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General absence of abnormal cortical asymmetry in childhood-onset schizophrenia: A longitudinal study

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ABSTRACT

Background: Childhood-onset schizophrenia (COS) is a rare, severe form of the adult-onset illness, with more salient neurobiological causes. Previous cross-sectional structural neuroimaging research has suggested that normal cortical asymmetry patterns [$(R-L)/(R+L)$] may be altered in adult schizophrenia, although these findings were not well replicated. Recent studies show dynamic changes in brain asymmetry during childhood and adolescence. We hypothesized that COS patients would show a lack of normal development of asymmetry and decreased overall asymmetry.

Methods: Prospective structural magnetic resonance scans were obtained at baseline and at two-year follow-up visits in 49 right-handed COS patients (mean baseline age: 14.72 ± 2.63, 117 scans) and 50 age and sex-matched, right-handed healthy controls (mean baseline age: 15.15 ± 3.37, 125 scans). Cortical thickness was calculated at 40,962 homologous points across each cerebral hemisphere using a fully automated, validated method. Differences in developmental asymmetry patterns across the cortical surface were analyzed using a linear mixed effects regression model.

Results: No significant asymmetry differences were found either for cross-sectional comparisons of COS and healthy controls across the lateral and medial cortical surfaces or with respect to timing of developmental changes in asymmetry.

Conclusions: The present findings do not support asymmetry differences for this severe, early form of schizophrenia.

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1. Introduction

Childhood-onset schizophrenia (COS) is a rare, debilitating form of the illness characterized by onset of psychotic symptoms prior to the thirteenth birthday and premorbid I.Q. of at least 70 (American Psychiatric Association, 2000). Current research suggests COS as neurobiologically continuous with adult-onset schizophrenia (AOS), with a more severe clinical presentation and generally poor prognosis. The cause of schizophrenia is unknown, but research increasingly supports a neurodevelopmental model with a strong genetic predisposition (Rapoport et al., 2005).

Deviance from normal cortical asymmetry has been implicated in the pathogenesis of schizophrenia (Crow 1990; Bilder et al., 1994). Cortical asymmetry is a defining feature of the healthy human brain. Lateralized specialization of the two hemispheres has evolved over time with implications for a multitude of sensorimotor functions. A typical developmental course of structural asymmetries in the human brain has been associated with normal motor and cognitive lateralization (Toga and Thompson 2003).

Normal asymmetry is widely defined by *petalias*, which describe right frontal and left occipital hemispheric protrusions (Kertesz et al., 1990; Chance et al., 2005). This pattern (also known as cerebral "torque," indicative of a counter-clockwise

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rotational force) has been believed to be related to the structure and development of language (Crow 1998; Angrilli et al., 2009), with the role of left hemisphere dominance in human language processing (Angrilli et al., 2009). Established findings include greater degrees of asymmetry in right-handed compared to non-right handed individuals (defined as both left handed and ambidextrous individuals). More specifically, the typically leftward asymmetry of the planum temporale is reduced or even reversed in left-handed individuals (Narr et al., 2007). Other reported normal asymmetry findings include leftward lateralization in the minicolumn structure of the planum temporale (Buxhoeveden et al., 2001), a longer, more horizontally placed left Sylvian fissure (Galaburda et al., 1978), and leftward lateralization of the pars triangularis (PTR) and pars opercularis (POP), implicated in speech-language production (Foundas et al., 1998).

Crow et al. theorized that abnormal hemispheric lateralization patterns are keys to the pathogenesis of schizophrenia (Crow et al., 1989; Crow 1990; Crow 1997). Specifically, previous findings in schizophrenia patients included increased left ventricular enlargement (Crow 1990; James et al., 1999), reduced left temporal lobe surface area (Johnstone et al., 1989; Rossi et al., 1990), reduced GM in the left superior temporal gyrus (Barta et al., 1990; Shenton et al., 1992), reduced left greater than right (L>R) asymmetry in the occipito-parietal region, and reduced R>L asymmetry in the premotor and prefrontal regions (Bilder et al., 1994; DeLisi et al., 1994).

However, there are numerous studies that do not support abnormal asymmetry as a characteristic of schizophrenia, finding normal L>R Sylvian fissure length (Bartley et al., 1993) and normal temporal lobe asymmetries in AOS (Frangou et al., 1997; Crespo-Facorro et al., 2004). Levitt et al. conducted a small volumetric MRI study of COS patients ($n=13$, mean age: 14.2 ± 3.8) and found no departure from normal temporal lobe asymmetry patterns (Levitt et al., 2001).

As part of a large prospective COS study, the abnormal cortical asymmetry issue was revisited. COS is a rare, severe phenotype with early neurodevelopmental delays, salient genetic influences (Addington and Rapoport 2009), and more prominent neurobiological features when compared to AOS (Rapoport et al., 2009). Thus, we hypothesized that COS patients might be more sensitive to potential departures from normal asymmetry development.

A recent longitudinal study in our group included developmental cortical asymmetry analysis in healthy children and adolescents (Shaw et al., 2009). Our healthy subjects manifested L>R cortical thickness in the orbitofrontal/inferior frontal gyrus progressing into a R>L pattern during adolescence, indicative of a relative right hemispheric gain. The reverse was found in the medial occipital and angular gyri where children showed a relative gain in left hemispheric thickness during adolescence. These findings indicate that normal adult patterns of cortical asymmetry emerge in childhood and develop progressively through adolescence. While cortical thickness is not a direct measure of torque, the distinct increases in right frontal and left occipital thickness are suggestive of potential torque development. In the present study, we compared COS and control subjects during childhood through young adulthood. We hypothesized that our COS cohort might manifest abnormal asymmetry at baseline or progressively during development.

2. Methods

2.1. Participants

Patients were recruited as part of an ongoing COS study at the National Institute of Mental Health (NIMH) in Bethesda, MD. The sample has been described at length elsewhere (Rapoport et al., 2009). All right-handed subjects with at least one MRI scan were selected ($n=49$, baseline age: 14.72 ± 2.63). Handedness was assessed using the Physical and Neurological Examination for Soft Signs (PANESS) where subjects indicate use of the right or left hand for twelve commonplace activities (Denckla 1985). Controls were part of a larger study ($n=358$) of normal brain development (Giedd et al., 1999; Shaw et al., 2006; Shaw et al., 2009). The current sample includes 50 of these right-handed, typically developing children (baseline age: 15.15 ± 3.37) who were individually matched with the COS patients for age, sex, and scan dates. Exclusionary criteria included history of neurological illness, psychiatric illness, or learning disabilities.

2.2. MRI acquisition and analysis

All scans were conducted with the same General Electric 1.5 T Signa MRI scanner (Milwaukee, WI). Head placement was standardized according to previously described protocols (Giedd et al., 1996). Three-dimensional ($256\times256\times124$ resolution), T1-weighted fast spoiled gradient (SPGR) echo MRI volumes were obtained longitudinally with contiguous 1.5-mm axial slides and 2.0-mm coronal slices. These resolution parameters, while no longer maximally precise, have been maintained since the beginning of the study for consistency. Imaging parameters were echo time: 5 ms, repetition time: 24 ms, flip angle: 45°, acquisition matrix: 256×192, and 24-cm field of view.

Image processing was conducted with a fully automated cortical surface extraction pipeline (Shaw et al., 2009). Raw scans were masked using the Brain Extraction Tool method (Smith 2002). Scans were registered into standardized stereotaxic space (MNI-ICBM152 non-linear sixth generation symmetric target) using a nine-parameter linear transformation. Following registration and correction for non-uniformity artifacts, volumes were divided into white matter (WM), gray matter (GM), cerebrospinal fluid, and background with an advanced neural net classifier (Zijdenbos et al., 2002; Tohka et al., 2004). The WM and GM interfaces were determined by generation of surface meshes using the Constrained Laplacian Anatomic Segmentation Using Proximities (CLASP) surface extraction procedure (Kim et al., 2005). The root mean square thickness between corresponding nodes was calculated in native space on the surface meshes to give a measurement of cortical thickness. Thickness measurements were aligned using surface registration to maximize thickness value corresponding in terms of gyral patterning between subjects. A 30-mm surface-blurring kernel, which minimizes false positives while optimizing statistical power (Lerch and Evans 2005), was implemented for noise reduction in thickness measurements. Results were projected onto a symmetrical left hemispheric template where positive values indicated L>R asymmetry at a given point and negative values represented R>L asymmetry.

2.3. Asymmetry index

Asymmetry was assessed by calculating the cortical thickness difference between 40,962 homologous points across each hemisphere with the asymmetry index:

$$(\text{left}-\text{right})/[0.5 * (\text{left} + \text{right})]$$

2.4. Statistical analysis

For demographic data, statistical assumptions were checked using the Levene and Shapiro-Wilk tests as well as visual inspection of raw data and normal q–q plots. When assumptions were violated, results from Welch's t-test and/or the Mann-Whitney U-test were comparable in meaning to the Student's t-test; thus, we report results from the Student's t-test.

Differences in developmental asymmetry between COS and controls across the cortical surface were analyzed using a linear mixed effects regression model at 40,962 cortical points. At each point, the dependent variable was the asymmetry index; fixed effects included the intercept (the control group's estimated average cortical thickness at the sample average age), group (difference between the COS and control groups' estimated average cortical thickness at the sample average age), age (cortical thickness development over time for controls, centered at the sample average age), and group * age (difference in asymmetry development between COS and control groups). We also included a random intercept per person to account for within-subject dependence. Type I error was controlled using the False Discovery Rate (FDR) procedure (Benjamini 1995). Although the samples were matched for sex and age, we ran the model with and without sex as a covariate.

Table 1
Sample demographics for COS patients and healthy controls.

	COS patients ($n=49$; 117 scans)	Healthy controls ($n=50$; 125 scans)	Test statistic	p-value
Males/Females	26/23	26/24		
IQ, mean ± SD	73.10 ± 20.30	113.37 ± 11.20	$t_{88} = -12.19$	<0.0001
SES, mean ± SD	61.81 ± 29.85	41.88 ± 20.28	$t_{97} = 3.85$	<0.01
Ethnicity				
Caucasian	22	38		
African American	17	6		
Asian	3	2		
Hispanic	4	1		
Other	3	3		
Age at scan, [range]	[9.12–31.51]	[10.36–32.38]		
Time 1	14.72 ± 2.63	15.15 ± 3.37	$t_{97} = -0.71$	0.48
Time 2	17.34 ± 2.93	17.49 ± 2.66	$t_{67} = -0.23$	0.82
Time 3	18.88 ± 3.14	20.58 ± 3.15	$t_{41} = -1.77$	0.08
Time 4	21.87 ± 3.10	22.42 ± 2.41	$t_{15} = -0.41$	0.69
Time 5	23.45 ± 3.78	24.14 ± 2.14	$t_{8} = -0.36$	0.73
Time 6	29.69 ± 2.58	28.10 ± 3.20	$t_{2} = 0.56$	0.63
No. of scans at				
Time 1	49	50		
Time 2	33	36		
Time 3	20	23		
Time 4	8	9		
Time 5	5	5		
Time 6	2	2		

COS: childhood-onset schizophrenia.
SES: socio-economic status.

3. Results

Demographic data are shown in Table 1. As expected for the healthy controls ($n=50$), current findings are consistent with previously published data from our group which also includes a depiction of longitudinal cortical thickness progression in our typically developing population (Shaw et al., 2009). With age, left cortical thickness increased relative to right in the superior frontal, superior temporal, and temporo-occipital regions. Also, over time the R>L difference became more extensive in lateral and inferior frontal regions. At the average age (which refers to the process of centering the age distribution around the mean age of subjects in the sample), cortical thickness manifested a R>L pattern in the anterior lateral, inferior frontal, and middle temporal regions; a L>R pattern was found in the parietal lobe and in a smaller region in the middle frontal cortex.

The cortical asymmetry trajectory (as measured with L–R cortical thickness) demonstrated a significant increase in right hemispheric thickness in the lateral orbitofrontal cortex. Over time, this R>L difference became more extensive in lateral and inferior frontal regions meaning that initially in childhood, these regions started out thicker in the left hemisphere relative to the right. However, throughout development this trend reversed and cortical thickness became greater in the right hemisphere relative to the left, consistent with normal adult asymmetry patterns. Similarly, from childhood to late adolescence, R>L asymmetry of the middle occipital and angular gyri reversed to a L>R pattern, indicating a relative left hemispheric gain.

After FDR correction for multiple comparisons ($q=0.05$; t-threshold = 2.67), no significant group effects were detected at the average age (see Fig. 1). Additionally, COS asymmetry development did not differ significantly from controls, except a small area in the posterior, superior frontal region. This is depicted in Fig. 1, which shows the sample point, but more illustrates an absence of further difference between the two groups. When sex was included as a covariate, group effects were the same at the intercept and over time.

4. Discussion

We present the first longitudinal MRI findings reporting no abnormal progression of cortical asymmetry in the COS population. Our healthy control sample demonstrated comparable asymmetry patterns and trajectories as seen in our recent study (Shaw et al., 2009). We did not see abnormal asymmetry patterns as have been reported in some studies of AOS, although results from studies of AOS remain inconsistent. Similarly, we did not find reduced L>R asymmetry of the anterior cingulate gyrus as reported in a prior small ($n=13$) COS study (Marquardt et al., 2005).

COS patients show profound, progressive GM and WM deficits (Rapoport et al., 2009), which on visual observation

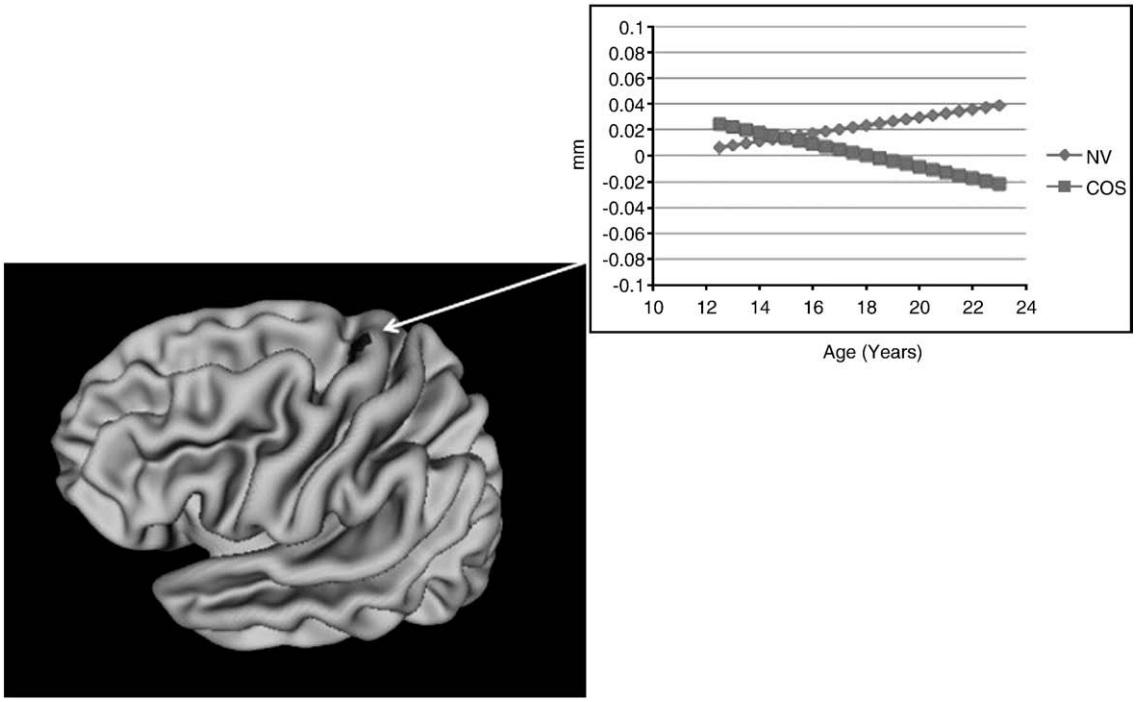

Fig. 1. Group * age interaction of cortical thickness over time ($q = 0.05$; t-threshold $= 2.67$) with sample cortical point plotted in a small region of the posterior superior frontal lobe. NV = Normal Volunteers; COS = childhood-onset schizophrenia patients.

appear greater in the right hemisphere (Greenstein et al., 2008). While GM thickness or volume is reduced in COS, the overall direction of hemispheric growth appears to progress normally. This study found no correlation between age of onset and degree of left posterior asymmetry, as similarly reported by Hadjulis et al. in adolescent onset patients ($n = 40$, mean age $= 15.7 \pm 2.1$) (Hadjulis et al., 200). Combined with other negative studies, these findings suggest normal cortical asymmetry development in young, severely ill schizophrenia patients. A higher degree of neuroplasticity in the developing brain may account for this relatively normal asymmetry pattern in this group.

This study has several limitations. First, the COS patients in our cohort had varying levels of exposure to neuroleptic and/or other psychotropic medications both at baseline and follow-up scans which could have potentially 'normalized' the GM trajectories, although most reports of abnormal asymmetry have been in medicated patients. Second, the age range covered (9–31 years) is still not typical of that reported in the adult studies. Our ongoing prospective follow-up of COS patients into adulthood however, shows no evidence of abnormal asymmetry development. Also, the mean age at Time 1 was approximately two years greater than the threshold for COS onset as it was not feasible to scan patients before or immediately after onset of psychosis to capture a true baseline. Furthermore, scans were conducted at two-year intervals and as time passed, the number of subjects able to return for a fourth or fifth follow-up visit dropped significantly. We accounted for that by matching the scan distribution between patients and controls. Demographically, patients and controls differed significantly with respect to IQ as deterioration in intellectual functioning is a potential characteristic of the COS phenotype. SES also differed significantly between the sample groups, which while unlikely, could influence results. With regard to imaging analysis, the use of localized thickness measures is limited by whether the 40,962 cortical points are truly homologous across subjects given the use of a symmetrical template. Finally, a significant portion of asymmetry research addresses whole lobe volume asymmetries as opposed to cortical thickness comparison across the cerebral hemispheres making the data from these previous studies of limited comparability with the present study.

In conclusion, our study does not support the development of abnormal cortical asymmetry in the COS population and highlights the importance of longitudinal designs in addressing this question.

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Contributors

Jennifer L. Bakalar, BA was the primary author of the manuscript. Deanna K. Greenstein, PhD and Liv Clasen, PhD performed the neuroimaging and statistical data analysis for the project. Julia W. Tossell, MD and Rachel Miller, PhD oversaw clinical management of COS patients in the sample. Anand A. Mattai, MD assisted with the composition and editing of the manuscript. Alan C. Evans, PhD was our primary collaborator and consultant for the image-processing pipeline. Judith L. Rapoport, MD and Nitin Gogtay, MD coordinated research design and execution for this project.

Conflict of interest

The authors have nothing to disclose financially and report no conflicts of interest.

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