Published in final edited form as:

Psychiatry Res. 2011 September 30; 193(3): 131–137. doi:10.1016/j.psychres.2011.02.010.

Cerebellar development in childhood onset schizophrenia and non-psychotic siblings

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Abstract

We explored regional and total volumetric cerebellar differences in probands and their unaffected full siblings relative to typically developing participants. Participants included 94 (51 males) patients diagnosed with childhood onset schizophrenia (COS), 80 related non-psychotic siblings (37 males) and 110 (64 males) typically developing participants scanned longitudinally. The sample mean age was 16.87(SD=4.7; range 6.5 to 29). We performed mixed model regressions to examine group differences in trajectory and volume. The COS group had smaller bilateral anterior lobes and anterior and total vermis volumes than controls. The COS group diverged from controls over time in total, left, right, and bilateral posterior inferior cerebellum. Siblings did not have any fixed volumetric differences relative to controls but differed from controls in developmental trajectories of total and right cerebellum, left inferior posterior, left superior posterior, and superior vermis. Results are consistent with previous COS findings and several reports of decreased cerebellar volume in adult onset schizophrenia. Sibling trajectories may represent a trait marker, although the effect size for volumetric differences in early adulthood may be small.

Keywords

MRI; Psychosis; Neurodevelopment

1. Introduction

Childhood onset schizophrenia (COS) is a severe form of the disorder, often treatment refractory, and resembles poor outcome adult schizophrenia. Over the past 20 years, the NIMH COS project has documented developmental cortical brain abnormalities in COS with COS cortical grey matter abnormalities in early adulthood resembling those seen in adult onset schizophrenia (Greenstein et al., 2006).

The cerebellum is also an important brain structure to explore in schizophrenia. It is now seen as playing a role in cognition and behavior (Leiner et al., 1991; Andreasen and Pierson 2008; Strick et al.2009), and cerebellar lesions have been shown to result in negative

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Disclosures and acknowledgments: We have no conflicting or competing interests.

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symptoms, and mood and behavior dysregulation (Tavano et al., 2007). Cross sectional structural MRI studies on adulthood onset schizophrenia (AOS) patients show mixed results with several studies reporting smaller volumes in the vermis, anterior, bilateral superior posterior lobes, right and left hemispheres, and total volumes, and some reporting no significant results (see (Bottner, Bachmann et al. 2005) for a review) (Gaser, Volz et al. 1999; Okugawa, Nobuhara et al. 2007; Edwards, Newman et al. 2008; Tanskanen, Ridler et al. 2008; Thomann, Roebel et al. 2009). Notably, because there is only one longitudinal AOS study (Mane, Falcon et al. 2009), there is minimal information regarding the evolution of cerebellum abnormalities over time in adulthood. Earlier results from smaller subsamples of COS patients included in the present study have supported progressive total cerebellar loss during adolescence as well as smaller total vermis and posterior lobe measures in COS patients (Jacobsen, Giedd et al. 1997) (Keller, Castellanos et al. 2003). However, only one of these studies was longitudinal, yielding a total of two reports of longitudinal cerebellar development in schizophrenia.

In addition to the a paucity of information on subregional cerebellar developmental in the literature, a second issue is the extent to which the brain changes seen in schizophrenia probands at any age are trait markers or reflect the illness and/or its treatment. For example, twin studies indicate that some cortical abnormalities seen are illness related (Cannon, Thompson et al. 2002). One way of addressing this is the study of non-psychotic full siblings who share 50% of their genes with the probands but who have no clinical evidence of schizophrenia or related disorders, and have never received treatment. A few studies have investigated cerebellar abnormalities in nonpsychotic siblings of AOS probands (Staal, Hulshoff Pol et al. 2000; Honea, Meyer-Lindenberg et al. 2008), with one study reporting that with relaxed significance level ($p < 0.001$, uncorrected), siblings have decreases in parts of the left cerebellum (Honea, Meyer-Lindenberg et al. 2008). The only study that has examined cerebellar development/change in this population (Brans, van Haren et al. 2008) did not report significant disease or familial effects with a 5-year follow-up in adulthood (mean age at baseline=41). Because early sibling gray matter differences appear to normalize by early adulthood (Gogtay, Greenstein et al. 2007), it is especially important to examine development from childhood through early adulthood to avoid false negatives. Also, NIMH developmental studies indicate that the cerebellum is among the last brain structures to achieve adult volume (Tiemeier, Lenroot et al. 2009), and shows relatively lower heritability in childhood and adolescence (Wallace, Eric Schmitt et al. 2006). This has led to speculation that the cerebellum may mediate later compensatory/adaptive plastic changes in relation to pathology.

In the present study, longitudinal data were used to explore developmental cerebellar differences in regional cerebellar volume between non-psychotic full siblings, affected probands, and age and sex matched controls. Based on a prospective study of cortical development in non-psychotic full siblings (Gogtay, Greenstein et al. 2007), we hypothesized that sibling cerebellar abnormalities in childhood would be diminished by early adulthood. Based on our previous longitudinal study (Keller et al., 2003), we hypothesized that for total and regional cerebellar measures, the COS group would have smaller volumes and would diverge from the control trajectory.

2. Methods

2.1 Subjects

All probands are volunteers in an ongoing study of COS at the National Institute of Mental Health and met DSM-IV criteria for schizophrenia with the onset of psychosis before their 13th birthday. Exclusion criteria are a history of significant medical problems, substance

abuse, or a premorbid IQ below 70. Further details of patient selection are described elsewhere (McKenna et al., 1994; Kumra et al., 1996).

In addition to following COS participants over time, we have also followed their siblings (SIB) at approximately two year intervals. Of the 127 full siblings in our study, 106 have not met criteria for a schizophrenia spectrum disorder (schizophrenia, schizoaffective disorder, avoidant, paranoid and schizoid personality disorders), and 80 of these 106 have had at least one passing scan between the ages of 6 and 30. Typically developing (TD) participants were selected from a larger sample of volunteers recruited from the community as part of a prospective study of normal brain development (see Giedd 1999 for further details). TD participants were selected to match the COS and SIB groups for sex, age, and number of repeated scans. The distribution of age at scan was similar for COS, SIB and control groups.

2.2 MRI acquisition

T1-weighted images with contiguous 1.5-mm sections in the axial plane and 2.0-mm sections in the coronal plane were obtained using three-dimensional spoiled gradient recalled echo in the steady state on a Signa 1.5-T scanner (General Electric Medical Systems, Milwaukee, Wisconsin) (echo time=5 msec; repetition time=24 msec; flip angle=45°; acquisition matrix=256°×192; number of signals acquired=1; field of view=24 cm). The original MR images were registered into standardized stereotaxic space using a linear transformation and corrected for nonuniformity artifacts (Sled, Zijdenbos et al. 1998).

We parcellated the cerebellum using the method developed by Pierson and colleagues at the University of Iowa (Pierson, Corson et al. 2002) implemented in the BRAINS2 software package (Magnotta, Harris et al.). Briefly, trained tracers used 31 manually defined landmarks in combination with a neural net algorithm to generate surface masks of each cerebellar subregion. The surface masks were reviewed, edited manually, and subregion volumes were measured and summed to provide the total cerebellar volume. The subregions were created by dividing the left and right cerebellar cortices into anterior (lobules I–V and delineated by the primary fissure), superior-posterior (lobule VI and crus I of VIIA, delineated in part by the by the horizontal fissure), and inferior-posterior lobes (lobules VIIA-tuber through X) using the nomenclature of Larsell and Jansen (1972). The three hemispheric lobes consist predominantly of gray matter, although white matter branching off into the folia was included in the lobes.

The vermis was defined in each coronal slice by manual tracing with reference to guide traces. A midline guide trace in the sagittal plane marked the superior, inferior, anterior, and posterior limits of the vermis, and guide traces in the axial plane were used to define the lateral borders. Regional subdivision was accomplished through placement of limiting boundaries in the sagittal plane, because the primary and prepyramidal fissures were readily apparent throughout the vermis (Mackie et al., 2007).

2.3 Reliability

As was reported elsewhere (Mackie et al., 2007), for cerebellar lobes, initial intrarater and interrater intraclass correlations (ICCs) were greater than 0.80 for all 5 tracers. For the vermis, initial intrarater ICCs were greater than 0.80, and interrater ICCs were greater than 0.68. Following the initial phase of measuring, two tracers continued measuring cerebellar lobes over a four-year span. Longitudinal lobar (left and right anterior, superior posterior and inferior posterior) intrarater ICCs over this period ranged from 0.69 (superior vermis) to 0.99. All of these ICCs were approximately or at least 0.70, which is a qualitatively acceptable (good) level of reliability (based on Fleiss (1986) who proposes a standard of 0.40 to 0.75 as fair to good reliability, and above 0.75 as excellent). Concurrent lobar

interrater ICCs were excellent and ranged from 0.91 to 0.99, and longitudinal lobar interrater ICCs were good to excellent and ranged from 0.72 to 0.96. ICCs were calculated using the “one -way random” option in SPSS. In addition to calculating ICCs, measurements were graphed to examine tracer drift and systematic biases within tracers.

In the current sample, one tracer completed all of the vermis measurements that followed the initial phase of measuring. Longitudinal ICCs for the vermis were 0.92 for the total vermis, and ranged from 0.70 to 0.98 for the three vermal subregions (anterior, superior and inferior). Finally, we attempted to ensure that tracers received a random assignment of probands, siblings, and/or controls. Also, all raters were blind to demographic data. However, all tracers did not trace cerebella from all groups, as they were not all employed during all cerebellum-related projects.

2.4 Clinical measures

We used age-appropriate versions of the Global Assessment of Functioning Scale (Shaffer et al., 1983) (APA, 1994) (GAS), the Brief Psychiatric Rating Scale (BPRS) (Guy 1976), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984), and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1983), to assess clinical symptoms in COS probands (ICCs for all measures > 0.80). We restricted ratings to NIH inpatient medication-free assessments to approximate comparable rater, treatment and environmental effects across participants. For siblings, we completed GAS scores, and we assessed DSM axis I and II symptoms with the Schedule for Affective Disorders and Schizophrenia for School-Age Children for siblings under 18 (Kaufman et al., 1997), the Structured Clinical Interview for DSM-IV-TR Axis I Disorders—Patient Edition for siblings 18 and older, (First 2001) and the Structured Interview for the DSM-III Personality Disorders for siblings 18 and older, (Stangl et al., 1985) (ICCs > 0.80). Parent socioeconomic status (SES) was measured using Hollingshead Scale (1975).

2.5 Cognitive measures

We used age-appropriate versions of the Wechsler intelligence scales to assess the COS, TD, and sibling (SIB) groups. Because this study has been ongoing for over 15 years, we have used several versions of the Wechsler scales, including: the WISC-R (Wechsler 1974), WAIS-R (Wechsler 1981), WISC-III (Wechsler 1991), WAIS-III (Wechsler 1997), and the WASI (Wechsler 1999). Siblings were only administered the Vocabulary subtest from one of the above Wechsler tests to approximate IQ and age-appropriate versions of the California Verbal Learning Test (Delis 1994; Delis 2000). One thing to note is that COS post-onset IQ scores are often below 70 but IQ before illness and NIH admission is always at least 70 (see above exclusion criteria).

2.6 Statistics

We tested for group demographic differences using one-way ANOVA for continuous variables and chi-square test of independence for categorical variables. When the ANOVA group effect was significant, we used Tukey post hoc tests.

Polynomial mixed model regression analyses were used to examine cerebellar development. Mixed model regression has several advantages over more common statistical techniques such as repeated measures ANOVA. Specifically, mixed model regression accounts for unbalanced data measured at irregular time intervals and within-person correlation (Singer and Willett, 2003). We were thus able to include participants with varying numbers of scans and increase the statistical power with which we examined volume and age relationships. In these models, individuals with one scan contribute less information to slope parameters than participants with multiple scans. Because we include all scans from all individuals, to

account for within-person and within family correlations, we included two random intercepts—one for person nested within family and one for family. These intercepts are treated as normally distributed, independent random effects, whereas beta coefficients for age (centered at the sample mean age of 16.87), group and age by group terms were modeled as fixed effects. For a given structure, the i th measurement from the j th individual nested within the k th family was initially modeled as

$$\text{Volume}_{ijk} = \text{Intercept} + \beta_1(\text{age} - \text{mean age}) + \beta_2(\text{age} - \text{mean age})^2 + \beta_3(\text{age} - \text{mean age})^3 + d_k + d_{jk} + e_{ijk},$$

β_1 , β_2 , and β_3 show how volume changes with age. The intercept and β terms were allowed to vary by diagnostic group, producing three growth curves with different height and shape characteristics. For each cerebellar volume measure, we first determined the order of the developmental growth curve (cubic, quadratic, or linear) using an F test of the combined explanatory power of the three highest order polynomial effects (one per group). Total cerebellum, right and left hemispheres, left anterior and left inferior posterior lobes were modeled as cubic curves. The right anterior and right superior posterior trajectories were quadratic curves, and vermal and inferior posterior trajectories were linear. After the order was established, we used F tests to determine group differences in the shape and height parameters of the curves.

To explore group differences in early adulthood for regions with significant COS/TD and/or SIB/TD trajectory differences, we took two approaches: 1) using all scans, we re-centered age at 23, which is at the 90th percentile of our age range and 2), we calculated t tests (COS vs. TD and SIB vs. TD) and Cohen's d (Cohen 1988) using each person's last (or only) scan after age 20.

For regions where COS had smaller cerebellar volume across the age range, we explored clinical and cognitive correlates of cerebellar volume using mixed model regression analyses. By including a random intercept per COS proband, we were able to examine relationships between clinical and cognitive measures and cerebellum volumes while accounting for within person dependencies present when multiple scans per proband are used. For each regression, the dependent variable was cerebellar volume and the independent variable was a clinical or cognitive measure; we also included age and sex as covariates in these models.

For regions with significant COS/TD and SIB/TD trajectory differences, we explored clinical and cognitive correlates of percent volume change (volume at last scan-volume at first scan)/volume at first scan). We used percent change to approximate linear and curvilinear change over time and to examine the relationships between volumetric change and clinical and cognitive correlates in a straightforward, easily accessible manner. For the COS percent change/clinical and cognitive correlate analyses, we used Pearson product moment correlations. For the SIB percent change/clinical and cognitive correlate analyses, we used a series of mixed model regressions in light of the presence of multiple siblings per family. For each regression, the dependent variable was cerebellar volume and the independent variable was a clinical or cognitive measure. In view of the relatively large number of statistical tests, we set our alpha level at 0.01 for curve parameter comparisons, t-tests comparing volumes in early adulthood, and cognitive and clinical correlate analyses. Statistical assumptions were checked for ANOVAs, t-tests, mixed model regression and correlation analyses, and data were screened for outliers. We used SAS 9.2 for all analyses.

3. Results

3.1 Demographics

There were no significant group differences in age, race, and sex (see Table 1), but groups differed in mean Vocabulary, IQ, and parent SES (see Table 1). Because SES, IQ and Vocabulary differences can be conceptualized as disease-related, they were not included as covariates, as controlling for them would be controlling for illness-related variance. The unequal numbers at each time point (and age) does not reflect attrition, rather, the unbalanced data reflects varying age at admission and length of time since study entry (<1 to approximately 20 years), and failed scans, to a lesser extent

3.2 Longitudinal analyses

Results are summarized in Table 2. The COS group's developmental trajectory diverged from the TD group trajectory in total cerebellum, bilateral inferior-posterior lobes, and right and left cerebellar hemisphere volumes. Notably, like the COS group, the SIB group's development also diverged from the TD trajectory in total cerebellum, left inferior posterior, and total right hemisphere volumes (see Figure 1). The SIB group uniquely diverged from the TD trajectory in the left superior posterior lobe and converged with the TD trajectory in the superior vermis.

The COS group had smaller volumes than the TD group over time (significant difference at average age without significant group*age interaction) in the following regions: bilateral anterior lobes, anterior vermis and total vermis. The SIB group did not have any significantly smaller regional or total volumes than the TD group over time. However, the SIB group had greater superior vermis volumes than the TD group in adolescence, but this difference diminished over time.

The COS group had smaller volumes than the SIB group over time in total, superior and anterior vermis. The SIB and COS trajectories only significantly diverged in the left anterior lobe.

3.3 Group differences in early adulthood

When we re-centered age at 23 (rather than the sample average age) to determine if trajectory differences confer volume differences in early adulthood, the COS group's estimated volume was smaller than the TD group's for all regions with significant COS/TD trajectory differences (total, left and right hemispheres, and bilateral inferior-posterior lobes) (see Figure 2 for total, right hemisphere, and left inferior posterior volumes). Also at age 23, the SIB group's right cerebellar ($P=0.009$) (see Figure 2) and left superior posterior ($P=0.01$) estimated volumes were significantly smaller than the TD group's estimated volume, and a trend was evident for smaller SIB total cerebellum (see Figure 1).

When we included only one scan per person ages 20 and above, neither the SIB ($n=39$) nor the COS ($n=34$) group significantly differed from the TD group ($n=39$) for any regional or total volume for which there were initial SIB/TD or COS/TD trajectory differences, respectively. Cohen's d values were generally in the small (0.30) and small-to-medium (between 0.30 and 0.50) ranges with three d values less than 0.30 (COS v NV-- total cerebellum $d=0.38$, right cerebellum $d=0.39$, left cerebellum $d=0.36$, left inferior posterior $d=0.22$, right inferior posterior $d=0.17$; SIB v NV-- total cerebellum $d=0.44$, right cerebellum $d=0.45$, left inferior posterior $d=0.34$, left superior posterior $d=0.33$, superior vermis $d=0.29$).

3.4 Clinical and cognitive correlates

3.4.1 COS clinical and cognitive correlations for regions with stable COS/TD differences—

For regions where the COS group had smaller volumes across the age range (bilateral anterior lobes and anterior and total vermis), mixed model regression results yielded significant positive relationships between Full Scale IQ and left anterior ($p=0.01$), right anterior ($P=0.0005$), anterior vermis ($P=0.0003$) and total vermis ($P<0.0001$). Verbal IQ was significantly positively related to anterior vermis and total vermis volumes ($P=0.002$ and $P<0.001$, respectively), and Performance IQ was significantly positively related to right anterior lobe volume, anterior vermis and total vermis volumes ($P=0.01$, $P=0.01$, $P=0.0005$, respectively). When we included total grey matter plus total white matter (GMWM) as a covariate, all 3 total vermis/IQ relationships remained significant, as did the Full Scale IQ and anterior vermis and right anterior lobe relationships ($P<0.01$). The remaining significant cerebellum, IQ, PIQ, and VIQ relationships became trend level ($P=0.04$ to 0.07) relationships when controlling for GMWM. When we included both TD and COS groups in a mixed effect regression model and tested group differences in IQ/volume relationships, no volume/IQ score relationship was significantly different between COS and TD groups. However, these comparisons should be interpreted with caution as the range of IQ scores differs for COS and TD groups (COS IQ scores range from 44 to 126 and the TD group ranges from 78 to 141).

GAS score was significantly positively related to total vermis ($P=0.006$) (better functioning, greater vermis volume), although no other clinical measure (SAPS, SANS, BPRS) was significantly correlated with bilateral anterior lobes, anterior vermis or total vermis volumes. The SIB group did not have regions with consistently smaller volumes across the age range and as such, we did not perform a comparable set of analyses.

3.4.2 Percent change and clinical and cognitive correlations—When we calculated percent change for the regions where the COS/TD trajectories diverged and correlated these change scores with the COS group's IQ (Full Scale, Verbal and Performance IQ) scores and clinical measures (GAS, SAPS, SANS, BPRS), no Pearson correlation coefficients were statically significant.

When we calculated percent change for the regions where the SIB/TD trajectories diverged or converged and correlated these change scores with siblings' scaled Vocabulary scores, GAS scores, number of schizophrenia spectrum symptoms (total of paranoid, schizoid, schizotypal, and avoidant personality disorder symptoms) and CVLT standard scores (Trials 1–5 T score, short free and cued z scores, and long free and cued z scores), no significant relationships emerged.

4. Discussion

Our findings are consistent with previous reports of cerebellar abnormalities in schizophrenia. Specifically, the divergent total cerebellum trajectory and the stable total vermis difference between COS and TD groups are consistent with a previous study that included a subset of the current sample (Keller et al., 2003). Also, smaller unadjusted total cerebellum volume using the same semi-automated method has been reported in the cross-sectional AOS literature (Thomann et al., 2009), suggesting some consistency in the presence of total cerebellar abnormalities in COS and AOS. Moreover, consistent with current results, smaller unadjusted anterior lobes (Edwards et al., 2008), and smaller unadjusted anterior and total vermis measures in medication-naïve first episode AOS (Nopoulos et al., 1999; Okugawa et al., 2007) have also been reported in the cross-sectional AOS literature. Notably, current findings include positive relationships for these regions

(anterior lobes and anterior and total vermis) and postonset IQ, and total vermis volume and GAS score.

The significant relationship between IQ and the vermis has also been reported in AOS studies (Nopoulo et al., 1999) childhood tumor studies (Puget et al., 2009) Joubert syndrome (vermal aplasia) (Steinlin 2007), and the fragile X literature (Mostofsky et al., 1998), suggesting that vermis/IQ relationships are not specific to schizophrenia and that congenital and/or later vermis abnormalities can both interfere with overall cognitive functioning. However, this is not consistent with Stoodley and Schmahmann's recent (Stoodley and Schmahmann 2010) conceptualization of cognitive impairment as localized in posterior cerebellar regions. We also found a significant positive relationship between total vermis volumes and GAS score in COS, which is more consistent with Stoodley and Schmahmann's conceptualization of neuropsychiatric disorders as linked to the vermis. However, the remainder of our symptom/vermis relationship findings did not support schizophrenia symptoms significantly correlating with vermal volume or change.

The SIB trajectories diverged from those of the TD group in a manner similar to COS for total, right, and left inferior volumes. This finding was counter to our hypothesis of a normalizing trend for siblings (based on cortical thickness results from Gogtay et al., 2007). The similarity between COS and SIB development in these regions also suggests the possibility of a deviant trajectory that may be related to how familial genetic risk factors and/or plastic response to risk affect brain growth. Although several SIB trajectories diverged from the control trajectory in a manner similar to their affected COS siblings, the ultimate "abnormality" in early adulthood is unclear. Based on the developmental curves, the SIB group has smaller volumes in early adulthood; however, limiting the data to one scan per person post 20 years, which is more representative of adult onset studies, did not support notable or significant adulthood volumetric cerebellar abnormalities in the SIB group. In addition, because no significant correlates of rate of change emerged, the clinical relevance of the diverging SIB and COS trajectories remains unclear. It would thus be of particular interest to obtain memory and theory of mind tests which have previously been shown to relate to the posterior cerebellum (Andreasen and Pierson 2008).

More consistent with our hypothesis of plastic developmental change in siblings, the sibling superior vermis volume was significantly greater than both COS and TD groups in adolescence and converged with the TD trajectory over time. The NIMH developmental studies indicate that the cerebellum is among the last structures to achieve adult volume (Tiemeier, Lenroot et al., 2009), and shows relatively lower heritability (Wallace, Schmitt. et al., 2006). This, combined with our present finding, suggests that the vermis, specifically, the superior vermis, may mediate a compensatory/adaptive plastic changes in relation to pathology.

Limitations to the study include the lack of germane cognitive measures for all groups. After compiling results from functional MRI studies, Andreasen and Pierson (2008) reported unique relationships between memory and theory of mind tasks and posterior regions of the cerebellum—regions for which either SIB and/or COS groups diverged from the TD trajectory. While our list learning task measures did not correlate with SIB changes in posterior cerebellum, ideally, we would also have complete list learning, theory of mind, story memory and facial recognition testing results from probands, siblings and controls to further understand the relationship between divergent posterior cerebellar development and cognition. While we currently lack this data, long-term follow-up and additional cognitive testing are ongoing. Another weakness is that we have had several cerebellum tracers over the years, and while we have made concerted efforts to train and monitor manual tracers, having multiple, nonoverlapping manual tracers is a drawback.

A third limitation involves the debate over whether or not to covary for total cortical volume. In informal analyses, when we included total grey matter plus total white matter (GMWM) as a covariate for TD/COS differences, many of the results which were significant (at $\alpha = 0.01$) were reduced to trend level (P values from 0.02 to 0.11) results (see supplementary table). It is thus not clear if developmental and static COS/TD differences in these regions are a function of overall smaller brain volumes in COS patients. However, it is arguable that covarying for GMWM, like controlling for IQ, is comparable to controlling for illness-related variance and would thus result in type II errors. As this study was exploratory in nature, we opted to air against type II errors and focus instead on uncorrected results in the manuscript while still presenting the reader with the covaried results.

A final weakness of this study is that many siblings and controls have not passed the age of risk for schizophrenia or related disorders. Because we continue to follow up the siblings and controls, we expect that this weakness will be attenuated over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Regions where shape of both COS ($n=94$, 208 scans) and sibling (SIB) ($n=80$, 165 scans) trajectories significantly differed ($P < 0.006$) from the typically developing control group's ($n=110$, 269 scans) developmental trajectory. Group differences in height of curves at the sample average age (16.87) and 23 years are also shown.

Table 1

Demographics for Childhood Onset Schizophrenia (COS), non-affected full siblings, and typically developing control groups

	COS (<i>n</i> =94)	Sibling (<i>n</i> =80)	Control (<i>n</i> =110)	<i>F</i> (<i>df</i>) or χ^2 (<i>df</i>)	<i>P</i>
Sex	43 F; 51 M	43 F; 37 M	46 F; 64 M	$\chi^2_{(2)} = 2.68$	0.26
Average age (all scans) mean(SD)	17.25(4.1)	16.88(5.83)	16.57(4.44)	$F_{(2,639)} = 1.22$	0.30
Age at first scan mean(SD)	14.6(2.8)	14.9(5.9)	14.2(3.7)	$F_{(2,281)} = .75$	0.47
Race	6A; 28B; 3O; 57W	3A; 15B; 3O; 59W	4A; 14B; 5O; 87W	$\chi^2_{(6)} = 11.1$	0.08
Vocabulary Score mean(SD)	6.24(3.5)	11.02(3.2)	11.69(2.5)	$F_{(2,234)} = 78.85^*$	<0.01
IQ, mean(SD)	74.1(18.39)	na	112.7(11.96)	$F_{(1,180)} = 294.2^+$	<0.01
Socio-Economic Status ^{***} , mean(SD)	62.5(30.46)	50.4(25.98)	40.68(19.1)	$F_{(2,272)} = 18.45^{**}$	<0.01
Axis I Diagnosis		40			
Mood Disorder	na	20	na		
Anxiety Disorder		16			
Alcohol &/or Substance Abuse		8			
Total Number of Scans	208	165	269		
Number of Scans at					
Time 1	94	80	110		
Time 2	54	40	80		
Time 3	36	30	48		
Time 4	14	11	22		
Time 5	7	4	8		
Time 6	3	0	1		

Race: A: Asian; B-Black/African-American; O-Other/Mixed Race; W=White

⁺ COS < NV

^{*} COS < NV/SIB

COS < NV/SIB; SIB < NV

SES is inversely scored (higher scores indicate lower SES)

Results from longitudinal analyses comparing regional and total cerebellar development of childhood onset schizophrenia probands (n=94, 208 scans), typically developing controls (n=110, 269 scans), and healthy siblings (n=80, 165 scans)

Table 2

		Estimated mean volume (in mm ³) (SE) at the sample average age (16.87 years)				p values for F test for height differences of curves at sample average age				p values for F test for group differences in shape of trajectory			
		COS	Control	Sibling		COS vs. Control	COS vs. Sibling	Sibling vs. Control		COS vs. Control	COS vs. Sibling	Sibling vs. Control	
Total Cerebellum	Left Anterior	129.4 (1.45)	133.9 (1.35)	130.64 (1.75)		0.02	0.51	0.14		0.0001	0.53	0.0006	
	Left. Inferior-Posterior	5.67 (0.14)	6.28 (0.13)	6.02 (0.18)		0.002	0.07	0.24		0.02	0.003	0.11	
Left Hemispheric	Left. Inferior-Posterior	27.3 (0.37)	28.26 (0.34)	27.78 (0.44)		0.06	0.32	0.39		0.0001	0.60	0.006	
	Left. Superior-Posterior	23.44 (0.32)	23.95 (0.29)	23.06 (0.39)		0.24	0.36	0.07		0.06	0.25	0.0004	
Total Left Cerebellum	Total Left Cerebellum	64.39 (0.72)	66.51 (0.67)	64.86 (0.87)		0.03	0.62	0.14		0.002	0.54	0.015	
	Right Anterior	5.74 (0.15)	6.31 (0.14)	5.92 (0.18)		0.005	0.37	0.09		0.45	0.31	0.72	
Right Hemispheric	Right Inferior-Posterior	27.71 (0.39)	28.75 (0.36)	28.46 (0.46)		0.05	0.15	0.62		0.001	0.40	0.05	
	Right Superior Posterior	23.85 (0.34)	24.32 (0.32)	23.54 (0.42)		0.32	0.47	0.14		0.02	0.14	0.02	
Total Right Cerebellum	Total Right Cerebellum	65.04 (0.74)	67.4 (0.69)	65.78 (0.89)		0.02	0.43	0.15		0.0003	0.56	0.0006	
	Superior	2.61 (0.05)	2.69 (0.05)	2.90 (0.06)		0.21	<0.0001	0.006		0.05	0.22	0.002	
Vermis	Inferior	3.12 (0.05)	3.30 (0.05)	3.27 (0.06)		0.02	0.03	0.73		0.32	0.76	0.57	
	Anterior	3.51 (0.06)	3.80 (0.06)	3.79 (0.07)		0.0004	0.0006	0.89		0.03	0.34	0.31	
Total	Total	9.23 (0.13)	9.79 (0.12)	9.95 (0.16)		0.002	<0.0001	0.41		0.02	0.82	0.05	