

Brain and behaviour in children with 22q11.2 deletion syndrome: a volumetric and voxel-based morphometry MRI study

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In people with velo-cardio-facial syndrome [or 22q11.2 deletion syndrome (22qDS)], a single interstitial deletion of chromosome 22q11.2 causes a wide spectrum of cognitive deficits ranging from global learning difficulties to specific cognitive deficits. People with 22qDS are also at high risk of developing attention-deficit/hyperactivity disorder and autism spectrum disorders in childhood, and schizophrenia in adolescence or adult life. However, the neurobiology of 22qDS, and the relationship between abnormalities in brain anatomy and behaviour, is poorly understood. Thus, we studied the neuroanatomy of 22qDS children using fully automated voxel-based morphometry (VBM) and manually traced single region-of-interest (ROI) analysis. Also, we investigated whether those brain regions that differed significantly between groups were related to behavioural differences within children with 22qDS. We compared the brain morphometry of 39 children and adolescents with 22qDS (mean age: 11 years, SD \pm 3, IQ = 67, SD \pm 10) and 26 sibling controls (mean age: 11 years, SD \pm 3, IQ = 102, SD \pm 12). Using VBM, we found, after correction for IQ, that individuals with 22qDS compared with controls had a significant reduction in cerebellar grey matter, and white matter reductions in the frontal lobe, cerebellum and internal capsule. Using single ROI analysis, we found that people with 22qDS had a significant ($P < 0.05$) reduction in bulk volume bilaterally in the occipital-parietal lobes, but a larger right caudate nucleus and lateral ventricles. Further, within people with 22qDS, there was a significant positive correlation between severity of (i) schizotypy score and grey matter volume of the temporo-occipital regions and the corpus striatum; (ii) emotional problems and grey matter volume of frontostriatal regions; and (iii) social behavioural difficulties and grey matter in frontostriatal regions. Thus, subjects with 22qDS have widespread changes in brain anatomy, particularly affecting white matter, basal ganglia and cerebellum. Also, within 22qDS, regionally specific differences in brain development may partially underpin behavioural differences. We suggest that there is preliminary evidence for specific vulnerability of the frontostriatal and cerebellar-cortical networks in 22qDS.

Keywords: velo-cardio-facial syndrome (VCFS); 22q11.2 deletion syndrome (22qDS); voxel-based morphometry; behaviour; children

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ASD = autistic spectrum disorder; ASQ = autism screening questionnaire; BMM = brain activation and morphological mapping; 22qDS = chromosome 22q11.2 deletion syndrome; FSIQ = full-scale IQ; SDQ = strengths and difficulties questionnaire; VBM = voxel-based morphometry; WMHs = white matter hyperintensities

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Introduction

22q11.2 deletion syndrome (22qDS), a genetically determined neurodevelopmental disorder caused by interstitial deletions of chromosome 22q11.2, is commonly associated with learning difficulties, specific cognitive deficits and high risk of neuropsychiatric disorders (Scambler *et al.*, 1992; Swillen *et al.*, 1997; Henry *et al.*, 2002). 22qDS is the most common microdeletion syndrome with an estimated prevalence of 1:2500–1:4000 live births (Tezenas Du Montcel *et al.*, 1996; Oscarsdottir *et al.*, 2004). Early studies of 22qDS reported a characteristic behavioural phenotype, with children reported to have poor social skills, bland affect with minimal facial expression and behavioural difficulties including high levels of social withdrawal, disinhibition and impulsivity (Golding-Kushner *et al.*, 1985; Swillen *et al.*, 1997, 1999a). Later studies have highlighted the high prevalence of psychopathology in 22qDS compared with that in the general population. One of the most common psychiatric problems experienced by children with 22qDS appears to be attention-deficit/hyperactivity disorder (ADHD). This is present in 35–55% of 22qDS children and is primarily of the inattentive subtype (Gothelf *et al.*, 2004a). In addition, a recent study employing strict diagnostic criteria indicated that ~14% of 22qDS children had an autistic spectrum disorder (ASD) and that these children were more developmentally delayed than those without ASD (Fine *et al.*, 2005). Other common psychiatric problems in 22qDS children include affective disorders such as bipolar disorder, depression and anxiety (Papolos *et al.*, 1996; Arnold *et al.*, 2001; Baker and Skuse, 2005). In adults, high rates of obsessive-compulsive disorder (OCD) (Gothelf *et al.*, 2004b) and schizophrenia (up to 25%) (Murphy *et al.*, 1999) have been reported. Indeed, several lines of evidence indicate that a deletion of chromosome 22q11.2 may represent one of the highest known genetic risk factors for schizophrenia (Murphy and Owen, 2001; Murphy, 2002).

Thus, people with 22qDS commonly have mental health problems, such as ASD, ADHD, affective disorders and schizophrenia. These disorders are associated with neurodevelopmental and/or neuroanatomical differences in the general population, the basis of which is most probably a poorly understood interplay between genetic and environmental factors. Hence, a study of 22qDS may offer a unique opportunity to understand the neurobiological associates of some mental health disorders. Some brain regions, and neural systems, are especially implicated in each of these disorders. ADHD has been most strongly linked with abnormalities of the prefrontal cortex, basal ganglia (particularly the caudate nucleus), corpus callosum and the cerebellum (especially the vermis) (Seidman *et al.*, 2005). Also, it has been hypothesized that the cognitive symptoms in ADHD are caused by dysfunction of frontostriatal and fronto-cerebellar circuits (Nigg and Casey, 2005). Prior *in vivo* studies of brain anatomy in people with ASD reported grey matter differences within the temporal lobes and in frontostriatal and parietal networks, in addition to differences

in subcortical and cerebellar white matter changes (Zilbovicius *et al.*, 2000; McAlonan *et al.*, 2002; Hollander *et al.*, 2005; McAlonan *et al.*, 2005). Further, it has been suggested that the social abnormalities of ASD are related to anomalies in frontostriatal circuits (McAlonan *et al.*, 2005). Affective disorders have been linked with structural and functional anomalies of the frontal lobes, superior temporal gyrus, limbic system, basal ganglia, thalamus and cerebellum (Sheline, 2000; Kanner, 2004; Strakowski *et al.*, 2005). There have been many studies investigating the neural substrate of schizophrenia, and the most common anomalies, as highlighted in a recent review, are ventricular enlargement, medial and superior temporal lobe, frontal lobe and subcortical anomalies such as cavum septum pellucidum, alterations of the basal ganglia, corpus callosum and the thalamus (Shenton *et al.*, 2001).

Similarly, structural brain anomalies have also been reported in 22qDS with qualitative studies reporting an increased prevalence of developmental midline anomalies (e.g. abnormalities of the septum pellucidum) (Chow *et al.*, 1999; van Amelsvoort *et al.*, 2001), polymicrogyria (Bingham *et al.*, 1998; Kawame *et al.*, 2000; Worthington *et al.*, 2000; Ghariani *et al.*, 2002), reduced corpus callosal volume (Ryan *et al.*, 1997), increased white matter hyperintensities (WMHIs) (Mitnick *et al.*, 1994; van Amelsvoort *et al.*, 2001), hypoplastic cerebellar vermis (Mitnick *et al.*, 1994; Vataja and Elomaa, 1998) and ventricular enlargement (Chow *et al.*, 1999).

Relatively few quantitative brain MRI studies on children with 22qDS have been published and these report decreases in total brain volume (by 8.5–11%) (Eliez *et al.*, 2000; Kates *et al.*, 2001; Simon *et al.*, 2005) and left parietal and right occipital grey matter (Eliez *et al.*, 2000; Kates *et al.*, 2001). Also, a recent voxel-based morphometry (VBM) study reported that people with 22qDS have reductions in grey matter volume in medial posterior portions of the cingulate gyrus, the parietal lobe and the anterior cerebellum, but increased grey matter in the right frontal and insular regions (Simon *et al.*, 2005). Recently, it has also been reported that reductions in temporal grey matter volume is predictive of 'thought problems' in people with 22qDS (Bearden *et al.*, 2005). Thus, there is increasing evidence that people with 22qDS have regional differences in grey matter volume, some of which may be associated with behavioural problems.

It has also been suggested that white matter may be particularly affected by a deletion at 22q11.2. Previous studies have reported reduced white matter volume in the right cerebellum (Eliez *et al.*, 2000) and white matter differences in bilateral frontal, parietal and temporal regions and the external capsules as well as increased fractional anisotropy in posterior brain regions including splenium, medial parietal lobe and posterior cingulum (Kates *et al.*, 2001; van Amelsvoort *et al.*, 2001; Barnea-Goraly *et al.*, 2003; Kates *et al.*, 2004; van Amelsvoort *et al.*, 2004; Simon *et al.*, 2005). Simon *et al.* (2005) suggested that increased fractional anisotropy in the

posterior brain regions may be indicative of a corpus callosum displacement due to enlarged cerebral ventricles in 22qDS. In summary, therefore, prior studies suggest that people with 22qDS have differences in both white and grey matter and that dysfunction within large-scale neural networks may underpin the cognitive and behavioural symptoms characteristic of the condition.

While these prior studies were important first steps towards understanding the neurobiological basis of 22qDS, they were limited by small sample sizes and the use of control groups who differed in socio-economic background. Thus, in the largest study of its kind to date, we compared the brain morphometry of children and adolescents with 22qDS and an age and socio-economic-status-matched sample of healthy sibling controls using both a VBM and region-of-interest (ROI) approach. We also carried out preliminary analysis to determine if anatomical differences that distinguish 22qDS from controls are associated with differences in the behavioural phenotype within people with 22qDS. On the basis of available data, we predicted that the 22qDS group would have differences from controls in limbic regions, cortico-subcortical networks (including cerebello-thalamo-cortical and frontostriatal) and posterior occipito-parietal association systems. As mentioned previously, frontostriatal and cerebellar abnormalities are associated with ADHD, ASD and affective disorders. Consequently, we hypothesized that children and adolescents with 22qDS, who are reported to have high rates of these disorders, have frontostriatal and cerebellar anomalies. On the basis of prior findings of structural alterations in schizophrenia, we hypothesized that schizotypal symptoms, as trait markers for schizophrenia susceptibility, are associated with abnormalities in frontal, temporo-occipital, frontal and corpus striatal regions.

Participants and methods

Participants

We included 39 children with genetically confirmed 22qDS (19 female and 20 male, mean age: 11 years, SD ± 3 , mean IQ: 67, SD ± 10) and 26 non-deleted sibling controls (10 female and 16 male, mean age: 11 years, SD ± 3 , mean IQ: 102, SD ± 12). All subjects had a detailed physical examination (41% had congenital heart defects and 79% had palatal anomalies) and a semi-structured interview to document past medical history. General intellectual functioning was assessed using the Wechsler Intelligence Scale for Children-III (WISC-III) (Wechsler, 1991). The strengths and difficulties questionnaire (SDQ) (Goodman *et al.*, 2000) was used to measure emotional symptoms (abnormal score ≥ 5), conduct problems (abnormal score ≥ 4), hyperactivity/inattention (abnormal score ≥ 7), peer problems (abnormal score ≥ 4) and pro-social behaviour (abnormal score ≤ 4). The autism screening questionnaire (ASQ) (short-version) measured autistic symptoms with a cut-off score of 7 for individuals who may have autism and who should have a more complete evaluation (Berument *et al.*, 1999). Finally, in view of the high rates of schizotypy reported in 22qDS adults (Murphy *et al.*, 1999), we wished to assess schizotypal traits in a 22qDS child population. However, as there is a lack of a validated

measure for schizotypy in learning disabled children, we constructed a preliminary comparative schizotypy scale derived from Diagnostic and Statistical Manual of Mental Disorders (DSM) IV (American Psychiatric Association, 2000). All behavioural assessments were completed by parents or primary caregiver.

All participants with 22qDS had a confirmed deletion of chromosome 22q11 using fluorescence *in situ* hybridization (FISH) (Oncor Inc, Gaithersburg, MD, USA). We excluded participants with the clinical phenotype of 22qDS but without the large 3 Mb 22q11.2 deletion, those with a clinically detectable medical disorder known to affect brain structure (e.g. epilepsy or hypertension), a history of head injury and those individuals with contraindications to MRI. A familial deletion was present in 20% of the group. A chromosome 22q11 deletion was excluded in all sibling controls. Approval for the study was granted by the local ethics committee. Parents or guardians and, in cases where the participants were 16 years or older, participants gave written informed consent after the procedure was fully explained.

MRI protocol

Image acquisition

All MRI data were obtained using a GE Signa 1.5 T Neuro-optimized MR system (General Electric, Milwaukee WI, USA) at the Maudsley Hospital, London, UK. Whole-head coronal 3D spoiled gradient acquisition in the steady state (SPGR) images [repetition time (TR) = 11.9 ms, echo time (TE) = 5.2 ms, 256 \times 192 acquisition matrix, 124 \times 1.5 mm slices] were obtained from all subjects. In addition, we obtained whole-brain axial dual-echo fast-spin echo images (TR = 4000 ms, TE1 = 20 ms, TE2 = 100 ms, 256 \times 256 acquisition matrix, 60 \times 3 mm slices) for radiological purposes. Three types of analysis were performed on the dataset, one qualitative and two quantitative, all blind to subject group status.

Image processing and measurement

Qualitative visual assessment of intracranial pathology

The MRI datasets were assessed qualitatively by a neuroradiologist blind to subject group status. The presence or absence of midline abnormalities such as cavum septum pellucidum and vergae, and other neurodevelopmental abnormalities were recorded as being present or absent. WMHIs were assessed using a standardized protocol (Kozachuk *et al.*, 1990) in which a four-point rating scale was used: grade 0 = ventricular WMHIs absent; grade 1 = frontal or occipital caps or pencil thin lining of the lateral ventricles; grade 2 = smooth halo surrounding the lateral ventricles and grade 3 = irregular ventricular WMHIs extending deep into 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.

Voxel-based morphometry

Statistical Parametric Mapping software (SPM2, Wellcome Department of Imaging Neurosciences, University College London) was used to pre-process the SPGR data and a detailed description of the image-processing steps have been published elsewhere (Ashburner and Friston, 2000; Good *et al.*, 2001). SPM implements a segmentation algorithm incorporating *a priori* knowledge of the probable spatial distribution of neural tissue types by using prior probability tissue maps that have been derived from a large number of subjects.

We created study-specific customized prior probability maps based on all 65 subjects in order to ensure the most reliable segmentation feasible. The following pre-processing steps were undertaken: (i) the brain images were segmented into probabilistic maps of grey and white matter and CSF by means of an adapted mixture model clustering algorithm; (ii) the segmented grey (white) tissue map was mapped to a grey (white) matter template and the derived warping parameters were applied to the original T_1 -weighted image to facilitate mapping it into standard space, hence preventing skull and other non-brain voxels from contributing to the registration, while circumventing the need for explicit skull-stripping; (iii) subsequently, the registered image was re-segmented, which is essential since the *a priori* knowledge included in the SPM2 segmentation algorithm means that to achieve optimal performance images are required to be in standard space. Finally, the segmented maps were corrected for volume changes occurring through the registration and then smoothed using a Gaussian filter of 5 mm full-width at half-maximum (FWHM). Total grey and white matter volumes were calculated from the segmented, normalized and modulated maps.

Manually traced ROI

Manual tracing of brain structures was performed on SPGR data sets, using Measure software (Barta *et al.*, 1997) (Johns Hopkins University, Baltimore, MD, USA) and using previously published anatomical definitions (van Amelsvoort *et al.*, 2004). Inter and intra-rater reliabilities (range: 0.89–0.92) were determined by intra-class correlation computation for brain regions traced by the operators and were highly significant (Bartko and Carpenter, 1976). We measured total intracranial space and bulk tissue volume (i.e. grey + white matter) of right and left cerebral hemispheres, frontal, parietal, temporal and parietal-occipital lobes. In addition, owing to the prior reports of differences in regional brain volume being associated with psychopathology in the general population, we also measured cerebral ventricles, hippocampus, caudate nucleus, putamen and cerebellum. The volume of each region was calculated by multiplying the summed pixel cross-sectional areas by slice thickness.

Statistical analyses

Demographic data

Between-group differences in age and full-scale IQ (FSIQ) were assessed using a one-way ANOVA (analysis of variance) and χ^2 -test for gender distribution ($P < 0.05$, two-tailed). Non-parametric Mann–Whitney U -tests were employed to compare between-group differences of behavioural characteristics ($P < 0.05$, two-tailed).

Qualitative data

Statistical analysis was carried out using SPSS (SPSS 11.0 for Windows, SPSS Inc, Chicago, IL, USA). Between-group differences in radiological assessment of the MRI scans were compared using χ^2 - or the Fisher Exact Probability Test depending on cell size. For between-group differences in extent of WMHIs, we used non-parametric Mann–Whitney U -test (two-tailed).

Analysis of MRI data using manual tracing

The manually traced data (Measure) were analysed using SPSS (SPSS 11.0 for Windows, SPSS Inc, Chicago, IL, USA). Data were examined for normality of distribution to conform to the assumptions of the statistical tests used. In variables where the assumption of normality was not met, a natural log transformation was applied to conform

the data to a normal distribution (right hippocampus, bilateral ventricles and third ventricle). To control for the relationship between head size and cerebral volume, hand-traced brain volumes were normalized as a percentage of the total intracranial volume. Manually traced total and regional brain volume group differences were calculated using a one-way between-groups multivariate analysis of variance (MANOVA) with group (22qDS or control) as a between-subject variable. Thereafter, univariate tests were performed to investigate volumetric differences of specific brain regions. The effect sizes were obtained from the SPSS output, partial eta squared (η_p^2) (small = 0.01, moderate = 0.06, large = 0.14). The level of significance was $P < 0.05$.

Analysis of MRI data using computerized Brain Activation and Morphological Mapping (BAMM) software

To assess statistical significance of between-group differences in grey and white matter volume, the data were analysed by fitting an analysis of covariance (ANCOVA) model at each intracerebral voxel in standard space, that is,

$$T = a_0 + a_1V + a_2X_2 + \dots + a_nX_n + e,$$

where T is a vector denoting the image value (tissue volume) at a given voxel for each individual in the cohort, V is the independent variable vector (representing group membership), e models the random variation and the X_n 's are covariate vectors representing covariates of no interest, in this case total grey or white matter volume and gender. In additional analysis, IQ was also used as a covariate in the between-group analysis. Structural brain changes are likely to stretch over a number of contiguous voxels; hence, test statistics incorporating spatial information such as 3D cluster mass (the sum of supra-threshold voxel statistics) are generally more powerful than other possible test statistics, which are informed only by data at a single voxel. Regional relationships were therefore tested at the level of voxel clusters. Full details are given elsewhere (Bullmore *et al.*, 1999; Sigmundsson *et al.*, 2001) but, briefly, the model was first regressed onto the observed data at each intra-cerebral voxel to yield a test statistic map $a^* = a_1/\text{StandardError}(a_1)$, known as the voxelwise test statistic. A reference null-distribution was then constructed via randomization, and voxels exceeding the two-tailed critical values at $P < 0.05$ were combined to form spatially contiguous clusters in 3D. Finally, the significance of each supra-threshold voxel cluster was assessed by a one-tailed randomization test of its 'mass', that is, the sum of supra-threshold voxel statistics it comprised, using a statistical threshold for cluster significance chosen so that the expected number of false-positive clusters was less than one false-positive per analysis. Finally, BAMM software provides anatomical mapping in the standard space of Talairach and Tournoux (Talairach and Tournoux, 1988), enabling identification of structural regions.

Having identified significant between-group differences, exploratory multiple regression models were performed using BAMM software, within the 22qDS group to test the association between regional grey and white matter volume and behavioural scores. It was predicted that, within regions identified in the main effects, there would be a relationship between previous volumetric grey/white matter alterations and (i) schizotypy scores; (ii) autism symptoms; (iii) hyperactivity/inattention; (iv) emotional symptoms; (v) pro-social behaviour; and (vi) peer problems. Chronological age and gender were included as covariates where they did not

correlate with the independent variable in order to control for the possibility that these factors confound brain anatomy and/or behaviour. For these analyses, a linear regression model was fitted at each voxel, that is,

$$T = a_0 + a_1V + a_2X_2 + \dots + a_nX_n + e,$$

where V is the independent variable vector (i.e. the behavioural score), and all other variables are as mentioned earlier. Permutation testing was used to assess statistical significance as for the between-group analyses. The significance value was set at $P < 0.001$ to attempt to control for multiple comparisons. In addition, the expected number of false-positive clusters was less than one false-positive per analysis (cluster threshold $P < 0.01$).

Results

Demographic data

There was no significant ($t = 0.425$, $P = 0.7$) difference in mean age between the 22qDS group and the sibling controls. The 22qDS group had a significant ($P < 0.05$) lower FSIQ (67 ± 10) compared with controls (102 ± 12). The 22qDS group had significantly higher levels of autistic symptoms, emotional symptoms, hyperactivity/inattention, pro-social and peer problems and higher schizotypy scores ($P < 0.05$). Table 1 shows the behavioural characteristics of the 22qDS group.

Qualitative neuroradiological findings

Midline anomalies, in particular those of the cavum septum pellucidum/vergae, were significantly ($P = 0.007$) more common in people with 22qDS (69%) than in sibling controls (35%). Additionally, the 22qDS group had a high prevalence of peripheral WMHIs (mean score: 0.38, SD ± 0.89) compared with the sibling control group in which these were completely absent. There were no differences in the number

of anomalies of the posterior fossa or the medial temporal lobe structures (e.g. malrotated hippocampus), in WMHI rating of deep and periventricular white matter, and in the number of arachnoid cysts between the 22qDS and sibling control groups.

VBM analysis

On average, the 22qDS group had a total grey matter volume of 612 ml and a total white matter volume of 341 ml compared with a total grey matter volume of 635 ml and total white matter volume of 358 ml in the sibling control group. These values corresponded to a total grey matter reduction of 9.6% and a total white matter reduction of 9.5% in the 22qDS group compared with the sibling control group. However, these differences were not significant ($P = 0.18$ and 0.07 , respectively). There were no significant correlations between either total white or grey matter and chronological age or FSIQ in either 22qDS or the sibling control group.

Figure 1 shows between-groups differences in grey matter regions corrected for total grey volume and gender. Subjects with 22qDS group had reduced grey matter volume in a large cluster centred in the left cerebellum and the left and right hippocampus, and the medial occipital and posterior cingulate cortices. In contrast, the 22qDS group had increased grey matter volume in left and right insula, corpus striatum and thalamus.

Figure 2 shows the between-groups differences in white matter regions corrected for total white volume and gender. The 22qDS group had a significant reduction in white matter volume as compared with sibling controls in the left cerebellum, bilateral temporo-occipital and parieto-occipital tracts, left and right internal capsules and small anterior frontal regions.

Figures 3 and 4 show between-groups regional differences in grey and white matter after correction for total tissue (grey

Table 1. Behavioural data

Behavioural measure	Group	N	Mean score	Range	$N \geq$ cut-off [†]	SD \pm	P-value
ASQ	22qDS	35	5.84	0–14	16	4.34	0.001**
	Siblings	21	2.38	0–10	2	2.8	
SDQ	22qDS	33	4.27	0–10	13	3.05	0.0005**
	Siblings	22	1.14	0–5	1	1.55	
Emotional symptoms	22qDS	33	2.09	0–6	9	1.81	0.128
	Siblings	22	1.36	0–6	1	1.56	
Conduct problems	22qDS	33	5.52	0–10	12	2.93	0.007**
	Siblings	22	3.23	0–9	3	2.62	
Hyperactivity/inattention	22qDS	33	3.61	0–10	16	2.54	0.0005**
	Siblings	22	0.9	0–7	2	1.69	
Peer problems	22qDS	33	7.21	1–10	4	2.42	0.04*
	Siblings	22	8.41	4–10	1	1.79	
Pro-social behaviour [‡]	22qDS	31	1.67	0–9	N/A	2.4	0.01*
	Siblings	21	0.33	0–3	N/A	0.86	

Abbreviations: ASQ = autism screening questionnaire; SDQ = strengths and difficulties questionnaire. Mann–Whitney U-test; * $P < 0.05$ ** $P < 0.001$. [†]Number of individuals who had a score above the cut-off limit for further investigations (ASQ) or abnormal scores (SDQ); [‡]scale reversed, i.e. higher scorer indicates lower ability.

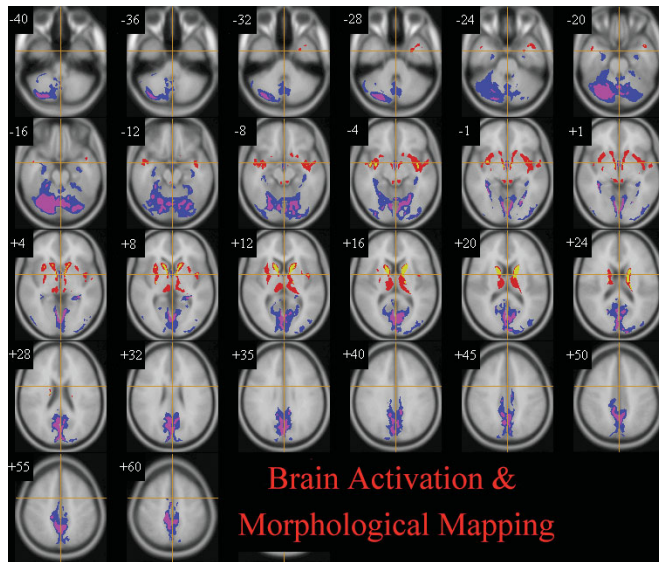


Fig. 1 Relative deficits (blue/pink) and excesses (red/yellow) in grey matter volume in 22qDS children compared with healthy sibling controls (cluster threshold = 0.01, $P = 0.003$, cluster size: $D = 15\,398$; $E = 3579$, corrected for gender and total grey volume). The maps are oriented with the right 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 and Tournoux (Talairach and Tournoux, 1988) is given in millimetres. Cluster size refers to number of voxels in total deficit (D) or excess (E) cluster(s).

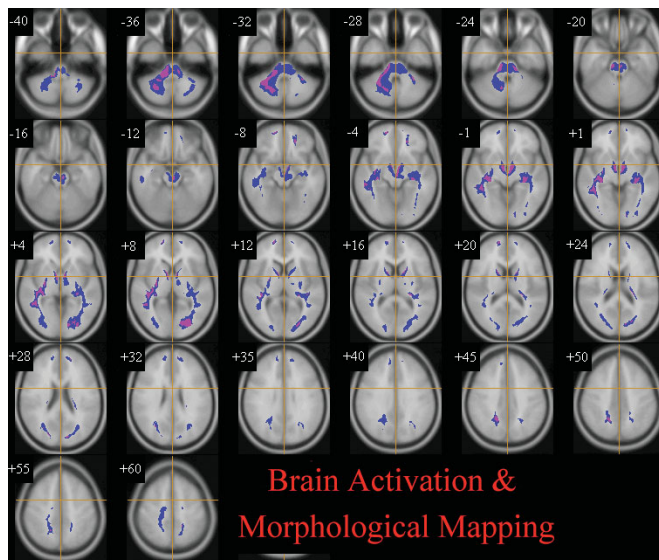


Fig. 2 Relative deficits (blue/pink) in white matter volume in 22qDS children compared with healthy sibling controls (cluster threshold = 0.01, $P = 0.008$, cluster size = 9453, corrected for gender and total white volume). See Fig. 1 legend for explanation.

or white) volume, gender and FSIQ. After correction, the 22qDS group had significant grey matter reduction in the cerebellum, and the ventromedial occipital and posterior cingulate cortex bilaterally (Fig. 3). Significant white matter reduction in the 22qDS group was found in the brainstem

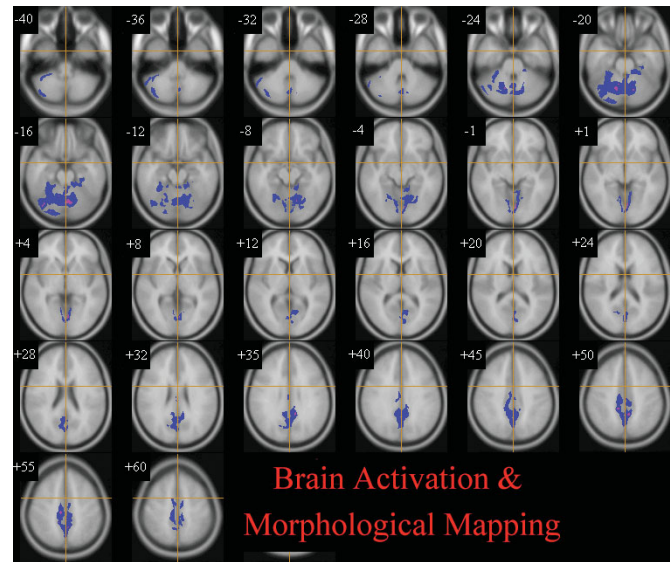


Fig. 3 Relative deficits (blue/pink) in grey matter volume in 22qDS children compared with healthy sibling controls (cluster threshold = 0.01, $P = 0.002$, cluster size = 6352, corrected for gender, total grey volume and FSIQ). See Fig. 1 legend for explanation.

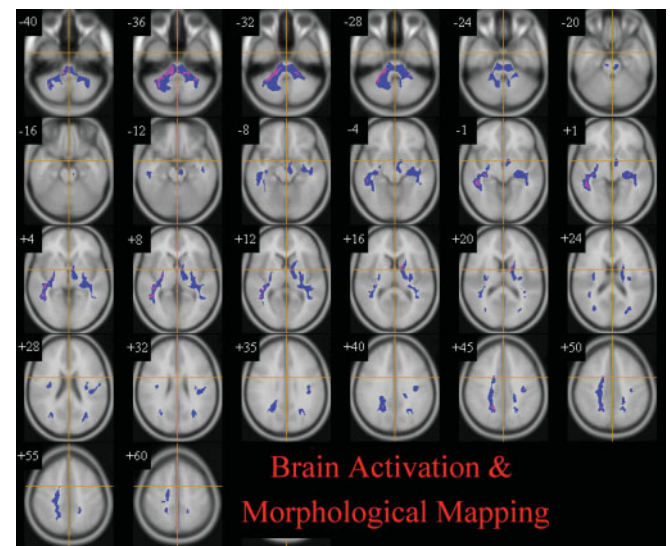


Fig. 4 Relative deficits (blue/pink) in white matter volume in 22qDS children compared with healthy sibling controls (cluster threshold = 0.01, $P = 0.008$, cluster size = 7833, corrected for gender, total white volume and FSIQ). See Fig. 1 legend for explanation.

and cerebellum bilaterally, the left internal capsule and right posterior limb of the internal capsule, left and right occipitotemporal white matter and right corona radiata (Fig. 4).

Brain volumes analysed using manual tracing

There was no significant difference between groups in total intracranial volume ($P > 0.05$). There was no overall effect

Table 2. Hemispheric and lobar brain volumes as defined by manual tracing in individuals with 22qDS and sibling controls

Brain structure	22qDS (n = 39)	Siblings (n = 26)	F (d.f. = 1, 63)	P-value	Effect size (η_p^2)	Power
Total intracranial volume	1511.6 (125.8) ^o	1576.9 (149.8)	3.565	0.06	0.05	0.46
Hemispheres total	1188.5 (112.8) ^o	1264.7 (125.1)	6.336	0.01	0.09	0.7
	78.6% (3.4) ⁺	80.2% (1.8)	4.720	0.03 [#]	0.07	0.57
Left	593.8 (55.1)	635.3 (63.3)	7.614	0.008	0.11	0.78
	39.3% (1.7)	40.3% (1.4)	6.598	0.01*	0.1	0.72
Right	595.3 (59.4)	632.2 (63.8)	5.457	0.02	0.08	0.63
	39.4% (1.8)	40.1% (1.0)	3.286	0.08	0.05	0.43
Frontal lobe total	602.5 (64.8)	619.5 (81.6)	0.878	0.35	0.01	0.15
	39.8% (2.48)	39.2% (2.9)	0.739	0.39	0.01	0.14
Left	300.6 (33.2)	309.0 (39.3)	0.849	0.36	0.01	0.15
	19.9% (1.31)	19.6% (1.5)	0.668	0.42	0.01	0.13
Right	301.9 (32.5)	310.5 (43.0)	0.857	0.36	0.01	0.15
	20.0% (1.27)	19.7% (1.6)	0.692	0.41	0.01	0.13
Parieto-occipital lobe total	134.5 (31.7)	178.8 (50.3)	18.958	0.0005	0.24	0.99
	8.9% (1.9)	11.3% (3.0)	16.251	0.0005**	0.21	0.98
Left	69.0 (16.7)	92.3 (26.6)	19.292	0.0005	0.24	0.99
	4.6% (1.0)	5.8% (1.6)	16.620	0.0005**	0.21	0.98
Right	65.5 (16.3)	86.7 (24.7)	16.918	0.0005	0.22	0.98
	4.3% (1.0)	5.5% (1.5)	14.178	0.0005**	0.19	0.96
Parietal lobe total	299.3 (53.8)	297.6 (50.4)	0.003	0.96	0.0005	0.05
	19.8% (3.3)	18.9% (3.0)	0.982	0.33	0.02	0.16
Left	149.9 (26.9)	148.9 (27.1)	0.004	0.95	0.0005	0.05
	9.9% (1.6)	9.5% (1.7)	0.879	0.35	0.01	0.15
Right	149.4 (27.3)	148.7 (25.0)	0.002	0.96	0.0005	0.05
	9.9% (1.7)	9.5% (1.4)	1.027	0.32	0.02	0.17
Temporal lobe total	142.3 (22.0)	155.1 (27.1)	3.745	0.06	0.06	0.48
	9.4% (1.3)	9.8% (1.4)	1.052	0.31	0.02	0.17
Left	70.1 (12.5)	75.7 (15.1)	1.992	0.16	0.03	0.29
	4.6% (0.8)	4.8% (0.8)	0.238	0.63	0.004	0.08
Right	72.2 (11.0)	79.4 (13.2)	5.401	0.02	0.08	0.63
	4.8% (0.6)	5.0% (0.7)	2.252	0.13	0.04	0.32

Univariate GLM for raw volume or ratio correction for total intracranial volume. Values are group means (SD); * $P < 0.05$, ** $P < 0.001$.
^oMean raw volume in ml (SD). ⁺% of intracranial volume (SD). [#]Significant result on Levene test of the homogeneity of variance.

of gender or FSIQ, neither was there a Group \times Gender or Group \times FSIQ interaction on corrected manually traced brain volumes; hence, the MANOVA was re-run without gender and FSIQ as covariates. There was a significant main effect of group [$F(23,39) = 2.04$, Wilk's Lambda = 0.454, $P = 0.02$]. People with 22qDS had a significantly smaller ratio-corrected volume of the total left hemisphere volume ($P < 0.01$; see Table 2). In addition, the total, left and right parieto-occipital lobe was smaller ($P < 0.0005$; see Table 2). In contrast, the right caudate nucleus ($P < 0.04$), the total, left and right lateral ventricles were significantly larger in the 22qDS group ($P < 0.0005$; see Table 3).

Brain and behaviour, post hoc analyses within 22qDS corrected for chronological age and gender

As noted above, we carried out a preliminary analysis in which we related behavioural measures to the volume of those brain regions that differed significantly between groups. Within people with 22qDS, there was a significant positive association between increased schizotypy score and two

clusters of regional grey matter: (i) a cortical cluster centred in the inferior and middle right temporo-occipital lobe (Tal: $x = 61.8$, $y = -37.6$, $z = 1.0$); and (ii) a subcortical cluster centred in the left lenticular nucleus (Tal: $x = -24.9$, $y = 6.5$, $z = 8.0$) (Fig. 5, top row). In addition, a cortical cluster centred in the right inferior and middle frontal gyri (Tal: $x = 47.1$, $y = 28.2$, $z = 24.0$) and a subcortical cluster centred in the left lenticular nucleus and head of caudate (Tal: $x = -24.7$, $y = 4.8$, $z = 4.0$) correlated positively with emotional symptoms. Finally, a large cluster centred in the left lenticular nucleus, head of caudate and extending into the insula (Tal: $x = -26.8$, $y = 3.9$, $z = 8.0$) correlated positively with peer problem (base row) scores. No other significant correlations were identified.

Discussion

In this study, we employed qualitative and complementary quantitative methodologies to investigate brain morphology and its relationship to the behavioural phenotype in children with 22qDS.

Table 3. Regional brain volumes of manually traced subcortical structures in individuals with 22qDS and sibling controls

Brain structure	22qDS (n = 39)	Siblings (n = 26)	F (d.f. = 1, 63)	P-value	Effect size (η_p^2)	Power
Hippocampus total	5.8 (0.7) ^o	6.3 (0.9)	6.083	0.02	0.09	0.68
	0.004% (0.0005) ⁺	0.004% (0.0005)	1.518	0.22	0.02	0.23
Left	2.8 (0.4)	3.1 (0.5)	3.861	0.05	0.06	0.49
	0.002% (0.0003)	0.002% (0.0003)	0.758	0.39	0.01	0.14
Right [†]	3.0 (0.4)	3.3 (0.5)	4.086	0.05	0.06	0.51
	0.002% (0.0001)	0.002% (0.0001)	0.742	0.39	0.01	0.14
Putamen total	6.7 (1.5)	7.1 (1.6)	0.738	0.39	0.01	0.14
	0.5% (0.1)	0.5% (0.1)	0.019	0.89	0.000	0.05
Left	3.5 (0.7)	3.6 (0.8)	0.576	0.45	0.01	0.12
	0.2% (0.1)	0.2% (0.1)	0.005	0.94	0.000	0.05
Right	3.3 (0.9)	3.5 (1.0)	0.585	0.45	0.01	0.12
	0.2% (0.1)	0.2% (0.1)	0.027	0.87	0.000	0.05
Caudate total	8.6 (1.3)	8.4 (1.3)	0.404	0.53	0.01	0.1
	0.57% (0.08)	0.5% (0.1)	3.835	0.06	0.06	0.49
Left	4.2 (0.7)	4.1 (0.7)	0.143	0.70	0.002	0.07
	0.28% (0.04)	0.2% (0.1)	2.461	0.12	0.04	0.34
Right	4.5 (0.8)	4.3 (0.6)	0.693	0.45	0.01	0.13
	0.3% (0.04)	0.2% (0.1)	4.597	0.04*	0.07	0.56
Lateral ventricle [†] total	15.2 (7.9)	9.6 (6.3)	12.910	0.001	0.16	0.94
	0.01% (0.005)	0.006% (0.004)	16.290	0.0005**	0.21	0.98
Left	7.4 (4.1)	5.3 (5.0)	8.178	0.006	0.12	0.80
	0.005% (0.003)	0.003% (0.003)	10.377	0.002*	0.24	0.99
Right	7.9 (4.2)	4.2 (1.9)	15.438	0.0005	0.20	0.97
	0.005% (0.003)	0.003% (0.001)	19.013	0.0005**	0.21	0.89
Third ventricle [†]	0.6 (0.9)	0.3 (0.2)	13.156	0.001	0.18	0.95
	0.0004% (0.0007)	0.0002% (0.0001)	2.585	0.11	0.04	0.35
Cerebellum	125.2 (13.9)	134.4 (16.8)	5.935	0.02	0.09	0.67
	8.32% (1.03)	8.5% (1.0)	1.043	0.31	0.02	0.17

Total and regional brain volumes (ml). Univariate GLM for raw volume or ratio correction for total intracranial volume. Values are group means (SD); * $P < 0.05$, ** $P < 0.001$. Mean raw volume in ml (SD). ^o% of intracranial volume (SD). [†]Natural log transformation to obtain normal distribution.

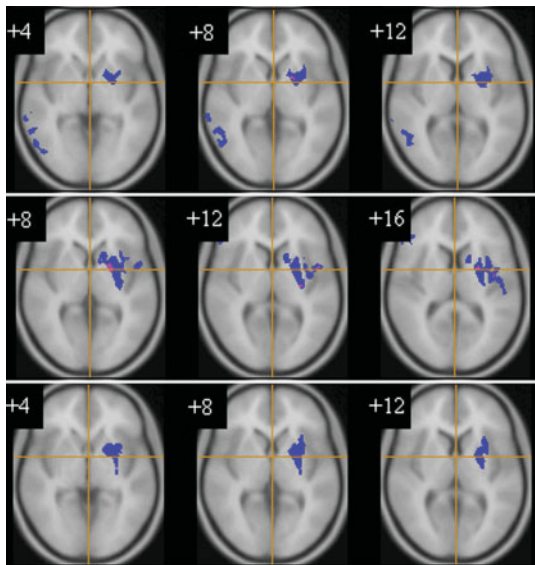


Fig. 5 Positive regional correlations between behavioural measures and regional grey matter volume in 22qDS children corrected for chronological age and gender. The order of the images is as follows: (i), top row—schizotypy (cluster threshold = 0.01, $P = 0.001$, cluster size = 1356); (ii) middle row—emotional symptoms (cluster threshold = 0.01, $P = 0.001$, cluster size = 644); (iii). Base row—peer problems (cluster threshold = 0.01, $P = 0.001$, cluster size = 2069). See Fig. 1 legend for explanation.

Qualitative analysis of our data confirm prior reports (Kates *et al.*, 2001; Shashi *et al.*, 2004) of an increased number of peripheral (but not total, deep or periventricular) WMHs and a high prevalence of midline brain anomalies, such as cavum septum pellucidum et vergae in people with 22qDS. The cavum septum pellucidum is a fluid-filled cavity located between the membranes of the septi pellucidi (the cavum vergae is a cavity within the septum pellucidum), which can be visualized sonographically in normal foetuses between 18 and 37 weeks gestation and in ~50% of term infants. The presence of a cavum septum pellucidum et vergae is a relatively common finding in other genetic and neurodevelopmental disorders such as Apert syndrome, holoprosencephaly and schizophrenia, and may reflect non-specific neurodevelopmental abnormalities in midline structures of the brain (Kasai *et al.*, 2004; Yacubian-Fernandes *et al.*, 2004).

Our VBM and ROI analysis found that the 22qDS group had significant cortical and subcortical grey matter changes compared with controls. The 22qDS group had significantly smaller volume of total, particularly left hemisphere brain volume, and the occipitoparietal lobes and an enlarged right caudate nucleus. This increase was not due to neuroleptic medication (no subject was on medication) known to alter the volume of basal ganglia structures (Chakos *et al.*, 1994). The finding of enlarged lateral ventricles in the 22qDS

group compared with sibling controls is consistent with earlier quantitative findings (Chow *et al.*, 1999).

VBM identified reductions of posterior grey matter and bilateral increased grey matter volume in insular, temporal and striatal regions. When FSIQ was corrected for, grey matter reductions in the cerebellum and medial temporo-occipital lobe and posterior cingulate cortex remained. These findings confirm earlier suggestions that non-frontal cortical involvement and more significantly cerebellar grey matter reductions may be a core feature of 22qDS (Eliez *et al.*, 2000; Kates *et al.*, 2001; van Amelsvoort *et al.*, 2001).

We also identified extensive white matter anomalies in people with 22qDS, located in regions likely to involve (i) the major longitudinal projection fibres, either ascending fibres from subcortical structures (e.g. lateral geniculate nuclei, thalamus) and projecting to the occipitoparietal cortex or descending fibres from the parietal and frontal cortex and projecting to subcortical structures through the internal capsule; and (ii) association tracts of the posterior regions of the cerebral hemispheres. These findings remained significant after correction for FSIQ. Thus, our data support the hypothesis that people with 22qDS have abnormalities in white matter connectivity (Barnea-Goraly *et al.*, 2003; Simon *et al.*, 2005). Such changes could be attributed to reduced axonal density and/or myelination of these long tracts as suggested by diffusion tensor imaging studies of brain development in normal children (Huppi *et al.*, 1998; Neil *et al.*, 2002) and subjects with 22qDS (Barnea-Goraly *et al.*, 2003; Simon *et al.*, 2005). In subjects with 22qDS, reduced fractional anisotropy, an index of microstructural ordering of fibres, could be attributed to maldevelopment (delayed or arrested) of long white matter tracts (Barnea-Goraly *et al.*, 2003; Simon *et al.*, 2005). However, post-mortem studies will be needed to identify the exact neuropathological substrate of white matter anatomical differences in 22qDS.

Thus, a deletion at chromosome 22q11 affects brain anatomy and is associated with a complex range of regional increases and decreases of grey matter volume and white matter loss. This may reflect the interaction of genetic and environmental effects on programmed cell death, which may lead to too few or too many neurons, depending on the area-insult-time interaction (see below).

We also found that children and adolescents with 22qDS have a higher prevalence of schizotypal traits, emotional symptoms, hyperactivity/inattention and social behavioural difficulties. It is possible that the differences in grey and white matter (alone or combination) we found may be related to the behavioural phenotype in 22qDS. In support of this, we found anatomical differences in brain regions implicated in schizophrenia, including the cerebral ventricles, the hippocampus, the temporal lobes and the striatum, and a significant positive relationship between schizotypal traits and grey matter volume of the right temporo-occipital lobe and the left corpus striatum. It has been suggested that larger volumes of the caudate nucleus and lenticular nuclei are associated with earlier onset of schizophrenia (Jeste *et al.*, 1998). In future

longitudinal studies, it would be interesting to investigate if the presence of decreased hippocampal volume combined with increased volume of the cerebral ventricles and basal ganglia in some individuals with 22qDS may be indicative of future development of psychosis. Also, social behavioural problems (expressed as high scores on peer problems) were related to increased grey matter in frontostriatal regions. We have previously reported that people with autism have abnormalities in the development of these brain regions, and these were related to social behaviour problems within people with autism (McAlonan *et al.*, 2002; Murphy *et al.*, 2002). Thus, we do not suggest that the relationship between abnormalities in regional brain development (programmed cell death) and behaviour is unique to 22qDS; rather we suggest that people with 22qDS have neurodevelopmental abnormalities in brain regions known to influence social behaviour within the general population and in other people with abnormal brain development. Finally, emotional symptoms that may be indicative of affective disorders were also related to increases of frontostriatal grey matter brain regions known to be implicated in affective disorders such as bipolar disorder and depression (Sheline, 2000; Kanner, 2004).

Our study was limited by the cross-sectional design, the lack of an FSIQ-matched control group, and the multiple comparisons we carried out (and hence our increased risk for type 1 error). However, we did control for socio-economic and family factors that are likely to impact on brain development because we used sibling controls. Also, we deliberately did not include a learning disabled control group as our research question was how people with 22qDS differ from the normal population. Further, it would be practically impossible to recruit a 'perfect' control group of non-22qDS sibling controls with the same degree of learning disability as the 22qDS probands. In addition, we explored the effect of FSIQ on brain anatomy statistically in the study, although controlling for a defining variable such as FSIQ between two groups that are partially defined by IQ differences potentially increases the risk of a type 2 error. Furthermore, in the computerized voxel-by-voxel analysis of regional differences, the level of significance was adapted in order to yield less than one false-positive cluster. Therefore, we feel type 1 errors are unlikely to fully explain our results. A further limitation of this study is the absence of normative data for the schizotypy scale and, consequently, the high prevalence of schizotypy reported in this study awaits replication by other groups.

In summary, we found that people with 22qDS have significant differences in the anatomy of brain regions, and systems, which are implicated in neuropsychiatric disorders such as schizophrenia, ADHD, and autism. In this study, we did not relate brain anatomy to cognitive function (that is the focus of ongoing work). However, the brain regions we report as abnormal in 22qDS (e.g. frontostriatal systems) are crucial to attention and executive functions—cognitive domains known to be impaired in 22qDS (Swillen *et al.*, 1999b; Woodin *et al.*, 2001; Henry *et al.*, 2002; Sobin *et al.*, 2004).

Hence, it is likely that the increased prevalence of some neuropsychiatric disorders (and perhaps some specific cognitive deficits) in people with 22qDS may partially be explained by neurodevelopmental differences in these brain regions (Papolos *et al.*, 1996; Bassett *et al.*, 1998; Murphy *et al.*, 1999; Gothelf *et al.*, 2004a).

The biological basis of the neurodevelopmental differences we found is unknown, but most likely reflects a complex interaction between a direct effect of genetic variation on brain development and indirect effects through other neurochemical factors. For example, the deleted region in 22qDS contains many neurodevelopmental genes as well as the gene for catechol-*O*-methyltransferase (COMT), which regulates dopamine metabolism. We do not know if our findings are due to a direct effect of the COMT gene on brain development or if they are secondary to an effect on dopamine. For example, it has been reported that COMT regulates prefrontal dopamine flux (Chen *et al.*, 2004), and results from animal and human studies suggest that dopamine has a trophic action during early brain maturation and later influences prefrontal cortical specification (Nieoullon, 2002). Individuals with 22qDS have significant differences in the anatomy of dopamine-rich brain regions and these may combine with genetically determined differences in COMT activity and hence dopaminergic function. This may lead to an increased risk for neuropsychiatric disorders such as schizophrenia. However, the brain-behaviour relationship is bi-directional and developmentally dynamic (Johnson *et al.*, 2002) and the large heterogeneity within the syndrome may account for some of the differences reported. Hence, there is a need for future longitudinal imaging studies of brain function, neurochemistry and white matter tract integrity in 22qDS. These issues were not addressed in this study but are the focus of ongoing work.

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