Abnormalities of the corpus callosum in nonpsychotic children with chromosome 22q11 deletion syndrome

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Abstract:

Chromosome 22q11 deletion syndrome (22q11DS) is associated with elevated rates of schizophrenia and other psychoses in adulthood. Childhood morphologic brain abnormalities are frequently reported, but the significance of these and their relationship to the development of schizophrenia are unclear. We sought to delineate midline neuroanatomical abnormalities in nonpsychotic children with 22q11DS and their age- and sex-matched controls and compare these to those reported in individuals with schizophrenia. On qualitative analysis, we found a high incidence of midline developmental abnormalities (cavum septum pellucidum, or CSP). On quantitative analysis, the total corpus callosum (CC) area was significantly increased in the patient group and among the subregions, the patients had a significantly larger isthmus. These findings of an increased area of the corpus callosum, specifically the isthmus, have not been reported before in individuals with 22q11DS. We also found a relative lack of the age-related increase in the size of the corpus callosum in the children with 22q11DS. There were no differences in cerebellar vermis measurements between the patient and control groups. Our findings are indicative of frequent midline brain anomalies, including dysgenesis of the corpus callosum, in nonpsychotic children with 22q11DS. Although the increased size of the corpus callosum in our 22q11DS patients is in direct contrast to the decrease seen in schizophrenia, the high frequency of structural midline abnormalities in these nonpsychotic children with 22q11DS is similar to that seen in schizophrenia. Further longitudinal studies on these children will help determine which of these structural abnormalities is/are pertinent to the development of psychosis.

Article:

Introduction

Chromosome 22q11 deletion syndrome (22q11DS) is a common genetic condition, with a prevalence of 1/2000 to 1/4000 [Shprintzen, 2000], [Tezenas du Montcel et al., 1996] and [Wilson et al., 1994]. Also known as DiGeorge or velocardiofacial syndrome, the deletion causes variable manifestations, mainly consisting of developmental delays and learning disabilities (80–100%), mental retardation (50%), congenital heart disease (70%) and palatal problems (70%) [Gerdes et al., 2001], [Moss et al., 1999], [Shprintzen et al., 1981] and [Swillen et al., 1997]. The diagnosis is made by chromosome analysis and fluorescence in situ hybridization (FISH), demonstrating the deletion at band q11.2 on chromosome 22. Most deletions occur sporadically—in 10–15% of patients, an affected parent is found on FISH analysis.

Recent retrospective studies have reported that children with 22q11DS have a markedly heightened risk (approximately 40%) of developing schizophrenia and mood psychoses in adulthood [Murphy et al., 1999], [Papolos et al., 1996], [Pulver et al., 1994] and [Shprintzen et al., 1992]. These preliminary findings provide the strongest known link between psychosis and an identified genetic abnormality. Conversely, about 1–6% of individuals with schizophrenia have been found to have a deletion of 22q11.2 [Karayiogou et al., 1995], [Murphy et al., 1998] and [Yan et al., 1998]. Thus, 22q11DS represents a specific genetic subtype of schizophrenia, but the pathophysiology remains poorly understood.

In the last decade, qualitative MRI studies in children and adults with 22q11DS have shown structural brain abnormalities. In children, a small cerebellar vermis, white matter hyperdensities, cysts adjacent to the anterior horns, cerebellar and midline anomalies, and enlarged Sylvian fissures have been reported [Bingham et al., 1997], [Lynch et al., 1995], [Mitnick et al., 1994], [Papolos et al., 1996] and [Vataja and Elomaa, 1998].

With the application of quantitative (morphometric) MRI analyses, additional structural brain abnormalities have been described in nonpsychotic children with 22q11DS. These include reduced total brain volume, increased mid-corpus callosum area, white matter reductions in nonfrontal areas, gray matter reduction in the parietal lobe, relatively large frontal lobes, decreased right cerebellar tissue volume, small temporal lobe, superior temporal gyrus and hippocampus and increased basal ganglia volume [Eliez et al., 2000], [Eliez et al., 2001], [Eliez et al., 2002], [Kates et al., 2001] and [Usiskin et al., 1999].

In adults with 22q11DS who had developed schizophrenia, midline developmental abnormalities (45%), white matter hyperdensities (90%) and cerebellar atrophy (36%) were seen on a qualitative MRI analysis (Chow et al., 1999). On quantitative MRI studies, septum pellucidum abnormalities (40%), smaller cerebellum, gray matter deficits and large ventricles were reported [Chow et al., 2002] and [van Amelswoort et al., 2001]. Frontal lobe size was reduced in the second study, similar to the findings in schizophrenia in the general population (Lawrie and Abukmeil, 1998), but in contradiction to the studies in young nonpsychotic children with 22q11DS discussed above. Thus, while several abnormalities have been described in nonpsychotic and psychotic individuals with 22q11DS, there are differences from one study to another and the relationship between these and the development of schizophrenia is unclear.

The CC is a key midline white matter structure that carries fibers that connect cortical areas in a topographical manner. Changes in the CC provide a way of examining anatomical abnormalities in the corresponding cortical areas. Studies of the CC in schizophrenia have provided insights into various underlying neurodevelopmental abnormalities (reviewed by [Keshavan et al., 2002] and [Shenton et al., 2001]).

We performed a cross-sectional study in nonpsychotic preadolescent and adolescent children with 22q11DS to characterize neuroanatomical abnormalities by qualitative and quantitative methods, and to compare and contrast these changes to those found in individuals with schizophrenia. We hypothesized that we would see a high frequency of midline structural developmental abnormalities such as cavum septum pellucidum and decreased size of the corpus callosum (CC) based on the reports of decreased intracranial volume in 22q11DS children and the frequent reports of decreased CC area in individuals with schizophrenia. Based on previous reports of relatively large frontal lobes in children with 22q11DS, we expected to find differences in size between the subregions of the CC. We also expected to see cerebellar hypoplasia, a common feature in 22q11DS and in schizophrenia.

Materials and methods

Subjects

Thirteen children with 22q11DS between the ages of 7 and 18 years were recruited into the study. All had had confirmation of the diagnosis by FISH analysis. Thirteen control subjects were matched by age (within 9 months) and gender to the patients. The patients were recruited from the Medical Genetics Clinic at Wake Forest University School of Medicine (WFUSM) and

the control subjects from Pediatric Clinics at WFUSM and from private practices outside the medical school. A three-generation pedigree was obtained by an experienced board-certified genetic counselor (MNB). The family history was assessed for the presence of mental illness, learning disabilities and other problems that may indicate other individuals affected with either 22q11DS, or another developmental or genetic disorder. Control subjects who had either a family or personal history of a psychotic illness, or a history of mental retardation/developmental delay were excluded from the study. For children with 22q11DS, the occurrence of psychosis in other family members who are affected by 22q11DS was not considered as an exclusion criterion. However, the occurrence of psychosis in family members who did not have 22q11DS would result in exclusion from the study. A history of multiple congenital anomalies was also used as an exclusion criterion since those could be indicative of an underlying genetic disorder.

Medical evaluation

The medical information on patients and control subjects was carefully reviewed for medical and psychological problems. A detailed structured history, including prenatal and perinatal events that may have had a bearing on development, was obtained. None of the patients or control subjects had a psychotic illness at the time of the study. Control and patient subjects received a targeted examination to detect subtle dysmorphic features.

One control subject and three patients were on stimulant medications for ADHD. Two other patients were on Valproate for a seizure disorder.

MRI studies

Imaging studies were performed at Wake Forest University School of Medicine, with a General Electric (GE) 1.5-T Signa System running 8.4 M4 software. A set of sagittal scout images (2D fast spin echo, TR = 2500 ms, echo time (TE) = 88 ms, FOV = 240 mm, approximately 10 slices, slice thickness = 5 mm, slice gap = 1.5 mm, NEX = 1, matrix = 256×128, scan time = 50 s) was collected to verify patient position, cooperation and image quality. The midsagittal slice was required to show full visualization of the cerebral aqueduct. A set of proton density and T2-weighted axial images was then collected covering the whole brain (2D fast spin echo, TR = 3000 ms, TE = 36 and 96 ms, echo train length (ETL) = 8, FOV = 26×26, approximately 110 slices, slice thickness = 3 mm, slice gap = 0 mm, NEX = 1, matrix = 256×192). Three-dimensional spoiled gradient echo imaging was performed in the axial plane (spoiled gradient recalled, SPGR sequence, TR = 25 ms, TE = 5ms, nutation angle = 40°, FOV = 180 mm in the phase encoding direction and 240 mm in the read direction, slice thickness = 1.5 mm, NEX = 1,

matrix = 256 × 192, scan time = 10 min and 18 s) to obtain 124 images covering the entire brain. The MR images were examined qualitatively for clinical abnormalities by a pediatric neurologist (CCS).

Morphometric evaluation

Morphometric measurements were conducted by a single trained rater (SM) blinded to the study hypotheses, subject identification and clinical data, using software (NIH IMAGE; Version 1.62), which allows manual tracing with a cursor, stripping of noncerebral tissues and reliable segmentation of gray and white matter and CSF (Keshavan et al., 1995). There was no motion artifact on any of the scans measured. The midsagittal view was selected (best visualization of the CC, the septum pellucidum, the cerebellum and the aqueduct) and was confirmed in the orthogonal plane. The rater manually traced the outline of the CC. A line was drawn connecting the most anterior part of the genu to the most posterior part of the splenium (the A-P line). The CC was divided into the genu, the body, the isthmus and the splenium (Witelson, 1989). These areas of the CC were further divided to measure specific parts of the CC that we expected to find changes in our patient population (Fig. 1).
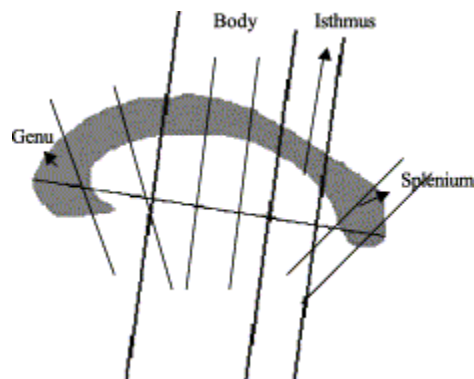

Fig. 1. Diagrammatic representation of the scheme used to divide the CC into its subregions.

The midpoint of the A-P line within the genu was connected to the midpoint of the line separating the genu from the body. This line was trisected by two perpendicular lines, thus dividing the genu into its anterior, middle and posterior parts. The splenium was divided by a line connecting the midpoint of the A-P line in the splenium to the midpoint of the line separating the isthmus and the splenium. Two perpendicular lines trisecting this line divided the splenium into anterior, middle and posterior regions (Fig. 1). Intracranial area was calculated by tracing along the inner table of the skull, along the basisphenoid and across the foramen magnum. The interrater reliabilities (interclass r) for these measurements were very high on 10 scans measured by two raters (SM and SS) (r = 0.97–0.99). Intrarater reliabilities (intraclass r),

based on the same rater (SM) measuring 10 scans twice about a month apart, were also high ($r > 0.96$).

Statistical analysis

Multiple analysis of covariance was used to test for differences in the parts of the CC (the genu, body, isthmus and splenium), using intracranial area as a covariate, using an α level at $P < 0.10$. On multiple analysis of covariance (MANOVA) with intracranial area as a covariate, an $F = 2.92$ and $P < 0.04$ were found. Where significant, individual analysis of covariance (ANOVA) was examined for the subregions of the CC. Correlations between age and the CC measurements were computed separately after partialling out the intracranial area. We also performed statistical analyses using head circumference as a covariate. Since some of our patients were on medications due to ADHD and seizures, we reran the analyses by using medication status as a covariate.

Results

Medical status

The patients with 22q11DS had many medical problems, such as congenital heart disease, palatal problems (velopharyngeal insufficiency with or without a submucous cleft) and less frequently hypoparathyroidism and immune deficiency. All had experienced developmental delays and learning difficulties in school. Of t he 13 patients, five had a parent affected by 22q11DS. One of the affected parents has been diagnosed with paranoid schizophrenia.

Of the control subjects, none had medical or developmental problems; two had attention deficit hyperactivity disorder (ADHD). Pertinent characteristics of the patient and control subjects are listed in Table 1.

Table 1.

	22q11DS patients ($n = 13$)	Control subjects ($n = 13$)
Age[a]	10.04 (4.05)	10.8 (4.2)
Sex (M/F)	8/5	8/5
CHD[b]	5/13	none

	22q11DS patients ($n = 13$)	Control subjects ($n = 13$)
Palate abnormal	12/13	none
ADHD/ODD	6/13	2/13

ADHD/ODD = attention deficit hyperactivity disorder, oppositional defiant disorder.

a The values for age indicate the mean (SD).

b Congenital heart disease.

Quantitative (morphometric) MRI analysis

The total area of the CC was significantly increased in patients with 22q11DS compared to control subjects (F = 10.52, P = 0.004) (Table 3 and Fig. 2). When the regions of the CC were separately analyzed, the area of the isthmus of the CC in patients with 22q11DS was larger in the children with 22q11DS compared to the controls (F = 4.68, P = 0.04). There was a trend for the genu to be larger as well in the patient group (F = 3.64, P = 0.07). Measurements of the other subdivisions of the CC and the cerebellar vermis were not significantly different between the two groups. Correlations between age and the CC area after partialling out the intracranial area showed an absence of a positive correlation between the age and the size of the CC in the patient group (β = 0.05, P = 0.93) compared to the control group (β = 0.93, P = 0.03) (Fig. 3). ANOVA carried out with diagnosis as the grouping variable and head circumference as a covariate revealed a significant diagnosis effect on total CC area (df = 1,23; F = 7.25; P = 0.01) and on isthmus size (df = 1,23; F = 4.66; P = 0.04). Thus, the group differences for total CC area remained significant, indicating that intracranial volume (head circumference is an indirect measure of intracranial volume) was not a confounding factor. Lastly, the MANOVA and ANOVA were rerun, comparing the 22q11DS and control subjects, using medication status as a covariate. The MANOVA and ANOVA for the total CC area remained significant (P < 0.01) and the ANOVA for the isthmus was marginally significant (P < 0.10).

Table 3. CC subregions (cm^2) in 22q deletion subjects vs. healthy controls

Area	22q11DS patients	Control subjects	*F*	*P*
Total CC	6.65 (1.69)	5.44 (1.22)	10.52	0.004
Genu	2.49 (1.03)	1.99 (0.53)	3.63	0.07

Area	22q11DS patients	Control subjects	F	P
Anterior body	0.86 (0.81)	0.55 (0.14)	1.74	0.20
Posterior body	0.60 (0.16)	0.53 (0.13)	2.14	0.16
Isthmus	0.62 (0.20)	0.49 (0.12)	4.68	0.04
Splenium	1.78 (0.63)	1.68 (0.41)	0.20	0.66
ICA	140.41 (26.41)	138.52 (22.86)	0.04	0.84

Values are means (SD).MANOVA with ICA as a covariate Rao $R(5,19) = 2.92$; $P < 0.04$. Individual ANOVAs with ICA as covariate ($df = 1,23$) are presented in the table.Values are mean (SD).Measurements expressed as cm^2.ICA = intracranial area.
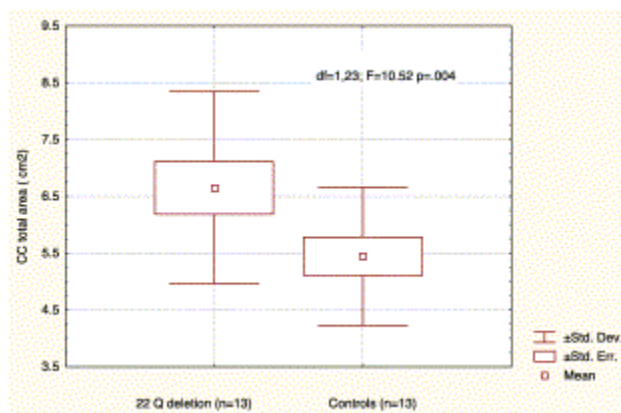

Fig. 2. Representation of the CC area in the 22q11DS patients compared to control subjects.

Age correlations with CC size in 22 q subjects vs healthy controls

Healthy controls
Beta=.91; p=.03;
Intracranial area partialled out

22q deletion subjects
Beta=.05; p=.93;
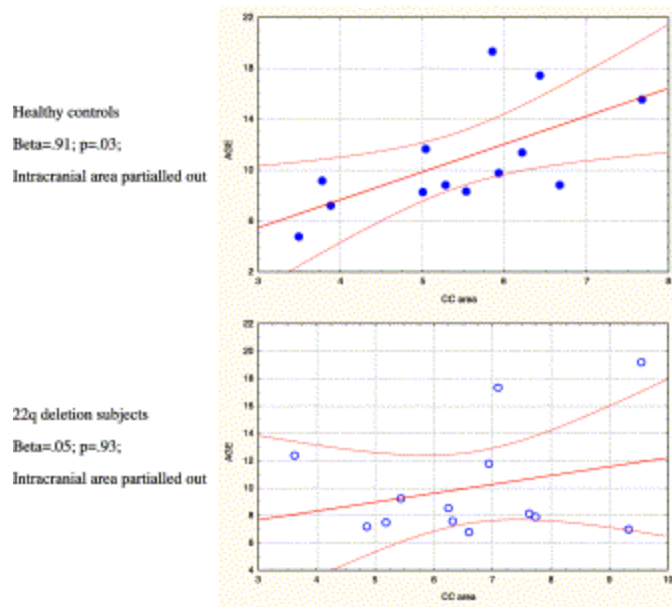Intracranial area partialled out

Fig. 3. Graphic representation of the correlation of the CC area and age, in the patients and control subjects, after partialling out the intracranial area.

Discussion

On qualitative analysis, structural brain abnormalities were common in our patients with 22q11DS compared to their age- and sex-matched control subjects. The most frequent abnormality was one of midline aberrancy (cavum septum pellucidum). A cavum septum pellucidum (CSP) is a common developmental abnormality, in which the leaflets of the septum pellucidum do not fuse in the midline, partially or completely (then known as cavum vergae) and is seen in about 1% of the general population [Nopoulos et al., 1997] and [Nopoulos et al., 1998]. A CSP has been reported to occur in up to 45% of individuals with schizophrenia (reviewed by Shenton et al., 2001). It has been reported with the same frequency in adults with 22q11DS who have schizophrenia (van Amelswoort et al., 2001). CSP has also been reported to occur with a higher frequency in early onset schizophrenia (Nopoulos et al., 1998) and is postulated to be related to early onset/severe illness in these cases, indicating brain dysgenesis, which is thought to be a major factor in the causation of schizophrenia. A CSP is thought to be reflective of developmental abnormalities of the structures bordering the septum pellucidum, such as the corpus callosum and the hippocampus (structures frequently reported to be abnormal in schizophrenia). The exact significance of the CSP in our patients is hard to determine in this cross-sectional study. To date, there are no longitudinal studies in children with 22q11DS that have examined the correlation between CSP and the occurrence of schizophrenia. However, since CSP is a marker of abnormal neurodevelopment (including the CC and the hippocampus), finding it frequently in a population at high risk for schizophrenia such as 22q11DS lends

credence to the neurodevelopmental hypothesis of schizophrenia. Our hypothesis of finding cerebellar abnormalities as part of the brain dysgenesis was not substantiated on quantitative analysis, although on qualitative analysis, we found two individuals with hypoplasia of the cerebellar vermis.

Our quantitative measurements of the CC and its regions children in with 22q11DS showed an increase in the total area of the CC and the isthmus compared to age- and sex-matched control subjects. These findings have never been reported before in nonpsychotic children with 22q11DS to the best of our knowledge. Increased size of the midbody of the CC has been described in children with 22q11DS who had schizophrenia, but in a small sample size of three patients (Usiskin et al., 1999). The finding of an increased area of the CC in our study sample is intriguing, since typically, abnormalities of the CC seen in other genetic conditions (e.g. Williams syndrome, Fragile X syndrome) as well as in nonspecific mental retardation consist of atrophy or hypoplasia/agenesis of the CC and not hypertrophy [Brunberg et al., 2002], [Schmitt et al., 2001], [Soto-Ares et al., 2003] and [Tomiaulo et al., 2002]. Since cognitive abnormalities are seen in these genetic conditions as well as 22q11DS, it seems likely that the unique finding of a larger CC in patients with 22q11DS is more likely to be related pathogenetically to psychosis which is also a distinctive feature of this condition.

We also compared the CC findings in our study with CC changes reported in other common childhood conditions—attention deficit hyperactivity disorder (ADHD), Tourette syndrome and obsessive compulsive disorder (OCD). Several studies have documented a smaller total area of the CC and variably smaller subregions of the CC in children with ADHD [Bumgardner et al., 1996], [Giedd et al., 1994], [Hill et al., 2003], [Hynd et al., 1991], [Lyoo et al., 1996], [Paule et al., 2000] and [Semrud-Clikeman et al., 1994]. In Tourette syndrome, studies have not been consistent—both an increase in CC area [Bumgardner et al., 1996] and [Moraiarty et al., 1997] and decreased CC area have been reported (Peterson et al., 1994). In the few quantitative brain MRI studies done on OCD in children, the findings range from hypoplasia of the CC (Farchione et al., 2002), no significant findings [Jenike et al., 1996] and [Kellner et al., 1991] to an increase in total CC area and subregions except the isthmus (Rosenberg et al., 1997). Our findings of an increased area of the CC is in direct contrast to that described in ADHD and thus cannot be ascribed to the occurrence of ADHD in our patients. In addition, analyses performed using medication status as a covariate showed that medication status (for ADHD and seizures) did not account for the differences between the 22q11DS and control groups. None of our patients had Tourette syndrome or OCD that could have been a confounding factor.

The CC connects the two cerebral hemispheres and continues to develop throughout childhood into adulthood, unlike other areas of the brain (Pujol et al., 1993). The subregions (genu, body, isthmus and the splenium) carry interhemispheric fibers from the heteromodal and unimodal regions of the cortex. Thus, changes within specific areas of the CC may indicate underlying abnormalities of the corresponding cortical areas. The increased size of the isthmus, which carries fibers that have heteromodal functions from the inferior parietal cortex, may be reflective of increased axonal size/number of the fibers originating from this area. Interestingly, the parietal cortex has been thought to be related to the visual–spatial and phonological processing deficits in children with 22q11DS [Kates et al., 2000] and [Kates et al., 2001]. However, the findings in that quantitative study of MRI in children with 22q11DS showed white matter reductions in the parietal areas, in contrast to the study by Eliez et al. (2000) which showed reductions in the gray matter of the parietal lobe. Both of these studies did not have data on the measurement of the CC. We suggest that the increased size of the isthmus of the CC may be due to increased size or number of axons from the inferior parietal cortex. There was a trend for increased size of the genu in our patient group. Since the genu connects the frontal cortices, this may suggest an increased size or number of axons from this area. Corroborating this is the finding of relatively large frontal lobes in two previous quantitative MRI studies [Eliez et al., 2000] and [Kates et al., 2001].

The finding of a dampening of the age-related increase in the size of the CC in our patient group compared to our control group has not been reported before in 22q11DS. Normally, the area of the subregions of the CC increases with age during childhood and early adulthood up to the early 20s, except for the isthmus (Keshavan et al., 2002). This increase in size is thought to be related to an increase in axonal size or due to continued myelination, long after other areas of the brain have matured. Myelinated axons propagate neural signals in a fast manner that is critical for normal cognition and motor development. Our finding of a lack of this age-related increase in the CC size in 22q11DS children may be due to the lack of increased myelination that would normally be expected to occur through childhood. Interestingly, this finding is similar to the CC changes in children with OCD (Rosenberg et al., 1997). However, none of our patients had OCD at the time of MRI imaging and thus it is unlikely that this change is due to concurrent OCD. Rather, it may be indicative of underlying abnormal neurodevelopment in both children with 22q1DS and those with OCD.

Although our findings of an increased size of the CC in 22q11DS children and lack of the age-expected increase in the size of the CC in the same patient group may seem contradictory, they can be explained by the hypothesis that an initial increased size of the CC (due to either increased size or number of axons) is followed by an age-related relative failure of myelination of these axons, resulting in the absence of an age-related increase in the size of the CC.

We compared our CC findings to those seen in schizophrenia in the general population and schizophrenia associated with 22q11DS. CC abnormalities are well described in individuals with schizophrenia ([Keller et al., 2003] and [Keshavan et al., 2002]; reviewed by [Shenton et al., 2001] and [Woodruff et al., 1995]) with most studies reporting a decrease in the size of the CC, specifically the anterior genu, anterior body, isthmus and anterior splenium, consistent with the reductions of the structures that are connected by these regions of the CC—the prefrontal, temporal and inferior parietal cortices (Schlaepfer et al., 1994). There is a paucity of quantitative data on CC structure in 22q11DS individuals who have already developed psychosis, with the two studies published thus far lacking precise measurements of the CC and its subregions [Chow et al., 2002] and [van Amelswoort et al., 2001]. Our finding of a lack of the expected positive correlation between age and CC area is similar to that reported in adolescents and young adult individuals with schizophrenia not associated with 22q11DS (Keshavan et al., 2002). This finding was indicative of a neurodevelopmental abnormality in these patients that persists into adulthood. Our similar findings provide further evidence of abnormal neurodevelopment in individuals at high risk of schizophrenia.

The strengths of our study are that: (A) we used a group of nonpsychotic children at high risk for schizophrenia-like psychotic disorders and thus the data obtained are indicative of abnormal neurodevelopment preceding the onset of illness; (B) this is the only report that we are aware of that has evaluated the CC and its subregions by morphometric analysis, in children with 22q11DS; (C) we also have qualitative MRI data that corroborate the abnormal midline development. The weaknesses are that our sample size is small and the data may be not be significant if IQ differences between the patient and control groups were corrected for. However, it is to be noted since low IQ is common in 22q11DS, controlling for IQ may remove the precise findings that are of interest and other investigators have stressed this point (Chow et al., 2002). We also did not measure regions of the brain that have been the focus of other studies, such as gray and white matter volumes and the frontal, temporal and parietal lobes. However, our CC findings provide indirect evidence of abnormalities in the inferior parietal cortex and abnormal CC maturation with age in children with 22q11DS. The high frequency of CSP suggests underlying abnormal neurodevelopment of the hippocampus and the CC. Future studies that would specifically measure these areas of the brain should provide further information.

In conclusion, our study demonstrated differences in midline development and CC morphology in nonpsychotic children with 22q11DS relative to normal controls. The finding of a larger size of the CC is a unique finding in this study. Further imaging studies in a longitudinal fashion in

these children will help clarify the relationship of these structural abnormalities and the occurrence of schizophrenia.

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