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## Cognitive correlates of gray matter abnormalities in adolescent siblings of patients with childhood-onset schizophrenia

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### ABSTRACT

Patients with childhood onset schizophrenia (COS) display widespread gray matter (GM) structural brain abnormalities. Healthy siblings of COS patients share some of these structural abnormalities, suggesting that GM abnormalities are endophenotypes for schizophrenia. Another possible endophenotype for schizophrenia that has been relatively unexplored is corticostriatal dysfunction. The corticostriatal system plays an important role in skill learning. Our previous studies have demonstrated corticostriatal dysfunction in COS siblings with a profound skill learning deficit and abnormal pattern of brain activation during skill learning. This study investigated whether structural abnormalities measured using volumetric brain morphometry (VBM) were present in siblings of COS patients and whether these were related to deficits in cognitive skill learning. Results revealed smaller GM volume in COS siblings relative to controls in a number of regions, including occipital, parietal, and subcortical regions including the striatum, and greater GM volume relative to controls in several subcortical regions. Volume in the right superior frontal gyrus and cerebellum were related to performance differences between groups on the weather prediction task, a measure of cognitive skill learning. Our results support the idea that corticostriatal and cerebellar impairment in unaffected siblings of COS patients are behaviorally relevant and may reflect genetic risk for schizophrenia.

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### 1. Introduction

Childhood onset schizophrenia (COS) is a rare and more severe form of adult onset schizophrenia (AOS), in which psychosis develops before the age of 13. COS has a more pronounced genetic risk (Asarnow and Asarnow, 1994; Nicolson and Rapoport, 1999; Asarnow et al., 2001) and is clinically continuous with the adult onset form of schizophrenia (Rapoport et al., 2005).

Structural brain abnormalities are consistently detected in AOS in areas such as the striatum (Bogerts et al., 1985; Buchsbaum, 1990), hippocampus and other medial temporal lobe structures (Bogerts et al., 1985; Benes et al., 1991; Nelson et al., 1998), cerebellum (DeLisi et al., 1997; Volz et al., 2000; Ichimiya et al., 2001), and progressive gray matter (GM) loss is present in parietal, prefrontal and superior temporal cortices (Kuperberg et al., 2003; White et al., 2003; Wiegand et al., 2004; Narr et al., 2005).

There is evidence that these structural abnormalities are more profound in COS patients than their adult counterparts (Gogtay, 2008; Rapoport et al., 1999; Rapoport and Inoff-Germain; for a comprehensive review see Thermenos et al. 2013). In adolescence, COS patients exhibit widespread structural brain abnormalities. In adulthood, these abnormalities are more focal, but COS patients continue to show greater reductions in GM in prefrontal and superior temporal cortices compared to AOS (Greenstein et al., 2006). The GM abnormalities in schizophrenia potentially reflect a genetic vulnerability that adversely influences early brain development, resulting in dysfunctional neurodevelopment (Woods, 1998; Lieberman, 1999; Pantelis et al., 2003; Lieberman et al., 2005).

The non-psychotic siblings of COS patients share some of these same structural abnormalities in GM in prefrontal and temporal cortices (Gogtay et al., 2007) and in hippocampal volume loss (Boos et al., 2007) that are present in COS patients. These results suggest that GM deficits do not merely reflect the presence of schizophrenia and the treatments patients received for this disorder, but are possible endophenotypes for schizophrenia. Here, we examine how GM changes in adolescent siblings of COS patients relate to performance in this group on a cognitive skill learning task.

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Patients with schizophrenia show substantial deficits in cognitive skill learning (Schroder et al., 1996; Gimenez et al., 2003; Purdon et al., 2003; Foerde et al., 2008; Weickert et al., 2010), consistent with the hypothesis that the pathophysiology of schizophrenia involves dysfunction of corticostriatal circuits (Kleist, 1960; Buchsbaum, 1990; Buchanan et al., 1993). The corticostriatal system plays an important role in skill learning (Knowlton et al., 1996a, 1996b; Poldrack and Gabrieli, 2001). Non-psychotic relatives of COS patients also show deficits in cognitive skill learning (Weickert et al., 2010; Wagshal et al., 2012), suggesting that this system may be associated with genetic risk for schizophrenia. Thus, corticostriatal dysfunction may be an endophenotype of schizophrenia that is present in both patients and their unaffected relatives.

One cognitive skill learning task that has been used extensively in the neuropsychological literature is the Weather Prediction Task (WPT) (Knowlton et al., 1994). The WPT requires participants to learn the probabilistic associations between visually presented cues and binary outcomes, followed by feedback as to whether they chose the correct outcome. Previous work suggests that individuals can use explicit or implicit learning to solve the task, with initial performance in control subjects supported by explicit memory, with gradual implicit learning supporting performance as training progresses (Gluck et al., 2002). Performance on the WPT is impaired in patients with corticostriatal dysfunction (Knowlton et al., 1996a, 1996b), and patients with schizophrenia (Weickert et al., 2002; Keri et al., 2005; Foerde et al., 2008; Horan et al., 2008). There is also evidence that first-degree relatives of patients with schizophrenia show performance abnormalities on the WPT. Adult first-degree relatives of AOS patients, unlike controls, did not show evidence of developing automaticity of performance, on the WPT, and continued to rely on controlled processing even after extensive practice (Wagshal et al., 2014). In another study that split into subjects into good and poor learner groups based on WPT performance, the adult relatives of AOS patients were disproportionately represented in a poor learner group (Weickert et al., 2010).

In a prior behavioral study (Wagshal et al., 2012), we have also demonstrated profound learning deficits in the non-psychotic adolescent siblings of COS patients in early learning (the first 50 trials) of the WPT as well as a lower level of asymptotic performance than controls even after extensive training (800 additional trials). In an fMRI study with a subset of these subjects (Wagshal et al., 2013), the COS siblings showed a relative deactivation in frontal and striatal regions, as well as in the cerebellum, after extensive training on the WPT compared to controls. The results are consistent with the idea that corticostriatal dysfunction and potentially cerebellar impairment are part of the liability for schizophrenia.

In the present study, we were interested in determining if there are structural abnormalities in adolescent COS siblings, and whether these are related to impaired performance on the WPT task. Results from our prior behavioral and fMRI studies using the WPT (Wagshal et al., 2012, 2013) suggest that different neural process might underlie performance early and late in practice. Identifying structural abnormalities in the neural circuits supporting cognitive skill learning in the siblings of patients with schizophrenia is an important step in demonstrating that those circuits are associated with vulnerability to schizophrenia that are unrelated to disease processes or treatment.

## 2. Material and methods

### 2.1. Participants

Sixteen adolescent siblings (age range: 8–16) of COS patients and forty-five adolescent controls (age range: 8–18), who were right handed, and were matched in age, education, and gender to the COS siblings (Supplementary materials Table 1) participated in the study of group differences in GM volume across the brain. An analysis was also conducted on a subset of these subjects (thirteen siblings of COS

**Table 1**

Brain regions that showed significant volume reduction for COS siblings vs. controls. T-statistical maps were corrected for multiple comparisons with familywise error (FWE) correction and Threshold-Free Cluster Enhancement (TFCE) at  $p < 0.05$ . \*Note: all regions are bilateral (ROIs that extend into the contralateral hemisphere) unless otherwise indicated.

Region	Coordinate			Max T-value	Voxel size
	X	Y	Z		
<i>COS siblings &lt; controls*</i>					
Subcortical regions					
Right caudate	18	6	20	4.322	98
Brainstem	16	−24	−34	3.510	6
Right cerebellum	28	−68	−38	3.718	367
Parietal regions					
Precuneus cortex	14	−64	30	3.861	462
Occipital regions					
Occipital pole	−16	−90	24	4.467	889
Occipital fusiform gyrus	18	−88	−8	3.838	129
Lateral occipital cortex	−16	−88	24	4.637	266
Right lingual gyrus	16	88	−8	3.458	31
Cuneal cortex	−12	−88	24	3.829	259
<i>Controls &lt; COS siblings*</i>					
Subcortical regions					
Cerebellum	42	−68	−22	4.931	1484
Lingual gyrus	−6	−86	−14	4.381	162

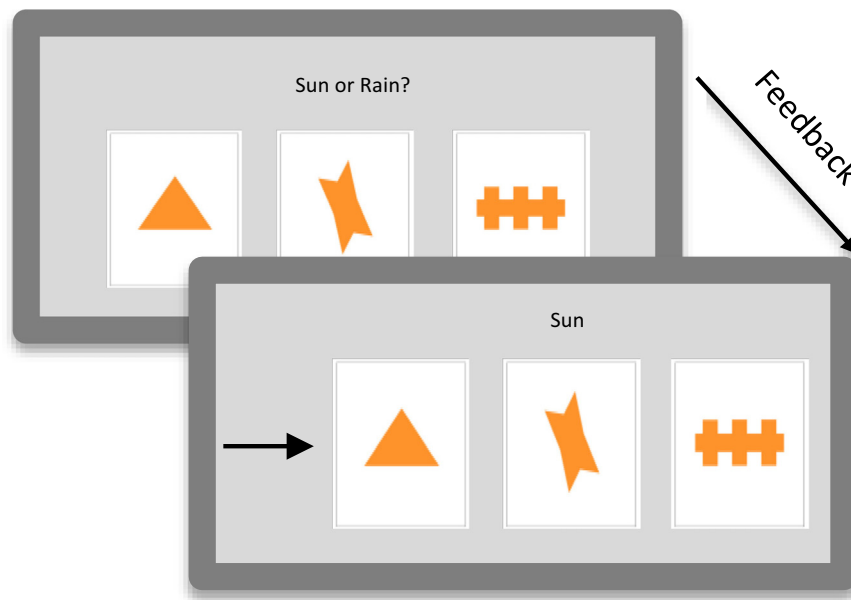
patients and thirty-nine controls) to investigate if these differences were related to WPT performance. Data from the subjects in the second analysis appeared in our previous behavioral and fMRI studies of WPT learning in siblings of COS patients (Wagshal et al., 2012, 2013). The 6 controls and 3 siblings of COS patients were excluded from the secondary analysis based on computer malfunction, not responding on more than 10% of the WPT trials, or not completing both days of WPT training.

The siblings of COS probands were recruited through previous participation in family studies of COS at the University of California, Los Angeles (UCLA). Families of potential control subjects who lived within a 25-mile radius of UCLA were identified by a survey research firm and were contacted by phone. All participants' parent or legal guardian provided informed consent while the participants themselves provided assent according to the procedures of the UCLA Institutional Review Board. Potential participants in both groups were screened and excluded for reports of prior treatments for psychiatric disorders including psychosis, attention-deficit hyperactivity disorder, learning disabilities, Tourette's Syndrome, traumatic brain injury, drug and alcohol abuse, and other neurological disorders that affect cognitive functioning or the presence of any psychotic symptoms. COS siblings did not have any psychotic symptoms or any schizophrenia spectrum diagnoses. Thus, in the present study, all subjects were free of clinical symptoms and were not taking medication for a psychiatric condition. Control subjects were also excluded if a first-degree relative had been reported to have been diagnosed with psychosis.

### 2.2. Task design and procedure

Participants were administered the WPT (Knowlton et al., 1994). The MATLAB (The MathWorks, Inc., Natick, MA) Psychophysics Toolbox (Brainard, 1997) version 7.4 was used to present the stimuli and to record responses on an Apple G4 PowerBook using the OSX operating system.

Subjects practiced the WPT (Fig. 1) for a total of one and a half hours, spanning two days. The details of the task are described elsewhere (Wagshal et al., 2012). On the first day, subjects were assessed for any neurological disorder or psychotic symptoms by a psychiatrist and completed the Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary and Block Design subtests (Supplementary materials Tables 1 and 2). All subjects then completed 50 trials of the WPT inside an MRI scanner. On the second day, all subjects were trained for an additional 800 trials outside the scanner occurring in two sets with an



**Fig. 1.** The WPT task. Participants were told to predict the weather (sun or rain) based on cues. On every trial between 1 and 3 cues (out of 4 possibilities) could appear, yielding 14 possible combinations. The cues were probabilistically related to the outcomes. The association of the different cues with different probabilities was randomized across participants.

intervening break of 30 min where another task (the serial reaction time task) was performed.

### 2.3. Imaging procedure

Scanning was performed on a 3-Tesla Siemens Allegra head-only MRI scanner in the Ahmanson–Lovelace Brain Mapping Center at UCLA. A structural image consisting of a magnetization-prepared rapid acquisition gradient echo image (MPRage) was collected: sagittal slices; slice thickness, 1 mm; TR = 2300 ms; TE = 2.1 ms; voxel size = 1.3 × 1.3 × 1.0 mm; 0.5 mm gap; flip angle = 8°; matrix, 192 × 192; field of view = 256.

### 2.4. Behavioral data analysis

Independent subject t-tests were performed to analyze group differences in age, education, and IQ (WASI Vocabulary and Block Design

subtests). A chi-squared test was used to examine gender differences between the groups. Performance on the WPT was analyzed early in learning (first 50 trials on Day 1) and late in learning (trials 751–800) when performance was at asymptotic levels in control subjects.

### 2.5. Imaging data preprocessing and analysis

Structural data were analyzed with FSL-VBM version 5.0.5 (Douaud et al., 2007; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM>), an optimized VBM protocol (Good et al., 2001) carried out with FSL tools (Smith et al., 2004). First, structural images were brain-extracted and GM-segmented before being registered to the MNI 152 standard space using non-linear registration (Andersson et al., 2007). The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific GM template. Second, all native gray matter images were non-linearly registered to this study-specific template and modulated to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated GM images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. Voxelwise statistics were carried out using FSL's Randomise (v.2.9) with 10,000 permutations and a standard GLM design. In the initial analysis, differences between the groups were analyzed using a two-sample unpaired t-test. For the secondary analysis, a two-sample unpaired t-test with a continuous covariate was applied to examine differences between the groups in relation to average WPT performance and to early and late WPT performance in regions that were significantly different in a prior fMRI WPT study (Wagshal et al., 2013). These regions in the prior fMRI study were created from a task-baseline contrast in which the Z-statistic images were created using a cluster-level threshold of  $z > 2.3$  and a corrected significance threshold of  $p < 0.05$  using cluster-based Gaussian random field theory. In addition, a two-sample unpaired t-test with two continuous covariates was applied to examine differences between the groups in relation to IQ (Verbal and Block Design WASI subtests). All analyses included total intracranial volume (TIV) as a covariate of no interest. A statistical threshold,  $p < 0.05$  corrected for multiple comparisons with familywise error (FWE) correction and Threshold-Free Cluster Enhancement (TFCE), was used for analyses. This option enables the finding of clusters without setting an initial cluster threshold (Smith and Nichols, 2009).

**Table 2**

Brain regions that showed a significant correlation between volume and late WPT performance in COS siblings. T-statistical maps were corrected for multiple comparisons with familywise error correction (FWE) and Threshold-Free Cluster Enhancement (TFCE) at  $p < 0.05$ . There were no other significant positive or negative correlations for controls or for COS siblings.

Region	Coordinate			Max T-value	Voxel size
	X	Y	Z		
<i>Positive correlation with controls and average WPT performance</i>					
Frontal region					
Right superior frontal gyrus	10	30	60	5.262	1704
<i>Negative correlation with COS siblings and average WPT performance</i>					
Subcortical region					
Right cerebellum	42	−76	−32	5.839	906
<i>Positive correlation with controls and late WPT performance</i>					
Frontal region					
Right superior frontal gyrus	24	2	42	5.327	1586
<i>Positive correlation with COS siblings and late WPT performance</i>					
Subcortical region					
Right cerebellum	38	−44	−48	5.674	200

### 3. Results

#### 3.1. Behavioral results

Similar to past results of studies of first-degree relatives of patients with schizophrenia, the COS siblings had significantly lower scores on two WASI subscales (Vocabulary,  $t(46) = 4.392$ ,  $p < 0.001$ , and Block Design,  $t(44) = 3.816$ ,  $p < 0.001$ ) than controls. Three COS siblings and 9 controls were not tested on the WASI subtests, and three COS siblings and 10 control participants were not tested on the Block Design subtest due to time constraints and were not included in these analyses. We also conducted a correlation analysis to determine if IQ was related to WPT performance. For the COS sibling group, there was no relationship between scores on the Block Design or Vocabulary subtests of the WASI and either early or late WPT performance ( $p$ 's  $> 0.05$ ). For the controls, there was a very modest correlation with the Vocabulary subtest and early WPT performance,  $r(37) = 0.325$ ,  $p = 0.05$ . No other correlations were significant. Lastly, a regression analysis showed that the IQ measures did not significantly predict performance during either early learning or asymptotic performance for either group ( $p > 0.05$ ).

#### 3.2. VBM results

We examined volumetric differences between the groups throughout the entire brain and found multiple regions in which COS siblings displayed smaller volumes than controls. These regions included widespread occipital and parietal areas, the striatum, and regions in the right cerebellum and the brainstem. In contrast, there were only 2 regions that displayed greater volume in COS siblings than controls, a different bilateral cerebellar region, and a region in the lingual gyrus (Table 1).

We then conducted an analysis to examine if the volumetric differences between the groups were related to average WPT performance as well as separate analyses for early and late WPT learning. For overall WPT performance, control subjects demonstrated a positive correlation with brain volume in the right superior frontal gyrus, while the siblings demonstrated a negative correlation with brain volume in the right cerebellum (Table 2). For late WPT performance, control subjects revealed a positive correlation with brain volume in the right superior frontal gyrus. In COS siblings there was a positive correlation with brain volume in the right cerebellum and late WPT performance (Fig. 2, Table 2). There were no other significant positive or negative correlations for controls or for COS siblings during average, early, or late learning.

**Table 3**

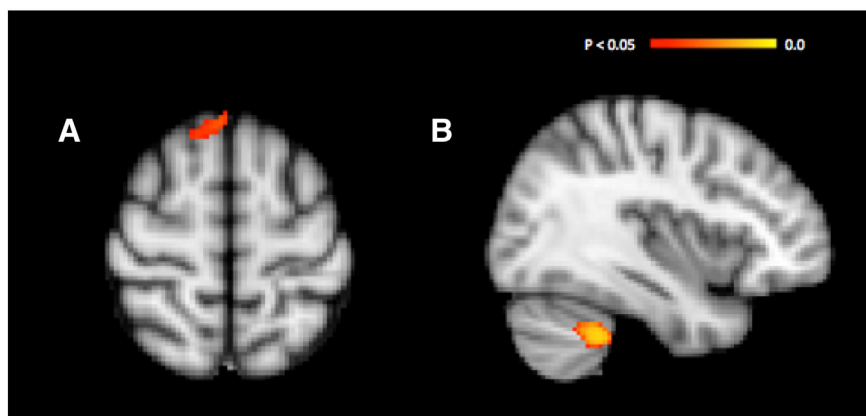
Brain regions that showed a significant negative correlation between volume and IQ in COS siblings (Verbal and Block Design subtests). T-statistical maps were corrected for multiple comparisons with familywise error correction (FWE) and Threshold-Free Cluster Enhancement (TFCE) at  $p < 0.05$ . There were no other significant positive or negative correlations for COS siblings or for controls.

Region	Coordinate			Max T-value	Voxel size
	X	Y	Z		
<i>Negative correlation with COS siblings and IQ</i>					
Parietal regions					
Left precuneus cortex	-28	-58	10	5.158	134
Occipital regions					
Left lateral occipital cortex	-46	-80	-20	5.009	33
Left intracalcarine cortex	-28	-60	10	4.998	85

Finally, we conducted an analysis to examine if the volumetric differences between the groups were related to IQ. There was a negative correlation between volumes of several brain regions in the parietal and occipital lobes in the COS siblings and IQ (Table 3). There were no other significant positive or negative correlations for COS siblings or for controls.

### 4. Discussion

Our results revealed smaller GM volume in COS siblings relative to controls in a number of subcortical, occipital, and parietal regions and greater volume relative to controls in the cerebellum. In addition, we found that GM volume was related to performance differences on the WPT. Poorer performance in later learning on the WPT was related to a smaller volume in the cerebellum in COS siblings and in the superior frontal gyrus in controls. Though our analysis revealed differences in IQ based on the lack of a strong relationship between either behavioral measures of verbal or performance IQ and WPT performance, it is unlikely that differences in general intellectual function between the groups could account for the findings of our study. Indeed, while asymptotic WPT performance was positively correlated with brain volumes in specific regions for both groups, there was actually a negative correlation between volume and IQ in the COS siblings that was most apparent in posterior and occipital cortical regions. The difference in the pattern of correlations suggests that WPT performance was not simply a manifestation of a generalized cognitive deficit reflecting diffuse brain abnormalities.



**Fig. 2.** Brain regions that showed a significant correlation with late WPT performance. T-statistical maps were corrected for multiple comparisons with familywise error (FWE) correction and Threshold-Free Cluster Enhancement (TFCE) at  $p < 0.05$ . A = positive correlation between controls and late WPT performance in the right superior frontal gyrus, B = positive correlation between COS siblings and late WPT performance in the right cerebellum.

The results here are consistent with the GM abnormalities found in past studies examining COS siblings, most notably GM volume loss in prefrontal, parietal, and cerebellar regions (Gogtay et al., 2003, 2007; Boos et al., 2007; Greenstein et al., 2011; Mattai et al., 2011). However, our results also demonstrated several novel findings: reduced volume in occipital regions and reduced caudate volume in adolescent COS siblings compared to controls. To the best of our knowledge, this is the first study to show reduced occipital and striatal volume in adolescent COS siblings and the first study to examine the association between performance on a skill learning task that taps corticostriatal function and brain volume in those regions. These novel results parallel similar findings in high risk AOS relatives in the same regions (Byun et al. 2012; Rajarethinam et al. 2007; Mamah et al. 2008).

These volumetric findings provide insight into findings from our previous fMRI study (Wagshal et al., 2013). Our fMRI study found reduced striatal activation in siblings of COS probands compared to controls during performance on the WPT. The smaller caudate volumes in the siblings of COS probands may be partially responsible for this finding. This finding of reduced caudate volume needs to be replicated in future cross sectional and longitudinal studies in order to further investigate the structure and function of the striatum and corticostriatal circuits as markers for genetic vulnerability for schizophrenia.

We also found that increased volume in the superior frontal gyrus in controls compared to COS siblings was related to the superior performance late in learning on the WPT in the controls relative to the siblings of COS probands. This finding is consistent with another study showing a contribution of prefrontal-cortical regions for performance on skill learning tasks (Poldrack et al., 1999). The larger volume in controls in this region may help to explain why there are WPT performance and brain activation differences between the COS siblings and controls (Wagshal et al., 2012, 2013). In COS siblings, smaller cerebellar volume was associated with performance late in learning on the WPT. In contrast, cerebellar volume in the controls did not predict WPT performance. It appears that different neural systems support performance late in learning in controls than in siblings of COS probands.

Previous studies have highlighted the role of the cerebellum in cognition (Leiner et al., 1991; Andreasen and Pierson, 2008; Strick et al., 2009). While there are conflicting findings concerning a smaller cerebellar volume in adult onset schizophrenia (Gaser et al., 1999; Okugawa et al., 2007; Edwards et al., 2008; Thomann et al., 2009; Tanskanen et al., 2010), studies of COS patients have provided evidence for progressive cerebellar loss (Jacobsen et al., 1997; Keller et al., 2003; Greenstein et al., 2011). However, there have been very few studies of siblings of patients with schizophrenia. One study of adult siblings of AOS patients (Honea et al., 2008) revealed a decrease in the left cerebellum of siblings, but with an uncorrected p-value ( $p < 0.0001$  uncorrected). Another longitudinal study of COS siblings (Greenstein et al., 2011) revealed no volumetric differences relative to controls in adolescence. However, they demonstrated that the COS siblings did differ from controls in the developmental trajectories of the cerebellum, reflecting a decrease in volume over time, which parallels the trajectory of the COS patients, possibly representing a trait marker. The findings here also suggest that the cerebellum is morphologically different in adolescent COS siblings compared to adolescent controls, and that the cerebellum may make different contributions to cognitive skill learning in the two groups.

Our results suggest that striatal and cerebellar abnormalities, evidenced by reduced caudate and cerebellum regional volume, were a potential endophenotype for schizophrenia. However, given the findings of a normalization of gray matter abnormalities in siblings of COS patients when they reach adulthood (Rapoport and Gogtay, 2011), these effects of genetic risk may be most apparent in adolescence. It is particularly important to conduct longitudinal studies in this group to see if the abnormal volumes of the striatum and cerebellum persist into adulthood or represent a developmental delay.

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#### Contributors

Dana Wagshal: first author: collection of data, performed analyses, and wrote the manuscript

Barbara J. Knowlton: major contribution to manuscript, advised study design

Jessica R. Cohen: assisted with data collection and writing of the manuscript

Susan Y. Bookheimer: assisted with the manuscript

Robert M. Bilder: assisted with the manuscript

Vindia G. Fernandez: assisted with data collection and writing of the manuscript

Robert F. Asarnow: major contribution to manuscript; principal investigator of the project, advise study design

#### Conflict of interest

None of the authors declares any conflict of interest.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.schres.2014.12.006>.

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