48	.02	+1.0 (.54)	+2.4 (.56)	+7.3 (.004)
Occipital	6.1 (1,95)	.02	.06	0.6 (2,95)	.56	.01	+10.6 (.13)	+4.6 (.60)	+12.4 (.004)
STG White	27.5 (1,93)	.0001	.23	1.7 (2,93)	.19	.04	+11.4 (.0001)	+7.0 (.038)	+7.9 (.001)
CSF									
Lat. Ventricles	0.4 (1,96)	.53	.004	0.36 (2,96)	.70	.01	−2.6 (.63)	−6.0 (.80)	−8.3 (.22)

Abbreviations: WBV: Whole Brain Volume; DLPFC: Dorsolateral Prefrontal Cortex; DMPFC: Dorsomedial Prefrontal Cortex; OLPFC: Orbitolateral Prefrontal Cortex; OMPFC: Orbitomedial Prefrontal Cortex; STG: Superior Temporal Gyrus

Table 3

Results of Zero-Inflated Poisson Regression Analyses of the Association Between Longitudinal Change in Brain Regions of Interest and Scores on the Scale of Prodromal Symptoms (SOPS) At Time 2 in Youth With VCFS

Neuroanatomic Region	SOPS_Total		SOPS_Positive Symptoms	
	z-score	p-value <	z-score	p-value <
Total Tissue				
DLPFC	−2.69	0.007	−1.44	0.150
DMPFC	0.50	0.614	−1.45	0.148
OLPFC	−5.10	0.0001	0.49	0.622
OMPFC	−4.19	0.0001	0.64	0.523
Amygdala	−2.73	0.006	−0.87	0.382
Hippocampus	−5.48	0.0001	−0.86	0.388
Cerebellum	−4.82	0.0001	−1.66	0.098
Gray Matter				
Cranial Gray	−3.66	0.0001	−1.99	0.047
Frontal	−2.45	0.014	−0.62	0.537
Parietal	−1.54	0.124	−0.70	0.485
Temporal	−5.43	0.0001	−3.14	0.002
Occipital	−3.31	0.001	0.22	0.827
STG	−2.96	0.003	−0.21	0.832
White Matter				
Cranial White	−5.23	0.0001	−0.17	0.863
Frontal	1.45	0.148	2.21	0.027
Parietal	−4.46	0.0001	0.55	0.579
Temporal	−4.58	0.0001	−1.56	0.118
Occipital	−4.78	0.0001	−0.24	0.810
STG	−5.07	0.0001	−0.01	0.993
Cerebral Spinal Fluid				
Ventricles	−2.86	0.004	0.30	0.765

Abbreviations: WBV: Whole Brain Volume; DLPFC: Dorsolateral Prefrontal Cortex; DMPFC: Dorsomedial Prefrontal Cortex; OLPFC: Orbitolateral Prefrontal Cortex; OMPFC: Orbitomedial Prefrontal Cortex; STG: Superior Temporal Gyrus