

# Brain Anatomy in Adults With Velocardiofacial Syndrome With and Without Schizophrenia

## Preliminary Results of a Structural Magnetic Resonance Imaging Study

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**Context:** Velocardiofacial syndrome is associated with interstitial deletions of chromosome 22q11, mild to borderline learning disability, characteristic dysmorphism, and a high prevalence of schizophrenia. The biological basis for this increased risk for schizophrenia is unknown, but people with velocardiofacial syndrome may have genetically determined differences in brain anatomy that predispose to the development of schizophrenia.

**Objective:** To determine whether there are differences in brain structure between subjects with velocardiofacial syndrome with and without schizophrenia.

**Design:** A cross-sectional quantitative structural magnetic resonance imaging study in 39 adult subjects.

**Setting:** Referrals were made through medical genetics clinics and psychiatric services throughout the United Kingdom.

**Participants:** Thirteen subjects with velocardiofacial syndrome and schizophrenia, 12 with velocardiofacial syndrome without history of a psychosis, and 14 healthy con-

trols volunteered to participate after screening for eligibility.

**Main Outcome Measures:** Total and regional brain volumes were analyzed by means of manual tracing, and gray- and white-matter densities were obtained by computerized voxel-based methods.

**Results:** People with velocardiofacial syndrome and schizophrenia, compared with both controls and non-schizophrenic patients with velocardiofacial syndrome, had a significant ( $P < .05$ ) reduction in volume of whole-brain (white + gray) matter and whole-brain white matter, and an increase in total and sulcal cerebrospinal fluid volume. Both velocardiofacial syndrome groups had a reduced cerebellar volume compared with controls.

**Conclusions:** Within velocardiofacial syndrome, schizophrenia is associated with generalized differences in brain anatomy, but white matter may be particularly implicated. Studies with larger samples are needed to replicate our findings.

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**V**ELOCARDIOFACIAL SYNDROME (VCFS), also known as 22q11 deletion syndrome or DiGeorge syndrome, is a genetic disorder that occurs in approximately 1 in 4000 to 5000 live births.<sup>1,2</sup> In 85% of people with VCFS, an approximately 3-megabase deletion of 22q11 is detected with fluorescence in situ hybridization.<sup>3</sup> The presence of VCFS is associated with a characteristic physical phenotype (including congenital cardiovascular anomalies and velopharyngeal insufficiencies), mild to borderline learning disability, and specific cognitive deficits (eg, in object perception, planning, and abstract reasoning).<sup>4-7</sup> In addition, psychiatric problems are frequently reported in children with VCFS. These include social with-

drawal, phobia, depression, attention-deficit/hyperactivity disorder, and autistic spectrum disorder.<sup>8-10</sup> In adult life, people with VCFS are at increased risk of developing psychosis, particularly schizophrenia.<sup>11</sup> The reported prevalence rate for psychosis (including bipolar disorder, and schizophrenia and related disorders) is approximately 30%, but methodologic differences complicate the interpretation of these studies, and some involve adults and others include adolescents.<sup>11-14</sup> In a large study, Murphy et al<sup>11</sup> found psychosis in 30% (schizophrenia in 24%) of adults with VCFS.

Schizophrenia is a heterogeneous disorder that is likely to be caused by interaction of several susceptibility genes and environmental risk factors. The morbid risk of schizophrenia for a patient with

VCFS is approximately 25 times that of the general population, and, thus, possession of chromosome 22q11 deletion, apart from being the offspring of 2 schizophrenic parents or having a schizophrenic monozygotic co-twin, is the highest known risk factor for the development of schizophrenia.<sup>15</sup> This suggests that deletion of 1 or more gene(s) mapping to chromosome 22q11 underlies susceptibility to psychosis in VCFS.<sup>15</sup> The study of VCFS therefore provides a unique opportunity to increase our understanding of the neurobiology of schizophrenia in the general population.

There is growing consensus from a large body of in vivo neuroimaging studies that people with schizophrenia have several structural brain abnormalities. Increased volume of cerebral ventricles is one of the most consistently reported findings, together with reduction in the volume of total brain and gray matter (for a review, see Shenton et al<sup>16</sup>). Also, localized volume and gray-matter reductions have frequently been described in several brain regions, mostly implicating temporolimbic and frontal neocortical regions, whereas there is less support for cerebellar abnormalities.<sup>16-18</sup> In contrast, there have been fewer studies on white-matter volumes, but recent studies using newer techniques including diffusion tensor imaging,<sup>19,20</sup> magnetic transfer imaging,<sup>21</sup> and microarray<sup>22</sup> suggest that white-matter integrity, including oligodendroglia and myelination, may be compromised as well in schizophrenia.<sup>23</sup>

There are relatively few neuroimaging studies of people with VCFS. Case reports and qualitative studies have reported that people with VCFS have a high prevalence of white-matter hyperintensities (WMHIs) (which may reflect abnormalities in myelination and high water content<sup>24</sup>), cavum septum pellucidum–cavum vergae, and a small cerebellar vermis.<sup>25-29</sup> Quantitative studies reported that learning-disabled children with VCFS, when compared with healthy children of normal intelligence, have a generalized reduction in volume of both cerebral hemispheres (mostly affecting white matter), combined with increased volume of frontal lobe and decreased volume of left parietal gray matter.<sup>30,31</sup> There are, to our knowledge, only 2 quantitative neuroimaging studies in adults with VCFS. Our group reported that, when compared with IQ-matched controls, adults with VCFS have a smaller cerebellar volume, widespread deficits in white matter, and localized gray-matter deficits in temporal and cerebellar regions.<sup>29</sup> That study, however, did not differentiate between individuals with VCFS with and without schizophrenia. Recently, Chow et al<sup>32</sup> compared adults with VCFS and schizophrenia and healthy controls without VCFS, and reported that adults with VCFS and schizophrenia had a smaller volume of total gray matter; regional differences in gray and white matter in frontal, temporal, parietal, and occipital lobes; and an increased volume of ventricular and sulcal cerebrospinal fluid (CSF) bilaterally. Although this study was an important first step, their control group was not matched for the presence of VCFS or IQ, and so it is unclear whether the differences they reported are due to the presence of VCFS, schizophrenia, learning disability, or all 3.

To our knowledge, there have been no studies comparing the brain anatomy of adults with VCFS with and

without schizophrenia. We therefore extended our previous work and examined the brain structure of schizophrenic (S-VCFS) and nonschizophrenic (NS-VCFS) adults with VCFS and chromosome 22q11 deletion, and a healthy IQ-matched control group by means of structural magnetic resonance imaging (MRI). We tested the hypotheses that (1) adults with S-VCFS have a significant reduction of brain volume in frontal and temporolimbic brain regions reflecting brain abnormalities associated with schizophrenia in the general population; and (2) both patients with S-VCFS and NS-VCFS would have a significant reduction of cerebellar volume reflecting a brain abnormality commonly associated with VCFS.

## METHODS

### SUBJECTS

Approval for the study was granted by the local ethics committee, and all subjects (or their guardians, in case subjects were unable to consent) gave written informed consent after the procedure was fully explained. All patients with VCFS and control subjects were screened for medical conditions affecting brain function by means of a semistructured clinical interview and routine blood tests. Full-scale intelligence was measured by means of the Canavan et al shortened version of the Wechsler Adult Intelligence Scale–Revised, consisting of 5 subtests: vocabulary, comprehension, similarities, block design, and object assembly.<sup>33</sup> We included 25 subjects with clinical features of VCFS and a 22q11 deletion detected by fluorescence in situ hybridization (Oncor Inc, Gaithersburg, Md). They volunteered and were eligible to undergo MRI. All individuals with VCFS were interviewed by one of us (K.C.M.) by means of a semistructured psychiatric interview (Schedules for Clinical Assessment in Neuropsychiatry)<sup>34</sup> to establish a DSM-IV diagnosis as described previously.<sup>11</sup> Fifteen individuals with VCFS (8 with schizophrenia and 7 without) were part of the original sample reported by Murphy and colleagues,<sup>11</sup> while 10 individuals with VCFS (5 with schizophrenia and 5 without) were recruited from the Behavioral Genetics Clinic, Maudsley Hospital, London, England. The VCFS group was subdivided into 2: those who met DSM-IV criteria for schizophrenia ( $n=13$ ; 7 women and 6 men; mean  $\pm$  SD age,  $34 \pm 11$  years; IQ,  $69 \pm 8$ ; all taking antipsychotic medication and having a duration of illness  $>1$  year, 2 hospitalized at time of scanning) and those who had no history of psychosis ( $n=12$ ; 8 women and 4 men; age,  $31 \pm 10$  years; IQ,  $74 \pm 9$ ). We included a healthy control group, recruited from local community centers for people with mild or borderline learning disabilities and/or by local advertising ( $n=14$ ; 8 women and 6 men; age,  $36 \pm 10$  years; IQ,  $75 \pm 16$ ). Controls were included after screening for psychiatric disorders and medical conditions affecting brain function and after a deletion at 22q11 was excluded by fluorescence in situ hybridization testing.

### IMAGE ACQUISITION

Magnetic resonance imaging of the brain was performed on a 1.5-T MRI system (Signa; General Electric Co, Milwaukee, Wis) at the Maudsley Hospital. A coronal volumetric spoiled gradient acquisition in the steady state data set covering the whole head was acquired (repetition time, 13.8 milliseconds; echo time, 2.8 milliseconds; 124 sections; 1.5-mm section thickness). This data set was used to perform manual tracing of brain volumes.<sup>35</sup> In addition, we acquired a whole-brain near axial dual-

echo fast spin-echo data set aligned with the anterior commissure–posterior commissure plane (repetition times, 4000 milliseconds; effective echo times, 20 and 85 milliseconds; 3-mm section thickness). This data set was used to determine between-group differences in gray- and white-matter volume by using a previously published method.<sup>29,36,37</sup> Three types of analysis were performed, one qualitative and two quantitative; all were blind to subject group status.

### QUALITATIVE ANALYSIS

Both MRI data sets were assessed qualitatively by a neuroradiologist. The presence and extent of ventricular white-matter hyperintensities (WMHs) were assessed by means of a 4-point rating scale adopted from Kozachuk et al<sup>24</sup> as follows: grade 0, ventricular WMHs absent; grade 1, frontal or occipital caps or pencil-thin lining of the lateral ventricle; grade 2, smooth halo surrounding the lateral ventricles; and grade 3, irregular ventricular WMHs extending into the deep white matter. Deep WMHs were graded as follows: grade 0, absent; grade 1, punctate foci either focal or symmetric; grade 2, mild confluence of foci; and grade 3, large confluence of foci. Peripheral WMHs were graded similarly to deep WMHs. Congenital abnormalities in cerebellum and cerebrum including cavum septum pellucidum–septum vergae were noted as being present or absent.

### MANUAL TRACING

As described previously, volumetric analysis of total and regional brain areas was performed on a reformatted spoiled gradient acquisition in the steady state data set by means of Measure software.<sup>35</sup> Total, right, and left caudate, putamen, hippocampus, amygdala, and frontal, occipitoparietal, and temporal lobes; cerebral hemispheres; and cerebellum, brainstem, and ventricular CSF volumes were traced by means of region of interest boundaries as previously described.<sup>29,36,38–40</sup> Right and left hemispheres, cerebral ventricles, and subcortical gray regions were measured on images aligned along the anterior commissure–posterior commissure line. The frontal lobe was defined as all supratemporal structures anterior to the sylvian aqueduct. Temporal lobe was defined, from the anterior pole of the temporal lobe to the sylvian aqueduct. The medial temporal lobe boundary was defined as a straight line from the angle of the medial temporal lobe, where it attaches to the temporal stem, to the midpoint of the operculum; the dura of the middle cranial fossa was then traced around each temporal lobe to complete the region. The parietal lobe was defined as brain matter posterior to the sylvian aqueduct, extending to the medial transverse fissure of striate cortex. Remaining caudal portions of the cerebral hemispheres were defined as parieto-occipital lobe. Regions of cerebellar brain and brainstem were measured in the posterior fossa.

Images were realigned parallel to the sylvian fissure for hippocampal and amygdalar measures. The hippocampus was measured starting at the section displaying the sylvian aqueduct. Continuing anteriorly, the superior border of the hippocampus merges with the inferior border of the amygdala. The hippocampus-amygdala delineation is marked by white matter and the temporal horn of the lateral ventricle. If that delineation is unclear, the inferior border of the posterior amygdala is marked arbitrarily by a horizontal line drawn medially from the head of the temporal stem to the medial border of the amygdala; the amygdala is taken to be gray matter superior to that line.

The volume of each region was calculated by multiplying the summed pixel cross-sectional areas by section thickness. Intrarater and interrater reliabilities (range, 0.90–0.99) were determined by intraclass correlation computation for all brain re-

gions traced by the operators and were highly significant ( $F > 4.0$  and  $P < .002$ ).<sup>41</sup>

### VOXELWISE ANALYSIS

Voxels representing extracerebral tissue were automatically set to zero,<sup>42</sup> and the probability of each intracerebral voxel belonging to gray matter, white matter, CSF, or dura-vasculature tissue classes was then estimated by a modified fuzzy clustering algorithm.<sup>43</sup> On the basis of previous results, we equated these probabilities to the proportional volumes of each tissue class in the often heterogeneous volume of tissue represented by each voxel.<sup>44</sup> Thus, for example, if the probability of gray-matter class membership was 0.8 for a given voxel, it was assumed that 80% of the tissue represented by that voxel was gray matter. Because the voxel size was predetermined (2.2 mm<sup>3</sup>), we then estimated the volume in milliliters of gray matter, white matter, and CSF in each voxel. Summing these voxel tissue class volumes over all intracerebral voxels yielded global tissue class volumes.

To allow estimation of between-group differences at each intracerebral voxel (spatial extent statistics), the short echo (proton density-weighted) fast spin-echo images were coregistered by means of an affine transformation<sup>45,46</sup> with a template image in the coordinate system of standard space as defined by Talairach and Tournoux.<sup>47</sup> This individually estimated transformation was then applied to each of that subject's gray- and white-tissue probability maps.

### STATISTICS

#### Demographic Data

Between-group differences in age and IQ were assessed by means of a 1-way analysis of variance and  $\chi^2$  test for sex distribution ( $P < .05$ , 2-tailed).

#### Qualitative Data

Group differences in frequencies of structural abnormalities were assessed with the  $\chi^2$  test, whereas between-group differences in extent of WMHs were assessed with a 1-way analysis of variance, with level of significance for both tests at  $P < .05$ , 2-tailed.

### ANALYSIS OF MRI DATA BY MANUAL TRACING

Manually traced volumes (Measure) were analyzed with SPSS 10.0 for Windows (SPSS Inc, Chicago, Ill). Data were first examined for normality to conform to the assumptions of the parametric statistics used. Between-group differences in uncorrected total regional brain volumes were calculated by means of a univariate general linear model (GLM) with group (schizophrenic [S-VCFS] or non-schizophrenic VCFS [NS-VCFS], controls) and sex (male, female) as the between-subject variables, and age and total intracranial volume (ICV) as covariates and, where appropriate, Bonferroni adjustments for multiple comparisons. The significance level was defined as  $P < .05$ , 2-tailed.

### ANALYSIS OF MRI DATA BY COMPUTERIZED VOXELWISE ANALYSIS

Fast spin-echo data were unavailable for 2 of the patients with S-VCFS and 3 of the controls. Total gray- and white-matter and CSF volumes in the S-VCFS, NS-VCFS, and control groups were compared by univariate GLM using sex, age, and ICV as covariates (SPSS 10.0) and, where appropriate, Bonferroni adjustments for multiple comparisons. Between-group differ-



**Table 1. Qualitative (Radiologic) Findings in S-VCFS, NS-VCFS, and Healthy Control Subjects**

Structure	S-VCFS (n = 13)	NS-VCFS (n = 12)	Controls (n = 12)
Small/abnormal cerebellar vermis, No.	0	1	0
Cavum septum pellucidum/vergae, No.	4	6	0*
Total presence of WMHs, No.	8	7	3
Ventricular WMHs, No.	1	4	1
Deep WMHs, No.	5	4	3
Peripheral WMHs, No.	7	3	4
WMHI rating, mean (SD)			
Ventricular	0.09 (0.30)	0.50 (0.90)	0.08 (0.29)
Deep	0.90 (1.20)	1.00 (1.50)	0.33 (0.65)
Peripheral	1.50 (1.30)	0.60 (1.20)	0.42 (0.67)

Abbreviations: NS-VCFS, nonschizophrenic patients with velocardiofacial syndrome; S-VCFS, schizophrenic patients with velocardiofacial syndrome; WMHs, white-matter hyperintensities.

\* $P = .02$ ,  $\chi^2$  test.

ences in gray and white matter were localized by fitting an appropriate GLM at each intracerebral voxel. Inference was via a permutation distribution of spatial extent statistics with significance levels set to control for multiple comparisons by having less than one estimated false-positive region (cluster) across the image ( $P < .001$ ). In brief, the processing proceeded as follows. Maps of the standardized GLM model coefficient of interest (group) at each voxel were thresholded such that only voxels with a probability less than .05 were retained. The sum of voxelwise statistics for each 3-dimensional suprathreshold cluster was the test statistic, the sign indicating a relative excess or deficit in local tissue density. Significance testing of the clusters was performed with a null distribution of this test statistic similarly obtained after repeatedly randomly permuting the relevant factor in the GLM and refitting of the model.<sup>48</sup>

## RESULTS

### DEMOGRAPHIC DATA

There were no significant between-group differences in age ( $F = 0.71$ ,  $P = .50$ ), IQ ( $F = 1.1$ ,  $P = .33$ ), or sex distribution ( $\chi^2 = 0.45$ ,  $P = .80$ ).

### QUALITATIVE (RADIOLOGIC) FINDINGS

The prevalence of cavum septum pellucidum–septum vergae was not equally distributed over the 3 groups: 31% (4 patients) in the S-VCFS group, 50% (6 patients) in the NS-VCFS group, and 0% in the control group ( $\chi^2 = 7.8$ ,  $P = .02$ ). However, there were no significant between-group differences in any other qualitative variable we measured or in severity of WMHs (**Table 1**). However, when both VCFS groups were combined, the presence of WMHs was more common than in controls ( $\chi^2 = 5.1$ ,  $P = .02$ ).

### BRAIN VOLUMES ANALYZED BY MANUAL TRACING

There was a significant group ( $F_{2,32} = 3.4$ ,  $P = .04$ ) and sex ( $F_{1,32} = 10.8$ ,  $P = .002$ ) effect on ICV, but no group  $\times$  sex

interaction. Pairwise comparisons with Bonferroni adjustments for multiple comparisons showed a significantly decreased ICV in the S-VCFS group compared with the control group and in the female compared with the male group. In addition, after ICV was added as a covariate to the model, there was a significant group effect on volume of total ( $F_{2,31} = 6.08$ ,  $P = .006$ ), left ( $F_{2,31} = 7.99$ ,  $P = .002$ ), and right ( $F_{2,31} = 5.1$ ,  $P = .01$ ) cerebral hemispheres; total ( $F_{2,31} = 5.4$ ,  $P = .01$ ), and right ( $F_{2,31} = 5.5$ ,  $P = .009$ ) frontal lobes; total ( $F_{2,31} = 5.1$ ,  $P = .01$ ), left ( $F_{2,31} = 6.02$ ,  $P = .006$ ), and right ( $F_{2,31} = 3.35$ ,  $P = .048$ ) temporal lobes; cerebellum ( $F_{2,31} = 14.1$ ,  $P < .001$ ); brainstem ( $F_{2,31} = 4.02$ ,  $P = .03$ ); and total sulcal CSF ( $F_{2,31} = 9.3$ ,  $P = .001$ ) (**Table 2**). Pairwise comparisons with Bonferroni adjustments for multiple comparisons showed that cerebellar volume was significantly smaller in both S-VCFS and NS-VCFS groups than in controls. Furthermore, total and left cerebral hemisphere volumes were significantly smaller and sulcal CSF volume significantly larger in the S-VCFS group compared with both the NS-VCFS and the control groups. Decreases in volume of right hemisphere; total and right frontal lobe; total, left, and right temporal lobe; and brainstem volume were observed in the S-VCFS group compared with the control group only. There was a significant effect of age on total ( $F_{1,31} = 9.14$ ,  $P = .005$ ), left ( $F_{1,31} = 6.36$ ,  $P = .02$ ), and right ( $F_{1,31} = 12.02$ ,  $P = .002$ ) frontal lobes, but no age  $\times$  group interactions. There were no significant effects of age and sex on any of the other brain structures.

When the level of significance was adjusted according to the number of tests performed ( $P = .001$ ), the only findings that remained significant were those of group effects on cerebellum and sulcal CSF.

### TISSUE CLASS VOLUMES ANALYZED BY COMPUTERIZED VOXELWISE ANALYSIS

Total tissue class volumes are shown in **Table 3**. There was no significant effect of group on total gray-matter volume. However, there was a significant effect of group on volume of total white matter ( $F_{2,26} = 8.73$ ,  $P = .001$ ) and total CSF ( $F_{2,26} = 8.57$ ,  $P = .001$ ). Pairwise comparisons with Bonferroni adjustments for multiple comparisons showed that total white-matter volume was significantly decreased and total CSF volume significantly increased in the S-VCFS group compared with both the NS-VCFS and the control groups. Also, there was a significant effect on age for total gray matter ( $F_{1,26} = 12.12$ ,  $P = .002$ ) and white matter ( $F_{1,26} = 10.56$ ,  $P = .003$ ), and a sex  $\times$  group interaction for white matter ( $F_{2,26} = 3.88$ ,  $P = .03$ ) (with men in the S-VCFS group showing a greater reduction in white-matter volume than women). After correction for the number of tests performed, we adjusted the level of significance to  $P = .001$ , and this still yielded significant group effects on white matter and total CSF volume.

The central coordinates and volumes of the 3-dimensional clusters of brain tissues that were significantly different ( $P = .001$ ) are shown in **Table 4**. The S-VCFS group compared with the control group had 6 significant gray-matter deficit regions, 2 in (left and right) cerebellum, 1 in right superior temporal gyrus, and 3 in right frontal (midfrontal, inferior frontal, and anterior cingulate gy-

**Table 2. Manual Traced Brain Volumes in S-VCFS, NS-VCFS, and Control Subjects**

Brain Structure	Brain Volume, Group Mean (SD), mL			P Value (df = 2,31)*	Effect Size	Power
	S-VCFS (n = 13)	NS-VCFS (n = 12)	Controls (n = 14)			
Total intracranial volume	1239.68 (181.22)	1298.40 (118.00)	1373.42 (124.24)	.04†	0.18	0.60
Hemispheres						
Total	928.13 (99.96)	1012.57 (89.06)	1065.62 (98.73)	.006‡	0.28	0.85
Left	458.23 (48.52)	500.02 (42.75)	524.83 (48.02)	.002‡	0.34	0.94
Right	463.73 (47.10)	507.22 (47.58)	534.79 (53.03)	.01‡	0.25	0.78
Frontal lobes						
Total	463.06 (49.60)	501.31 (41.73)	528.82 (53.22)	.01‡	0.26	0.81
Left	227.24 (26.60)	245.94 (20.94)	255.75 (24.14)	.05	0.18	0.58
Right	233.66 (21.82)	253.87 (22.81)	269.48 (31.93)	.009‡	0.26	0.82
Occipitoparietal lobes						
Total	346.24 (49.02)	380.78 (51.73)	395.61 (44.2)	.30	0.08	0.26
Left	175.16 (25.65)	190.40 (28.77)	201.53 (21.13)	.40	0.06	0.20
Right	170.65 (24.68)	189.88 (24.15)	203.94 (30.72)	.19	0.10	0.34
Temporal lobes						
Total	118.61 (16.17)	132.28 (18.05)	144.0 (15.07)	.01‡	0.25	0.78
Left	57.75 (8.29)	65.02 (8.41)	71.09 (6.93)	.006‡	0.28	0.85
Right	60.86 (9.10)	67.26 (10.12)	72.92 (8.82)	.05†	0.18	0.59
Putamen						
Total	6.98 (1.56)	6.69 (0.79)	7.63 (1.32)	.40	0.06	0.20
Left	3.60 (0.92)	3.38 (0.37)	3.92 (0.66)	.29	0.08	0.26
Right	3.39 (0.73)	3.31 (0.46)	3.71 (0.73)	.64	0.03	0.12
Caudate						
Total	7.69 (1.49)	8.05 (0.92)	8.08 (1.14)	.82	0.01	0.08
Left	3.85 (0.76)	4.04 (0.44)	4.04 (0.48)	.86	0.01	0.07
Right	3.85 (0.75)	4.03 (0.51)	4.04 (0.73)	.79	0.02	0.08
Lateral ventricles						
Total	26.57 (39.61)	14.08 (4.90)	20.76 (11.85)	.07	0.16	0.52
Left	13.62 (21.04)	7.11 (2.53)	11.27 (6.23)	.09	0.15	0.49
Right	12.71 (17.99)	6.96 (2.64)	9.56 (6.06)	.07	0.16	0.53
Third ventricle	1.24 (2.77)	0.51 (0.43)	0.85 (0.62)	.12	0.13	0.43
Sulcal CSF	162.31 (67.58)	139.59 (42.06)	133.67 (43.87)	.001‡	0.38	0.97
Hippocampus						
Total	4.81 (0.90)	5.17 (0.67)	5.38 (0.81)	.37	0.07	0.21
Left	2.27 (0.41)	2.51 (0.34)	2.54 (0.46)	.24	0.09	0.30
Right	2.54 (0.52)	2.66 (0.41)	3.0 (0.48)	.13	0.13	0.41
Amygdala						
Total	4.03 (0.96)	4.26 (0.71)	4.11 (0.42)	.61	0.03	0.12
Left	2.00 (0.49)	2.12 (0.37)	1.98 (0.26)	.53	0.04	0.15
Right	2.04 (0.50)	2.15 (0.39)	2.13 (0.32)	.70	0.03	0.10
Cerebellum	99.35 (13.43)	106.56 (14.85)	127.33 (11.79)	<.001‡	0.48	1.00
Brainstem	22.09 (3.72)	25.1 (3.40)	28.15 (4.23)	.03†	0.21	0.67

Abbreviations: CSF, cerebrospinal fluid; NS-VCFS, nonschizophrenic patients with velocardiofacial syndrome; S-VCFS, schizophrenic patients with velocardiofacial syndrome.

\*Univariate general linear model, controlling for age, sex, and intracranial volume.

† $P < .05$ .

‡ $P < .01$ .

rus) regions. Also, 1 gray-matter excess region was identified in the S-VCFS group; this was centered in the right anterior cingulate gyrus (**Figure 1**). The NS-VCFS compared with the control group had 1 gray-matter deficit region that was located in right cerebellum extending to left cerebellum (**Figure 2**). In addition, there were 3 gray-matter excess regions all centered in the precentral regions, both left and right. Comparisons between the 2 VCFS groups showed 2 gray-matter excess regions in the S-VCFS compared with the NS-VCFS group, located in left precentral regions. There were no gray-matter deficit regions in the S-VCFS group compared with the NS-VCFS group (**Figure 3**).

White-matter deficits in the S-VCFS group compared with the control group were concentrated in 4 spatially extensive regions all covering frontal lobe regions: 2 involving left and right precentral gyrus, 1 extending to left anterior cingulate, and 1 involving right medial frontal region (**Figure 4**). In contrast, 1 area of excess white-matter volume was observed centered in the brainstem of the S-VCFS group. In the NS-VCFS group, compared with controls, one cluster of white-matter deficit was identified, and this was centered in right fasciculus longitudinalis superior extending into right inferior frontal lobe (**Figure 5**). Also, in the NS-VCFS group, significant excess white matter was localized in 2

**Table 3. Tissue Class Volumes in S-VCFS, NS-VCFS, and Control Subjects**

Tissue Class	Volume, Mean (SD), mL			P Value (df=2,26)*	Effect Size	Power
	S-VCFS (n = 11)	NS-VCFS (n = 12)	Controls (n = 11)			
Gray matter	584.83 (91.48)	597.38 (87.14)	590.12 (61.47)	.94	0.005	0.06
White matter	534.82 (70.42)	569.01 (79.70)	643.82 (98.16)	.001†	0.400	0.95
CSF	213.88 (86.30)	158.62 (38.73)	162.03 (38.58)	.001†	0.400	0.95

Abbreviations: CSF, cerebrospinal fluid; NS-VCFS, nonschizophrenic patients with velocardiocardiofacial syndrome; S-VCFS, schizophrenic patients with velocardiocardiofacial syndrome.

\*Univariate general linear model, controlling for age, sex, and intracranial volume.

† $P < .01$ .

**Table 4. Coordinates of Regional Differences in Gray- and White-Matter Volume in Adults With S-VCFS and NS-VCFS Compared With IQ-Matched Control Subjects\***

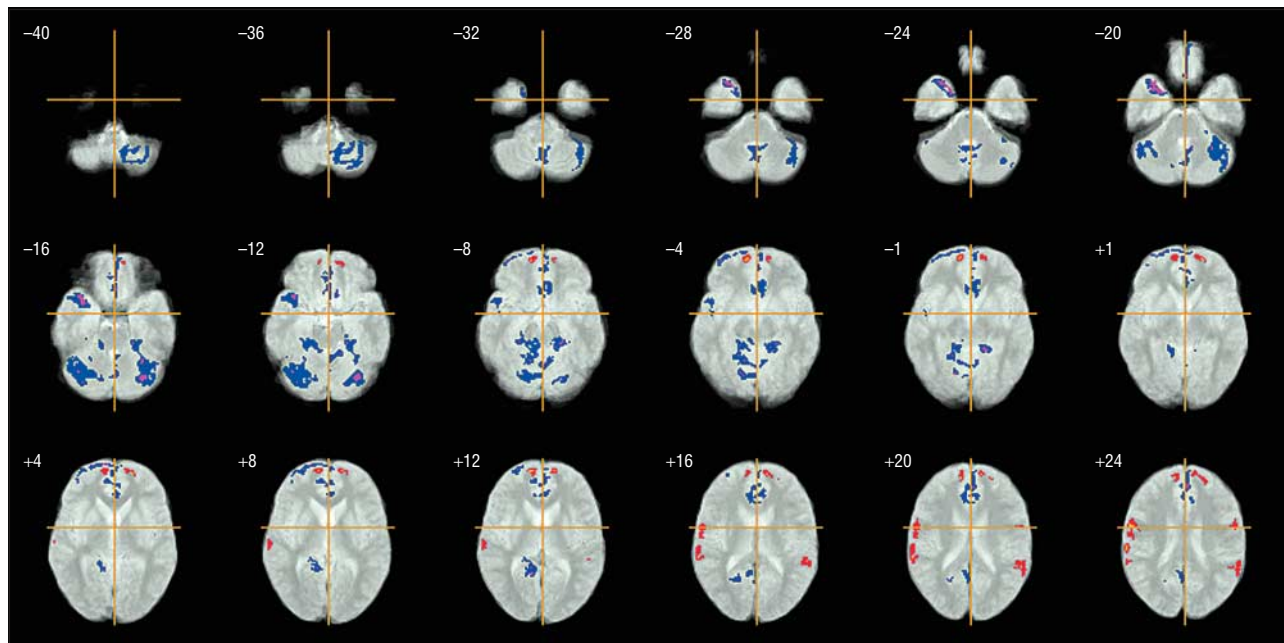
Cerebral Region	Brodman Area	No.	Tal x	Tal y	Tal z	Side
<b>S-VCFS – Controls</b>						
Gray-matter deficit						
Cerebellum		1814	-10.3	49.0	14.4	L
		542	29.2	-60.3	-13.1	R
Frontal						
Anterior cingulate	32	1133	3.8	42.7	6.6	R
Inferior frontal gyrus	47	329	34.0	13.0	-18.2	R
Midfrontal gyrus	10	8	38.2	48.5	4.2	R
Temporal: superior temporal gyrus	22	15	45.6	0.7	-3.8	R
Gray-matter excess						
Frontal: medial frontal gyrus	24	4774	1.2	-7.7	45.9	R/L
White-matter deficit						
Frontal						
Precentral regions		575	34.9	-5.4	42.6	R
Superior midfrontal regions		392	-23.2	-15.5	48.9	L
Superior frontal regions		245	13.8	53.5	3.4	R
Medial frontal regions		273	-24.9	42.8	-3.5	L
White-matter excess						
Brainstem		4079	0.9	-36.1	-11.4	R/L
<b>NS-VCFS – Controls</b>						
Gray-matter deficit						
Cerebellum		1360	-4.0	-61.0	-12.1	L
Gray-matter excess						
Frontal						
Precentral gyrus	4	228	39.1	-5.4	47.5	R
Precentral gyrus	4	228	-42.3	-8.3	43.5	L
Precentral gyrus	4	11	32.2	-20.3	59.5	R
White-matter deficit						
Fasciculus longitudinalis superior		415	33.7	15.5	13.5	R
White-matter excess						
Fasciculus occipitofrontalis		1067	-24.0	39.3	17.0	L
Fasciculus occipitofrontalis		830	24.3	-41.3	21.9	R
<b>S-VCFS – NS-VCFS</b>						
Gray-matter excess						
Frontal						
Precentral gyrus	4	378	-21.3	-24.2	58.8	L
Medial frontal gyrus	6	17	-4.7	-23.4	58.2	L
White-matter excess						
Posterior cingulate		173	0.7	-38.3	24.8	R/L

Abbreviations: NS-VCFS, nonschizophrenic patients with velocardiocardiofacial syndrome; S-VCFS, schizophrenic patients with velocardiocardiofacial syndrome; Tal, Talairach.

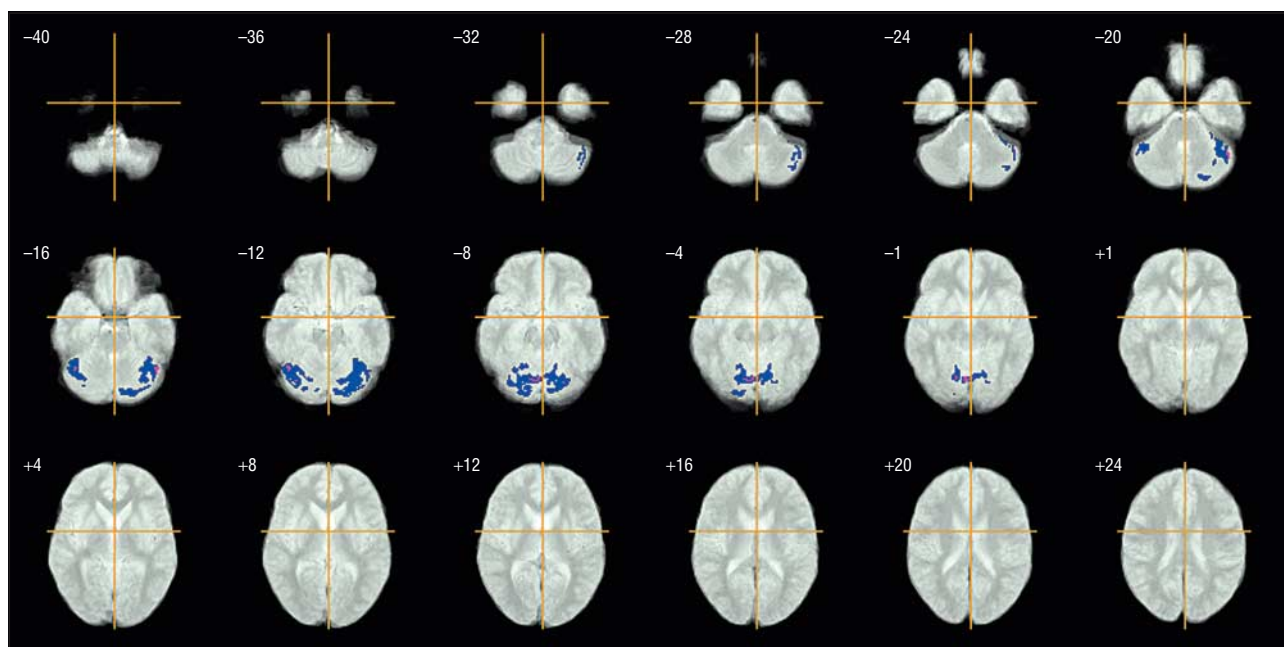
\*Location of each cluster's centroid is given in Talairach coordinates (Tal x, y, z, given in millimeters); n indicates number of voxels in each cluster. The clusterwise probability is  $P = .001$ , controlling for age, sex, and intracranial volume.

clusters, left and right fasciculus occipitofrontalis. Within-VCFS-group comparisons showed 1 cluster of white-matter excess in the S-VCFS group compared

with the NS-VCFS group, located in the posterior cingulate; there were no white-matter deficit regions (**Figure 6**).



**Figure 1.** Relative deficits (blue) and excesses (red) in gray-matter volume in schizophrenic patients with velocardiofacial syndrome compared with healthy IQ-matched control subjects. The maps are oriented with the right side of the brain shown on the left side of each panel. The z-coordinate for each row of axial sections in the standard space of Talairach and Tournoux<sup>47</sup> is given in millimeters.



**Figure 2.** Relative deficits (blue) and excesses (red) in gray-matter volume in nonschizophrenic patients with velocardiofacial syndrome compared with healthy IQ-matched control subjects. See Figure 1 legend for explanation.

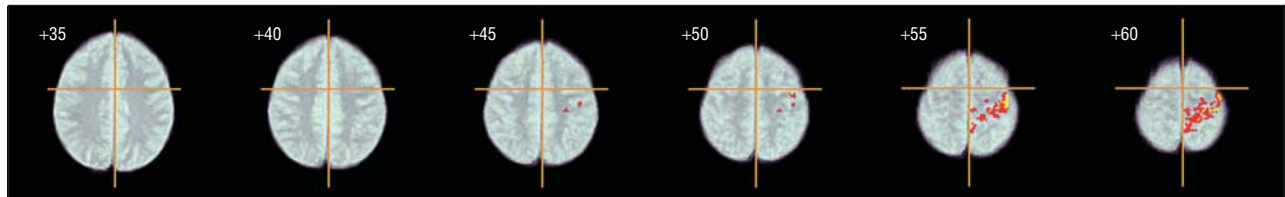
#### COMMENT

We believe that this is the first (preliminary) study to investigate brain anatomy in individuals with VCFS with and without schizophrenia with an IQ-matched healthy control group used as a reference. We found that both S-VCFS and NS-VCFS groups had a smaller volume of cerebellum and increased frequency of cavum septum pellucidum–septum vergae. In addition, the S-VCFS group (compared with both control and NS-VCFS

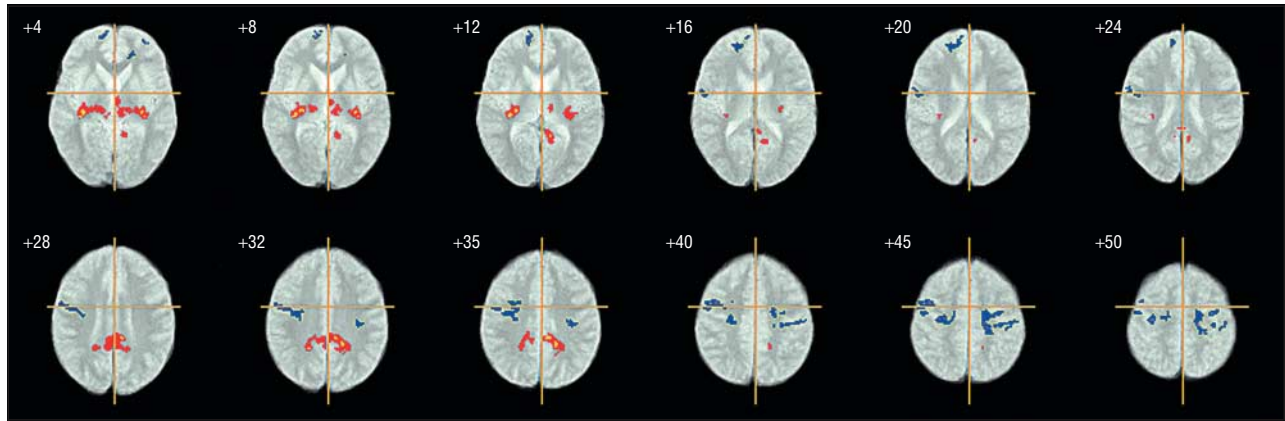
groups) had a significant reduction in volume of both total (white+gray) brain matter and total white matter. The S-VCFS group also had a significant increase in volume of total and sulcal CSF. It is unlikely that our findings can be explained by differences in IQ, age, sex, or nonspecific factors associated with being learning disabled, as the groups did not differ in IQ and we controlled for age and sex distribution.

Qualitative analysis of our data showed abnormalities that have been previously reported in people with

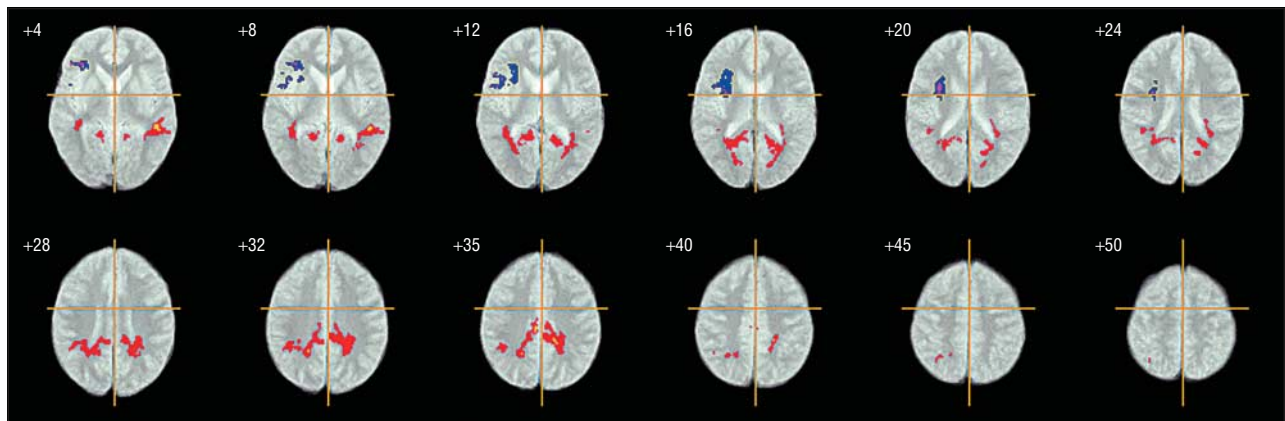




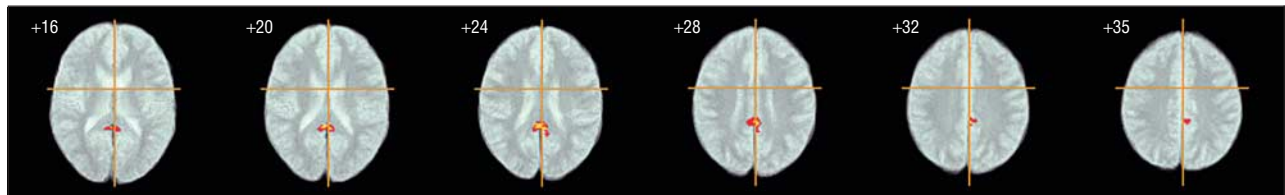
**Figure 3.** Relative deficits (blue) and excesses (red) in gray-matter volume in schizophrenic patients with velocardiofacial syndrome compared with nonschizophrenic patients with velocardiofacial syndrome. See Figure 1 legend for explanation.



**Figure 4.** Relative deficits (blue) and excesses (red) in white-matter volume in schizophrenic patients with velocardiofacial syndrome compared with healthy IQ-matched control subjects. See Figure 1 legend for explanation.



**Figure 5.** Relative deficits (blue) and excesses (red) in white-matter volume in nonschizophrenic patients with velocardiofacial syndrome compared with healthy IQ-matched control subjects. See Figure 1 legend for explanation.



**Figure 6.** Relative deficits (blue) and excesses (red) in white-matter volume in schizophrenic patients with velocardiofacial syndrome compared with nonschizophrenic patients with velocardiofacial syndrome. See Figure 1 legend for explanation.

VCFS<sup>27,28</sup> and in non-VCFS-related schizophrenia.<sup>49,50</sup> Cavum septum pellucidum was observed in both VCFS groups equally frequently, irrespective of whether schizophrenia was present. Septum pellucidum abnormalities are of unknown clinical significance and are also seen in people with and without learning disabilities without men-

tal illness<sup>29,51</sup> (although they were not present in our control group). The high prevalence of WMHIs in the majority of subjects in both VCFS groups at a relatively young age could indicate white-matter tract disruption possibly of a vascular origin, although we did not use a method that is sensitive to fiber tract visualization, like diffu-



sion tensor imaging.<sup>52</sup> However, in our study these abnormalities were equally common in patients with VCFS with and without schizophrenia; there were no significant between-group differences in frequency or severity of WMHIs, and WMHIs were also present in the control group. However, when the 2 VCFS groups were combined, the frequency of WMHI was significantly higher than in the control group. Thus, WMHIs and septum pellucidum abnormalities are frequently present in individuals with VCFS with and without schizophrenia and are most likely not related to the presence or absence of schizophrenia.

Our quantitative analysis showed that the S-VCFS group, compared with both the NS-VCFS and control groups, had a *generalized* reduction in total brain (gray + white matter) volume and total white-matter volume and an increase in total and sulcal volume of CSF. However, we also found that the S-VCFS group (compared with the control group only) had a reduction in volume of the frontal and temporal lobes, although these findings disappeared after correction for multiple comparisons. These findings are in agreement with results from other MRI studies of schizophrenia in both the general population<sup>18</sup> and children<sup>53</sup> and adults with VCFS.<sup>32</sup> That white matter may be particularly affected in VCFS has been supported by findings in children with VCFS,<sup>30</sup> and a recent diffusion tensor imaging study of children with VCFS has shown generalized white-matter tract disruption.<sup>54</sup>

In contrast to a previous report in people with VCFS,<sup>32</sup> we did not find a significant diffuse loss of gray matter in adults with S-VCFS. We suggest that our results differ from those of Chow et al<sup>32</sup> because they included non-VCFS controls with an above-average level of intellectual functioning (mean IQ, 116). Thus, the differences they observed in total gray-matter volume could have been confounded by differences in subject intelligence and health status; eg, there is increasing evidence that IQ is positively correlated with total brain matter and cortical gray-matter volume.<sup>55-58</sup> It is not generally agreed as to which is the “best” control group to use when studying people with genetically determined neurodevelopmental disorders such as VCFS. Our borderline-learning disabled control group is not representative of a healthy population, and we cannot exclude an effect of genetically and environmentally determined causes of cognitive impairment that we did not detect by our screening techniques. However, ability to match on IQ is important also in people with VCFS, as is supported by Kates et al,<sup>30</sup> who could not exclude an effect of IQ on their results.

Both the S-VCFS and NS-VCFS groups had a smaller total cerebellar volume and cerebellar gray-matter volume than the control group. This finding further supports the results from our previous work<sup>32</sup> and other qualitative<sup>25</sup> and quantitative<sup>39</sup> studies in children with VCFS. Others have suggested that in the general population schizophrenia is associated with cerebellar abnormalities.<sup>60</sup> Our results suggest that cerebellar abnormalities are more common in people with VCFS than IQ-matched controls; however, they are not related to the presence or absence of schizophrenia.

In contrast, the S-VCFS group demonstrated generalized loss of total brain (gray + white) and total white-matter volume, together with an increase in total and sulcal CSF volume, compared with both NS-VCFS and control groups. In addition, our quantitative analysis showed *regional* differences in gray and white matter. These were most pronounced as gray-matter deficits in cerebellar areas in both VCFS groups and differences in anterior-posterior distribution between deficit and excess clusters, particularly of white-matter frontal lobe regions in adults with S-VCFS and NS-VCFS compared with controls. Previous MRI studies in children and adults with VCFS reported differences in development of frontal lobe.<sup>30-33</sup> Moreover, abnormalities in the function, structure, and metabolism of frontal regions have been frequently reported in the non-VCFS schizophrenic population. For example, both gray-matter<sup>61</sup> and white-matter<sup>37,62</sup> deficits have been reported in frontal brain regions, and findings from longitudinal MRI studies<sup>63,64</sup> suggest a progressive volume reduction in frontal regions, including frontal white matter.<sup>65</sup> Normal brain maturation takes place last in the frontal regions during adolescence and is accompanied by both increased synaptic pruning and myelination, leading to a reduction of volume in gray matter and an increase in white matter.<sup>66</sup> We found that people with S-VCFS had a reduction in whole-brain volume, but with regional differences in gray and white matter with an anterior-posterior distribution between deficits and excess areas particularly affecting frontal regions. Thus, our findings might suggest that people with VCFS have abnormalities in frontal maturation, and this could predispose to the development of schizophrenia. We therefore suggest that 22q11 deletion is associated with the presence of a generalized disturbance in brain development that increases the liability for developing schizophrenia. However, schizophrenia may develop only when regionally specific neurodevelopmental differences of frontal regions also occur, leading to changes in the volume and tissue composition of frontal regions.

We did not find support for our hypothesis that people with S-VCFS have a reduced hippocampal volume, but we found deficits in temporal gray matter in our voxel-wise analysis and reduced temporal lobe volume compared with the healthy control group. This finding is in agreement with results by Chow et al,<sup>32</sup> who found reduced temporal gray-matter volumes in their sample of adults with VCFS and schizophrenia, compared with normal-IQ controls, a finding also frequently reported in non-VCFS-associated schizophrenia.

The cause of the differences in brain anatomy of people with VCFS, its relation to schizophrenia, and the time course of their development is unknown. Our study was cross-sectional, and therefore we cannot determine whether these differences in brain anatomy change across the lifespan. Nonetheless, we found that sulcal CSF volume was increased in adults with S-VCFS, and this adds tentative support to the hypothesis that schizophrenia is associated with an abnormal neurodevelopmental process that is not limited to an aberration in prenatal brain development, but may be progressive. Also, our results do not allow us to draw conclusions as to whether schizo-

phrenia in VCFS is due to a primary abnormality in gray-matter development (eg, differences in programmed cell death [apoptosis]), with secondary changes of white-matter structure, or vice versa. There is preliminary evidence to suggest that differences in programmed cell death may underlie the differences in brain anatomy we found in our study. For example, recent studies report that *PRODH*, a gene located at 22q11, is implicated in apoptosis<sup>67</sup> and that variation within the *PRODH/DGR6* locus at 22q11 might contribute to VCFS-associated schizophrenia,<sup>68</sup> although the latter study has not been replicated.<sup>69</sup> Alternatively, schizophrenia in VCFS may be related to developmental differences in white-matter structure (eg, possibly as a result of abnormal myelination), with consequent disturbances in connectivity between neocortical and limbic gray-matter regions. Schizophrenia in the general population is increasingly seen by some as a supraregional disorder involving differences in interconnecting white-matter tracts<sup>37</sup> and neuronal connectivity<sup>70</sup> possibly associated with oligodendroglial dysfunction resulting in abnormalities in myelin maintenance and repair.<sup>23</sup> In favor of this argument is the finding that in children with VCFS (who are at risk of developing schizophrenia) white matter may be more compromised than gray matter, and WMHs are common.<sup>30,31</sup> Also, we found overall white matter to be compromised in S-VCFS, whereas there were no between-group differences in total gray-matter volume.

Another potential candidate gene for schizophrenia in VCFS is the catechol *O*-methyltransferase gene (*COMT*; the enzyme that degrades dopamine). The *COMT* gene lies within the 22q11 region, and therefore people with VCFS have a reduced gene dose of *COMT*. Also, a recent study demonstrated that variation in activity of *COMT* may have neurobiological effects specific to the prefrontal cortex and may modulate the risk of schizophrenia in the general population.<sup>71</sup> Moreover, others have suggested that in schizophrenia, neurodevelopmental abnormalities of prefrontal dopaminergic systems result in enhanced vulnerability to sensitization during late adolescence and early adulthood.<sup>72</sup> Although there is little evidence yet that *COMT* plays a major role in the development of schizophrenia in VCFS,<sup>73,74</sup> it cannot be excluded that reduced gene dose of *COMT* affects the integrity of the dopaminergic system, including its prefrontal projections, and so increases susceptibility to schizophrenia in people with VCFS.

Our sample size and the cross-sectional design are limitations of this study, but we were still able to detect several significant differences with a large effect size and sufficient power; as noted by others,<sup>28</sup> the effect size for structural brain abnormalities in this group of patients is relatively large. In addition, we carried out multiple statistical comparisons and thereby increased the risk of a type I error (false-positive outcomes). However, we believe this is unlikely to fully explain our results. After adjusting for the number of tests carried out, the group differences in volumes of total white matter, total and sulcal CSF, and cerebellum remained. Also, we found significant effects on manually traced brain volumes (eg, reduced cerebellar volume) that were consistent with our computerized voxelwise

analysis. Moreover, in our computerized voxelwise analysis of gray- and white-matter volumes, the level of significance adopted was chosen specifically to yield less than one false-positive cluster. We did not control for effects of neuroleptic medication, parental IQ, and parental head circumference, and therefore we cannot exclude these as potential confounds of our results. All subjects in the S-VCFS group were taking antipsychotic medication, whereas none of the subjects in the other 2 groups did. We did not find a sex effect except in ICV. This may be due to the small sample size of our study. Alternatively, sex differences in raw volumes may have disappeared after controlling for ICV. Also, we did not quantify white-matter lesions and did not relate them to other outcome variables.

In conclusion, our results, although preliminary, suggest that structural brain abnormalities present in people with S-VCFS are partially similar to those seen in people with schizophrenia in the general population. Our findings are compatible with an abnormal neurodevelopmental process that may be progressive. We suggest that this results in generalized abnormalities in brain anatomy, but particularly affecting white matter and frontal brain regions. Larger and longitudinal studies are planned to replicate these findings, and to determine how genetic and environmental variables are related to the development of schizophrenia in VCFS.

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