Structural brain abnormalities associated with deletion at chromosome 22q11

Quantitative neuroimaging study of adults with velo-cardio-facial syndrome*

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Background Velo-cardio-facial syndrome (VCFS) is associated with deletions in the q11 band of chromosome 22, learning disability and psychosis, but the neurobiological basis is poorly understood.

Aims To investigate brain anatomy in adults with VCFS.

Method Magnetic resonance imaging was used to study 10 patients with VCFS and 13 matched controls. We carried out three analyses: qualitative; traced regional brain volume; and measurement of grey and white matter volume.

Results The subjects with VCFS had: a high prevalence of white matter hyperintensities and abnormalities of the septum pellucidum; a significantly smaller volume of cerebellum; and widespread differences in white matter bilaterally and regional specific differences in grey matter in the left cerebellum, insula, and frontal and right temporal lobes.

Conclusions Deletion at chromosome 22q11 is associated with brain abnormalities that are most likely neurodevelopmental and may partially explain the high prevalence of learning disability and psychiatric disorder in VCFS.

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Velo-cardio-facial syndrome (VCFS) is a common genetic disorder associated with variably sized deletions at chromosome 22q11 (Scambler *et al*, 1992). Characteristic physical features include cleft lip and/or palate, conotruncal heart defects, ear anomalies and characteristic facial features such as a prominent nasal bridge (Shprintzen *et al*, 1978). Neurodevelopmental abnormalities include dysarthric speech and ocular abnormalities, learning disability, behavioural problems (including attentional difficulties and poor social interaction), visuoperceptual–spatial deficits (Golding-Kushner *et al*, 1985; Mansour *et al*, 1987; Swillen *et al*, 1997) and a high prevalence of psychosis (10–30%) (Shprintzen *et al*, 1992; Pulver *et al*, 1994; Papolos *et al*, 1996; Murphy *et al*, 1999). However, the brain anatomy of people with VCFS is poorly understood. Qualitative neuroimaging studies in VCFS reported cerebellar atrophy, agenesis of the corpus callosum, white matter hyperintensities (WMHIs), cavum septum pellucidum/vergae and cerebral atrophy (Mitnick *et al*, 1994; Lynch *et al*, 1995; Chow *et al*, 1999). In addition, quantitative studies reported that people with VCFS have a reduced volume of total brain, left parietal lobe grey matter and right cerebellar white matter but relatively larger frontal lobes, increased midsagittal corpus callosum areas and enlarged Sylvian fissures (Bingham *et al*, 1997; Usiskin *et al*, 1999; Eliez *et al*, 2000). However, these studies did not control for IQ and, with one exception (Chow *et al*, 1999), were all performed in children. Therefore we used volumetric magnetic resonance imaging (MRI) to determine whether deletion at chromosome 22q11 is associated with abnormalities in the brain anatomy of adults with VCFS compared with controls of similar IQ, age, gender and socio-economic status (SES). We hypothesised that deletion at chromosome 22q11 is associated with specific abnormalities in brain anatomy.

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METHOD

Subjects

Approval for the study was granted by the local ethics committee, and all subjects 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 using a semi-structured clinical interview. Also, a semi-structured psychiatric interview was performed (Schedule for Clinical Assessment in Neuropsychiatry; Wing *et al*, 1990) to establish a DSM–IV (American Psychiatric Association, 1994) diagnosis using a methodology described elsewhere (Murphy *et al*, 1999). Full-scale IQ (FSIQ) was measured using a shortened version of the Wechsler Adult Intelligence Scale – Revised (Wechsler, 1987). We included ten subjects (seven females and three males) with clinical features of VCFS and a 22q11 deletion detected by fluorescence *in situ* hybridisation (FISH) (Oncor Inc., Gaithersburg, Maryland, USA). The mean age of the subject sample was 32 years (s.d.=9) with a mean FSIQ of 72 (s.d.=10) and a mean SES of 2.8 (s.d.=1.3). Five people with VCFS were free of mental illness; three met DSM–IV criteria for schizophrenia and two for major depression.

Thirteen control subjects (eight females and five males) were recruited from local community centres for people with mild or borderline learning disabilities. The mean age of the control sample was 37 years (s.d.=10) with a mean FSIQ of 72 (s.d.=12) and a mean SES of 2.5 (s.d.=0.5). A deletion at chromosome 22q11 was excluded by FISH. Seven control subjects were free of mental illness, two met criteria for schizophrenia, two for major depression and two for dysthymia.

Magnetic resonance imaging

Magnetic resonance imaging of the brain was performed on a GE Signa 1.5 Tesla system (General Electric, Milwaukee, Wisconsin, USA) at the Maudsley Hospital, London. A coronal three-dimensional spoiled grass (SPGR) data-set covering the whole head was acquired with repetition time TR=13.8 ms, echotime TE=2.8 ms, flip angle=20°, 1.5-mm slice thickness, one acquisition per phase encode step and flow compensation of 10 min. The matrix was 256 × 192 and the field of view was 22 cm, giving an in-plane resolution of

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0.859 mm. This data-set was used to measure whole and regional brain volumes. In addition, we acquired a whole-brain near-axial dual-echo fast-spin-echo (FSE) data-set aligned with the AC–PC line, with *TR*=4000 ms, effective *TE*=20 and 85 ms, 3-mm slice thickness, interleaved slices, flow compensation and echo train length=8 (8 min). The matrix was 256×192 and the field of view was 22 cm, giving an in-plane resolution of 0.859 mm. This data-set was used to estimate between-group grey and white matter differences using a previously published methodology (Suckling *et al*, 1999).

Three types of analysis were performed, all blind to subject group status. First, both MRI data-sets were analysed qualitatively by a neuroradiologist. Using a four-point rating scale adopted from Kozachuk *et al* (1990), the presence and extent of ventricular WHMIs was assessed as follows: grade 0=ventricular WMHIs 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 WMHIs extending into the deep white matter. Deep WMHIs were graded as follows: grade 0=absent; grade 1=punctuate foci, either focal or symmetrical; grade 2=mild confluence of foci; and grade 3=large confluence of foci. Peripheral WMHIs were graded similarly to deep WMHIs. Structural abnormalities in cerebellum and septum pellucidum were noted.

Secondly, volumetric analysis of total and regional brain areas was performed. The reformatted SPGR data-set was analysed using Measure software (Barta *et al*, 1997). Total, right and left caudates, putamen, hippocampus, amygdala, frontal, occipito-parietal and temporal lobes, cerebral hemispheres and ventricular and peripheral cerebrospinal fluid (CSF) volumes were traced using a previously described method (Murphy *et al*, 1992, 1993*a*,*b*). The volume of each region was calculated by multiplying the summed pixel cross-sectional areas by slice thickness. Intrarater and interrater reliabilities were determined for all brain regions of interest (ROIs) traced by the operators as part of this analysis. Highly significant interrater and intrarater reliabilities were obtained in all cases. The interrater correlation coefficients were $F>4.0$ and $P<0.01$ (Bartko & Carpenter, 1986).

The third analysis that we employed was a voxel-based method for the statistical analysis of grey and white matter differences. The FSE data-set was analysed using an automated software procedure. Voxels representing intracerebral tissue were identified using a set of linear scale–space features obtained from derivatives of the Gaussian kernel (Suckling *et al*, 1998). The probability of each intracerebral voxel belonging to each of four possible tissue classes (grey matter, white matter, CSF or dura/vasculature) was then estimated by a modified fuzzy clustering algorithm (Suckling *et al*, 1999). On the basis of prior results, we equated these probabilities to the proportional volumes of each tissue class in the often heterogeneous volume of tissue represented by each voxel (Bullmore *et al*, 1995). Thus, for example, if the probability of grey matter class membership was 0.8 for a given voxel, it was assumed that 80% of the tissue represented by that voxel was grey matter. Because the voxel size was predetermined (2.2 mm^3), we then estimated the volume in millilitres of grey 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, the short echo (proton-density-weighted) FSE images were co-registered using an affine transformation (Press *et al*, 1992; Brammer *et al*, 1997) with a template image in the coordinate system of standard space as defined by Talairach & Tournoux (1988). This individually estimated transformation was then applied to each of that subject's grey and white tissue probability maps.

Statistics

Analysis 1 (qualitative data)

Group differences in frequencies of structural abnormalities were assessed using a χ^2-test, whereas between-group differences in extent of WMHIs were assessed using a two-tailed independent sample *t*-test, with level of significance for both tests at $P<0.05$.

Analysis 2 (SPGR data)

Between-group differences in total and regional brain volumes were calculated by analysis of covariance (ANCOVA) using age, IQ and total intracranial volume as covariates, with a significance level at $P<0.05$.

Analysis 3 (FSE data)

Inference of between-group differences of grey and white matter probability maps was made with ANCOVA implemented by voxelwise linear regression. The model included covariates for age and gender. A test statistic was derived from clusters of spatially contiguous voxels significant at a probability threshold of $P<0.05$. The probability of significance of the clusters was determined using a randomisation procedure (Bullmore *et al*, 1999). The level of significance was set at $P<0.001$, giving an estimated number of false-positive or type I error clusters of <1 across the three-dimensional image volume.

RESULTS

Qualitative (radiological) findings

Cavum septum pellucidum/vergae was more common in people with VCFS (40%) than in controls (9%) (Table 1), although this difference was not statistically significant. Similarly, ventricular, deep and peripheral WMHIs were observed more frequently (although not significantly so) in people with VCFS (40, 30 and 40%, respectively) than in controls (18, 18 and 27%, respectively). The mean ratings for severity of WMHIs also did not differ significantly between groups.

Brain volumes

There were no significant group differences in total brain volume (F=0.4, d.f.=1, 22, P=0.6), although total intracranial volume tended to be smaller in people with VCFS (F=3.8, d.f.=1, 22, P=0.07). However, compared with controls, people with VCFS

Table 1 Qualitative (radiological) findings

Structure	VCFS (n=10)	Controls (n=11)
Cavum septum pellucidum/vergae (n)	4	1
Small/abnormal cerebellar vermis (n)	0	0
Ventricular WMHIs (n)	4	2
Deep WMHIs (n)	3	2
Peripheral WMHIs (n)	4	3
Mean rating ventricular WMHIs (s.d.)	0.4 (0.5)	0.2 (0.4)
Mean rating deep WMHIs (s.d.)	0.5 (1.0)	0.3 (0.6)
Mean peripheral WMHIs (s.d.)	0.7 (1.0)	0.4 (0.7)

VCFS, velo-cardio-facial syndrome; WMHIs, white matter hyperintensities.

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had a significantly smaller volume of cerebellum (F=16.0, d.f.=1, 22, P=0.001) (Table 2). No significant between-group differences were found in the volume of any other brain region or CSF.

Tissue class volumes

Total brain grey and white matter and CSF volumes were non-significantly smaller in people with VCFS by 5, 9 and 4%, respectively (Table 3).

Regional differences in grey matter volume

There was a significant difference between control and VCFS groups in grey matter volume at four spatially extensive three-dimensional voxel clusters. Two voxel clusters had a significantly reduced grey matter volume in the VCFS group: a cerebellar cluster (left side) and a temporal cluster (extending from the right uncus to the superior temporal gyrus and parahippocampal gyrus). In contrast, two voxel clusters showed relatively increased grey matter volume in the VCFS group: a temporal cluster (extending from the left insula to the superior and trans temporal gyrus) and a frontal cluster (extending from the left median gyrus to the medial and superior frontal gyrus) (Table 4 and Fig. 1).

The mean between-group difference in grey matter volume for the combined deficit regions was 27% (t=−4.2, d.f.=21, P=0.0001), and for the combined excess regions it was 30% (t=10.9, d.f.=21, P=0.0001).

Table 2 Total and regional brain volumes

Brain structure	VCFS (n=10)	Controls (n=13)	P value
Hemispheres			
Total	975.67 (114.60)	1045.68 (99.45)	0.56
Left	482.14 (51.35)	517.33 (48.40)	0.50
Right	487.09 (61.89)	525.39 (51.89)	0.30
Frontal lobe			
Total	485.63 (54.23)	519.11 (58.86)	0.80
Left	238.98 (26.90)	253.09 (25.10)	0.79
Right	245.73 (29.33)	263.46 (36.81)	0.57
Occipito-parietal lobe			
Total	361.79 (54.46)	386.48 (41.49)	0.89
Left	182.57 (27.18)	190.86 (24.32)	0.33
Right	179.20 (28.71)	194.71 (18.53)	0.44
Temporal lobe			
Total	130.59 (19.21)	140.80 (14.73)	0.78
Left	63.88 (9.60)	70.48 (6.29)	0.13
Right	66.72 (10.28)	70.32 (9.36)	0.42
Hippocampus			
Total	4.98 (0.92)	5.33 (0.82)	0.69
Left	2.33 (0.43)	2.53 (0.45)	0.90
Right	2.65 (0.53)	2.97 (0.52)	0.52
Amygdala			
Total	4.09 (0.61)	4.14 (0.40)	0.68
Left	2.04 (0.37)	1.98 (0.26)	0.41
Right	2.05 (0.30)	2.16 (0.28)	0.85
Putamen			
Total	6.90 (0.80)	7.86 (1.37)	0.15
Left	3.46 (0.42)	4.05 (0.69)	0.08
Right	3.45 (0.43)	3.81 (0.75)	0.33
Caudate			
Total	8.32 (1.03)	8.26 (1.12)	0.77
Left	4.13 (5.04)	4.10 (0.47)	0.99
Right	4.21 (0.54)	4.16 (0.72)	0.62
Lateral ventricle			
Total	14.76 (4.96)	20.04 (12.04)	0.74
Left	7.28 (2.63)	10.9 (6.37)	0.66
Right	7.49 (2.63)	9.22 (6.13)	0.84
Third ventricle	0.58 (0.45)	0.86 (0.64)	0.54
Peripheral CSF	132.73 (29.03)	131.26 (43.19)	0.10
Cerebellum	109.79 (12.48)	127.74 (11.95)	0.001**

Values are group means (s.d.); **P < 0.01.
VCFS, velo-cardio-facial syndrome; CSF, cerebrospinal fluid.

Regional differences in white matter volume

There was a significant difference in white matter volume between the VCFS and control groups at seven extensive three-dimensional clusters. People with VCFS had reduced white matter volume in six voxel clusters: two involved median, superior and medial frontal regions bilaterally; two included fasciculus longitudinalis superior (FLS) bilaterally, extending to temporo-parietal regions; one involved left fasciculus longitudinalis inferior (FLI) and optic radiation, and extended to left superior temporal regions; and the largest cluster extended from the left optic radiation bilaterally to occipital regions.

In contrast, one white matter voxel cluster had a relatively increased volume in people with VCFS; it extended from the splenium of the corpus callosum bilaterally to the optic radiation, posterior cingulate and parahippocampal regions (Table 4 and Fig. 2).

The mean between-group difference in white matter volume for the combined deficit regions was 33% (t=−15.5, d.f.=21, P=0.0001), and for the excess in white matter volume it was 29% (t=7.7, d.f.=21, P=0.0001).

DISCUSSION

We found that adults with a deletion at chromosome 22q11 have abnormalities in brain anatomy. To our knowledge, this is the first quantitative neuroimaging study to explore this by using controls from a

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Table 3 Volume (ml) of whole-brain grey and white matter and cerebrospinal fluid (CSF)

	VCFS (n=10)	Controls (n=13)	t	P value
Total grey matter	549 (90)	575 (66)	−0.8	0.4
Total white matter	580 (69)	634 (92)	−1.6	0.1
Total CSF	154 (43)	161 (36)	−0.4	0.7
Total combined grey matter deficit regions	3.5 (0.9)	4.8 (0.6)	−4.2	0.0001
Total combined white matter deficit regions	11 (0.8)	16 (0.8)	−15.5	0.0001

Values are group means (s.d.); d.f.=21.
VCFS, velo-cardio-facial syndrome.

Table 4 Regional differences in grey and white matter volume

Cerebral region	n	Tal (x)	Tal (y)	Tal (z)	Side
Grey matter	*Deficit*				
Cerebellum	1939	−27.3	−65.1	−19.4	L
Temporal lobe	1402	34.3	10.2	−19.5	R
	Excess				
Insula	1943	−39.4	−13.3	0.9	L
Frontal lobe	1324	−21.4	52.7	3.6	L
White matter	*Deficit*				
Occipital, optic radiation	3960	−5.7	−63.2	24.5	L
Frontal	1702	−20.8	49.5	−0.3	L
FLI, optic radiation	1364	−43.0	−26.4	9.3	L
FLS	1352	32.8	−30.8	36.0	R
FLS	1253	−38.5	−21.0	34.6	L
Frontal	1157	14.5	50.2	6.1	R
	Excess				
Corpus callosum	6909	−4.0	−39.5	20.6	L

Location of each cluster's centroid is given in Talaraich coordinates (Tal x, y and z, mm), n=number of voxels in each cluster. The clusterwise probability is P=0.001.
FLI, fasciculus longitudinalis inferior; FLS, fasciculus longitudinalis superior.

similar intellectual and socio-economic background.

Qualitative analysis

In our qualitative analysis, we found that abnormalities of septum pellucidum and (deep, ventricular and peripheral) WMHIs were (non-significantly) more often present in people with VCFS, and this is in agreement with observations from others (Mitnick *et al*, 1994; Vataja & Elomaa, 1998; Chow *et al*, 1999). Although their aetiology is not fully understood, WMHIs may reflect abnormalities in myelination and increased white matter water content (Kozachuk *et al*, 1990) and have been described in otherwise healthy people with cardiovascular anomalies. Velo-cardio-facial syndrome is also associated with cardiovascular malformations (Goldberg *et al*, 1993; Shprintzen *et al*, 1997; Chow *et al*, 1999) and therefore the development of white matter may be particularly affected in VCFS, possibly secondary to cardiovascular abnormalities affecting brain development in addition to genetically determined neurodevelopmental abnormalities. The clinical significance of septum pellucidum abnormalities is not clear but they are probably caused by a disturbance of midline brain development or maturation (Schaefer & Bodensteiner, 1999).

Quantitative analysis

In contrast to previous studies (Mitnick *et al*, 1994; Lynch *et al*, 1995), we did not find qualitative cerebellar abnormalities in people with VCFS, although our quantitative analysis revealed a significantly smaller cerebellum in people with VCFS compared with the controls. Traditionally the cerebellum has been associated with coordination of movement but recently attention has been drawn to cerebellar involvement in cognitive processing, possibly via neural circuits that link prefrontal, posterior parietal and limbic cortices (Schmahmann & Sherman, 1998). These brain regions are important for planning, problem solving and visuospatial processing: all cognitive domains that we have reported as being affected in people with VCFS (Henry *et al*, 2000). Thus, cerebellar abnormalities may contribute to the deficits in planning, problem solving and visuospatial processing exhibited by people with VCFS.

In addition, we found widespread loss of white matter, extending bilaterally in frontal, temporal and occipito-parietal regions. This is in agreement with a recent study in children with VCFS (Kates & Burnette, 2000), although their findings were more pronounced in posterior brain regions. Taken together, these results suggest that the cognitive phenotype in VCFS (i.e. a generalised decrement in cognitive ability, but with particular deficits in visuoperceptual–spatial function, mathematics, problem solving, planning and abstract thinking (Golding-Kushner *et al*, 1985; Goldberg *et al*, 1993; Swillen *et al*, 1997; Vataja & Elomaa, 1998; Henry *et al*, 2000)) may be associated with widespread abnormalities in white matter but with greater abnormalities in development and connectivity of brain regions implicated in these higher cognitive functions.

In contrast to the study by Eliez *et al* (2000) of children with VCFS, we did not find differences in total volume of frontal lobes in adults with VCFS. However, we did find differences in frontal grey and white matter volume. Thus, people with VCFS may have a relatively delayed frontal lobe maturation (Giedd *et al*, 1999; Sowell *et al*, 1999), which is detectable as differences in total frontal volume in childhood but subsequently normalises somewhat in adulthood, albeit with subtle differences in tissue composition remaining. In addition, others have noted a smaller total brain volume in children (Eliez *et al*, 2000) with VCFS, and cerebral atrophy in adults with VCFS (Chow *et al*, 1999). We found a trend towards smaller intracranial volume in adults with VCFS but no gross cortical atrophy.

Neurodevelopmental or neurochemical

The neurobiological basis for the high rates of learning disability and psychosis in people with VCFS is poorly understood but may include genetically determined abnormalities in brain structure and function

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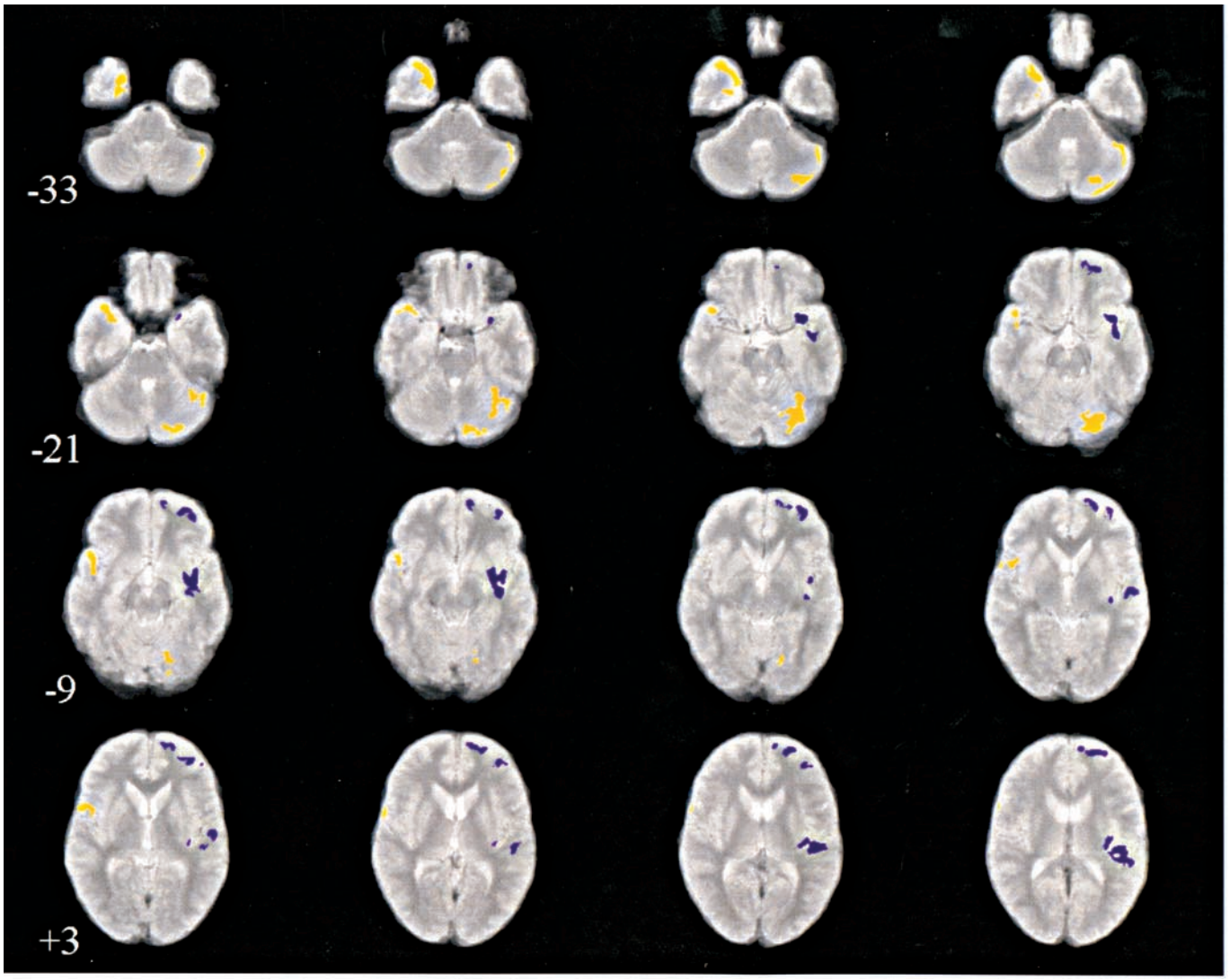

Fig. 1 Relative deficits (yellow) and excesses (blue) in grey matter volume in velo-cardio-facial syndrome compared with controls. The maps are oriented with the right side of the brain shown on the left side of each panel. The z-coordinate for each row of axial slices in the standard space of Talairach & Tournoux (1988) is given in millimetres.

resulting from hemizygosity for a gene or genes at chromosome 22q11. Many investigators favour the view that schizophrenia is a neurodevelopmental disorder, because individuals with schizophrenia have an increased frequency of minor physical anomalies (including midfacial anomalies) (Murphy & Owen, 1996) and midline brain anomalies such as cavum septum pellucidum and hypoplastic vermis (Lewis & Mezey, 1985; Martin & Albers, 1995). These abnormalities are also present in people with VCFS (Mitnick *et al*, 1994; Lynch *et al*, 1995; Vataja & Elomaa, 1998; Chow *et al*, 1999). In addition, we found a disproportionate excess of white matter in the posterior region of the corpus callosum, a midline brain structure reported to be affected in psychosis (Pearlson & Marsh, 1999) and in people with learning disability (Schaefer & Bodensteiner, 1999) and possibly reflecting abnormal myelination and/or abnormal interhemisphere connectivity with subsequent differences in brain structure and function. Moreover, in VCFS, defective development and migration of neural crest cells may play a significant role in the pathogenesis of midfacial, cranial and cardiac abnormalities (Scambler *et al*, 1992), and disruption in neural cell migration may therefore be a common neurodevelopmental mechanism in VCFS, its cognitive profile and psychosis (Chow *et al*, 1994). Although the genetic basis for this is not yet understood, there are several neurodevelopmental candidate genes that map to chromosome 22q11 (Demczuk *et al*, 1995, 1996; Wilming *et al*, 1997; Yamagishi *et al*, 1999). Consequently, haplo-insufficiency of one or more neurodevelopmental candidate genes (possibly by disrupting neural cell migration) may explain the high prevalence of learning disability and psychosis seen in people with VCFS. Our findings provide evidence that people with a 22q11 deletion have disrupted brain development (which may involve abnormal neural crest cell migration), and this might explain the cognitive profile, ocular abnormalities and cognitive phenotype of people with a deletion at 22q11 (Mansour *et al*, 1987; Kerstjens-Frederikse *et al*, 1999).

Disturbances in catecholamine neurotransmission also have been implicated in the aetiology of psychotic disorders, and offer an alternative explanation for the high

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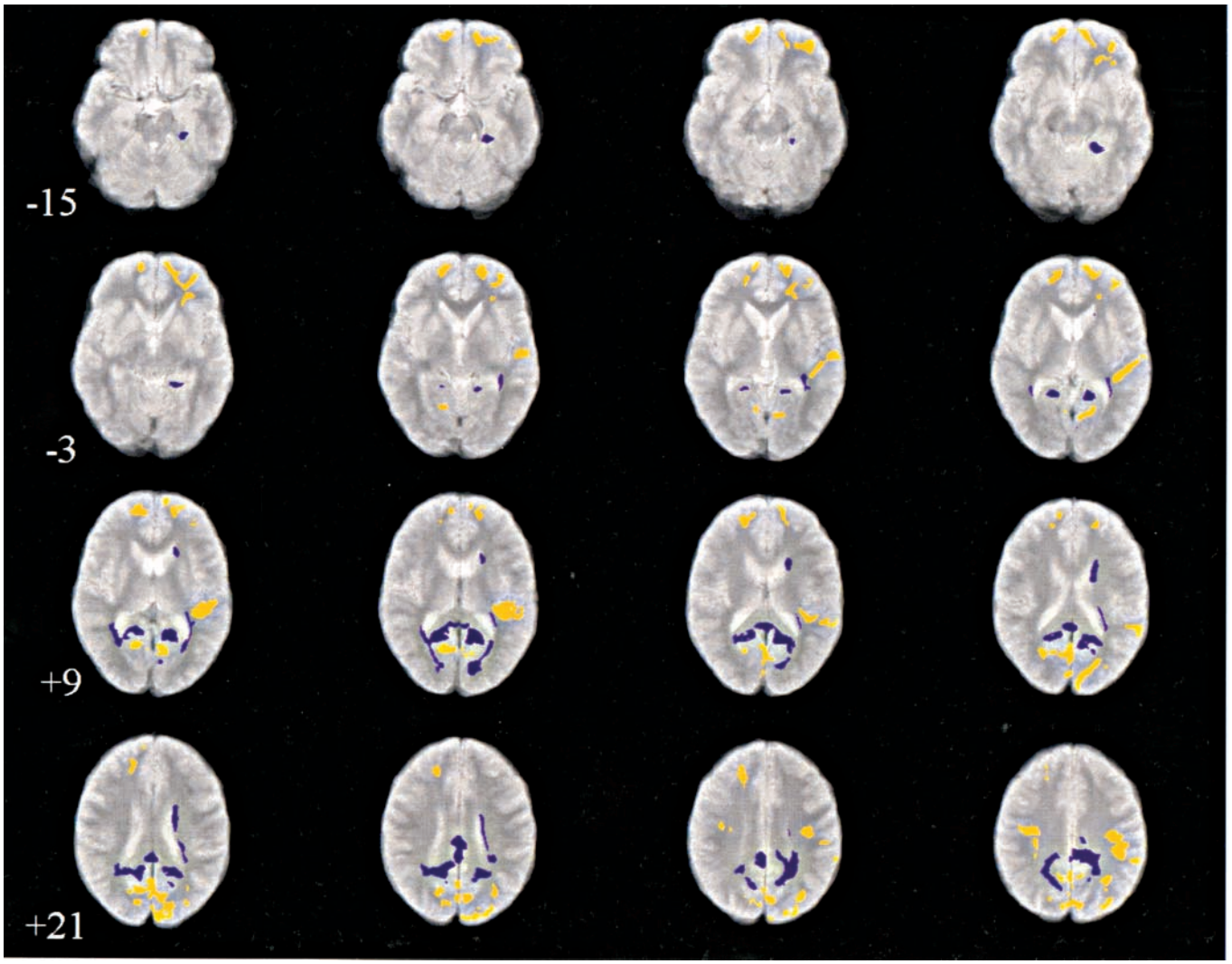

Fig. 2 Relative deficits (yellow) and excesses (blue) in white matter volume in velo-cardio-facial syndrome compared with controls. The maps are oriented with the right side of the brain shown on the left side of each panel. The *z*-coordinate for each row of axial slices in the standard space of Talairach & Tournoux (1988) is given in millimetres.

rates of psychosis in people with VCFS. The gene for catechol-O-methyltransferase (COMT), an enzyme involved in the degradation of dopamine, maps to chromosome 22q11. An amino acid polymorphism (val-108-met) determines high and low activity of this enzyme (Lachman *et al*, 1996). It has been hypothesised that individuals with 22q11 deletion who are hemizygous for COMT, as well as carrying a low-activity allele on their non-deleted chromosome, may be predisposed to the development of psychosis in VCFS (Dunham *et al*, 1992). However, we recently found no association between the low-activity COMT allele and the presence of psychosis in people with VCFS (Murphy *et al*, 1999). Consequently, our findings suggest that the neurobiology for the psychosis observed in VCFS may be more neurodevelopmental than neurochemical in origin.

Limitations and advantages of the study

Our control group consisted of people with borderline intellectual functioning, our study was relatively small and we carried out multiple statistical comparisons (thereby increasing the risk of a type I error). It is not generally agreed as to which is the 'best' control group to use when studying people with genetically determined neurodevelopmental disorders. Disadvantages of using people with borderline learning disability are the relative population heterogeneity, including people with genetically and environmentally determined causes of cognitive impairment that we did not detect using our screening techniques, and the fact that they are not representative of the healthy population. Advantages of asking them to volunteer as controls include ability to match on IQ (intellectual functioning is related to brain volume) (Andreasen *et al*, 1993; Reiss *et al*, 1996; Schaefer & Bodensteiner, 1999), and to attempt to control for clinically undetected birth trauma (because people with genetically determined learning disability also have an increased rate of birth trauma), which affects brain anatomy and cognitive function (Stewart *et al*, 1999). We included controls suffering from similar psychiatric disorders and there were no significant between-group differences in age, IQ, gender or SES, so the differences we found in brain anatomy are likely to

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be associated with a deletion at chromosome 22q11.

In conclusion, to our knowledge this is the first study to use quantitative MRI in adults with VCFS. Our results, although preliminary, demonstrate that people with a deletion at chromosome 22q11, when compared with people of a similar intellectual level, have differences in brain anatomy affecting: midline structures such as the septum pellucidum and corpus callosum; the cerebellum; widespread areas of white matter; and grey matter in temporal and left frontal regions. These abnormalities most likely reflect abnormal early brain development, and may partially explain the cognitive profile and neuropsychiatric problems seen in people with VCFS. Future, larger studies are planned to investigate how these brain abnormalities are associated with cognitive dysfunction and development of psychosis in VCFS.

CLINICAL IMPLICATIONS

- Chromosome 22q11 deletion is associated with differences in brain anatomy.
- This may underlie the cognitive phenotype of people with velo-cardio-facial syndrome.
- It will increase our understanding of the neurobiology of psychosis.

LIMITATIONS

- Small sample size.
- Some subjects in both groups had comorbid psychiatric disorder.
- Control group is not representative of general population.

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