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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.

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.; 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 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.

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		
*COS siblings < controls**					
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
*Controls < COS siblings**					
Subcortical regions					
Cerebellum	42	−68	−22	4.931	1484
Lingual gyrus	−6	−86	−14	4.381	162

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

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