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Gray matter volume deficits are associated with motor and attentional impairments in adolescents with schizophrenia ☆

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ABSTRACT

Cognitive deficits have been well described in adolescents with schizophrenia, but little is known about the neuroanatomical basis of these abnormalities. The authors examined whether neuropsychological deficits observed in adolescents with schizophrenia were associated with cortical gray matter volume deficits. Volumes of the superior frontal gyrus, anterior cingulate gyrus and orbital frontal lobe were outlined manually from contiguous MR images and automatically segmented into gray and white matter in 52 patients and 48 healthy volunteers. Subjects received a comprehensive neuropsychological test battery, assessing five different functional domains: executive, attention, verbal memory, motor and sensory motor. Children and adolescents with schizophrenia were found to have lower total cortical and lower superior frontal gyrus gray matter volumes and lower test scores across all functional domains compared to healthy volunteers. Among patients, the lower total cortical gray matter volume was associated with worse functioning on the attention and motor domains. Our findings point to widespread, perhaps multifocal, pathology as contributing to cognitive dysfunction in adolescents with schizophrenia.

1. Introduction

The prefrontal cortex is hypothesized to be an important site of dysfunction in schizophrenia and developmental changes in the connectivity of the prefrontal cortex may be critical for the appearance of the clinical features and cognitive impairments associated with the disorder (Lewis et al., 2004). Post-mortem studies of adults with schizophrenia have reported the presence of structural abnormalities in the dorsolateral prefrontal cortex, but not in ventral regions of the prefrontal cortex (e.g., Broca's area 44) that are consistent with a reduction of neuropil (Selemon et al., 2003). This work was conducted, however, in adults with long-standing mental illness who had a substantial medication history, raising concerns about confounding variables that could partially account for these findings.

In adolescence there is a considerable ongoing cortical development (Gogtay et al., 2004). Normative studies of adolescents have reported a postpubertal loss in the cortical gray matter during adolescence, particularly in prefrontal areas involved in executive function, attention and motor coordination (Gogtay et al., 2004). Adolescents with early-onset schizophrenia (EOS; onset of psychotic symptoms by 18 years of age) provide a unique subgroup of patients with schizophrenia to examine neurodevelopmental hypotheses of the disorder. For example, they may have a more severe form of the disorder and may be less affected by environmental factors that could potentially affect brain morphometry such as long-term antipsychotic exposure, substance abuse and chronic illness relative to their adult counterparts (Rapoport et al., 1999).

Anatomic brain magnetic resonance imaging abnormalities of the prefrontal cortex have been reported both in adolescents with childhood-onset schizophrenia (COS; onset of psychotic symptoms by age 13 years) (Rapoport et al., 1999) and adolescents with EOS (James

Abbreviations: AC-PC, anterior and posterior commissures; CI, confidence interval; COS, childhood-onset schizophrenia; CPT-IP, Continuous Performance Test, Identical Pairs Version; CVLT, California Learning Test; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; EOS, early-onset schizophrenia; FLAIR, FLuid Attenuated Inversion Recovery; FOV, Field Of View; IQ, Intelligent Quotient; MR, magnetic resonance; MRI, magnetic resonance imaging; NARSAD, National Alliance for Research on Schizophrenia and Depression; NSLIJ, North Shore-Long Island Jewish Health System; NV/I, Neuro Vascular Interactive; SD, standard deviation; SPSS, Statistical Package for the Social Sciences; TE, Echo Time; TR, Repetition Time; WAIS-III, Wechsler Adult Intelligence; Scale – Third Edition; WCST, Wisconsin Card Sorting Test; WISC-III, Wechsler Itelligence Scale for Children – Third Edition; WRAT-3, Wide Range Achievement Test 3.

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et al., 2004). However, the findings have been inconsistent in that some studies have not reported group differences in the volume of the prefrontal cortex (Kumra et al., 2000; Sowell et al., 2000; Giedd, 2001). This discrepancy may, in part, reflect methodological difficulties associated with using arbitrary internal landmarks and examining a large frontal region that may be insensitive to subtle neuromorphometric abnormalities (e.g., Kumra et al., 2000). To address these problems, we examined volumes of prefrontal subregions given that the frontal lobes are both structurally and functionally heterogeneous (Fuster, 2002).

Few studies have examined the regional specificity of gray matter structural alterations in the prefrontal cortex of patients with COS or EOS. One study that included 12 severely ill, treatment-refractory children with COS who were referred for an inpatient trial of clozapine examined the distribution of cortical gray matter deficits in the prefrontal cortex in adolescents with schizophrenia (Thompson et al., 2001). This study reported abnormalities primarily in dorsal frontal regions, but did not examine the neurocognitive correlates of these abnormalities. Also, the long-term effects of clozapine treatment on brain morphology remain unknown. Thus, additional studies in larger and more representative samples of adolescents with schizophrenia are needed.

In this study, we examined whether adolescents with EOS had volumetric abnormalities in discrete frontal lobe subregions representing the archicortical (superior frontal gyrus and anterior cingulate gyrus) and paleocortical systems (orbital frontal gyrus) (Sanides and Hoffman, 1969) as measured from MR images using methods for cortical parcellation adapted from Rademacher et al. (1992). Second, we examined relationships between prefrontal volumetric measures and neuropsychological test performance. Based on post-mortem (Selemon et al., 2003) and prior neuroimaging studies of adolescents with childhood-onset schizophrenia (Bertolino et al., 1998; Thompson et al., 2001) and adults with schizophrenia (Gur et al., 2000), we hypothesized that cortical gray matter deficits would be present in the superior frontal gyrus and anterior cingulate gyrus and that these would be associated with worse functioning on tests of attention and executive functioning in patients (Gur et al., 2000; Szeszko et al., 2000).

2. Methods and materials

2.1. Subjects

One-hundred children and adolescents (52 early-onset schizophrenia and 48 healthy comparison subjects) were included in this study. All patients had been treated with antipsychotic medication at the time of scanning including: quetiapine (n = 4), olanzapine (n = 8), risperidone (n = 9), ziprasidone (n = 2), clozapine (n = 5) and aripiprazole (n = 4). Four subjects were being treated with multiple antipsychotics. Six patients received prior treatment with conventional antipsychotics.

Recruitment and diagnostic procedures have been described in detail elsewhere (Kumra et al., 2004, 2005). In brief, patients were ascertained by means of screening consecutive admissions to the inpatient units of three large children's psychiatric facilities. Psychiatric diagnoses were based on clinical and structured interviews (Kaufman et al., 1997) with children and their parents, and supplemented by chart review and discussion with treatment teams. Inclusion criteria included: (1) diagnosis of schizophrenia (n = 34), schizoaffective disorder (n = 16) or schizophreniform disorder (n = 2) based on the DSM-IV criteria; (2) age 10 to 19 years; (3) absence of a documented history of mental retardation prior to onset of psychotic symptoms; (4) absence of any history of a neurological disorder that could produce psychotic-like symptoms and (5) a negative toxicology screen at the time of scanning. Patients' mean age at the onset of psychotic symptoms was 13.8 years (SD = 3.0), and their mean duration of psychosis was 2.4 years (SD = 2.0) at the time of the scan. Eighteen of 52 patients developed the onset of their psychotic symptoms prior to their thirteenth birthday and were classified as having childhood-onset schizophrenia.

Healthy volunteers matched for age, sex, and handedness were recruited from the community through medical clinics, churches, libraries, and community and recreation centers. Any physical or neurological disorder that could potentially affect brain development or a lifetime history of any Axis I psychiatric disorder in the probands was exclusionary. A diagnosis of schizophrenia or bipolar disorder in a first-degree relative was also exclusionary. Demographic characteristics for the entire subject pool are presented in Table 1. After a complete description of the study to the subjects and their parents, written assent and informed consent were obtained. The Institutional Review Board at the North Shore-Long Island Jewish Health System approved this study.

2.2. Magnetic Resonance (MR) imaging procedures

The details of the MR imaging acquisition protocols (Kumra et al., 2005), image analysis methods and anatomical definitions for the measured brain regions (Szeszko et al., 1999, 2004) have been detailed elsewhere. In brief, MR exams were conducted at the Long Island Jewish Medical Center on a 1.5T GE Neuro Vascular Interactive (NV/I) system. MR images were acquired in the coronal plane using a three-dimensional spoiled gradient echo pulse sequence prepped with an inversion pulse of 600 msec, flip angle of 20°, minimum TR and TE (default settings of the MR system), FOV = 220 mm, and matrix size of 256 × 192. This sequence produced 124 contiguous coronal slices (slice thickness = 1.5 mm) through the whole head with nominal in-plane resolution of 0.859 × 1.146 mm. For routine clinical purposes, an axial T2-weighted/proton density and FLAIR images were obtained to exclude visually detectable structural abnormalities on MRI scans.

Measurements were completed in the MEDx program (Sensor Systems, Inc., Sterling, Virginia) after alignment along the anterior and posterior commissures (AC–PC) for purposes of standardization. To remove laterality bias all 3D images were flipped randomly in the right–left axis. The action of rotation and the group status of the subjects were not annotated on any of the images. A well-trained and reliable operator completed all measurements (JW). The operator was blind to the subject's group membership during the measurement. Using the Brain Extraction Tool (Smith, 2002), MEDx (Sensor Systems, Inc., Sterling, Virginia), and an in-house program, intracranial volume was calculated for each subject.

2.3. Measurement delineation criteria

Detailed methods for measuring the anterior cingulate gyrus, superior frontal gyrus and orbital frontal cortex have been described previously (Szeszko et al., 1999). The boundaries of the anterior cingulate gyrus were (anterior, posterior, ventral, and dorsal): the tip of the cingulate sulcus, the connection of the superior and precentral sulci, the callosal sulcus, and the cingulate sulcus. The boundaries of the superior frontal gyrus were (anterior, posterior, lateral, and medial): the tip of the cingulate sulcus, the connection of the superior and precentral sulci, the superior frontal sulcus, and the cingulate

Table 1
Subject demographics.

Sample characteristic	Healthy comparison subjects (n = 48)		Schizophrenia spectrum disorders (n = 52)	
Sex (M, F)	30	18	29	23
Mean age (years, SD)	16.38	2.91	16.02	2.15
Handedness (dextral, nondextral)[a]	44	4	48	4
Parental social class (high, low)[b]	45	1	42	8
Race (Caucasian, Non-caucasian)	13	35	23	29

[a] The patient group had 1 ambidextrous person.
[b] Hollingshead Redlich Score (Hollingshead and Redlich, 1958) where 1 = highest and 5 = lowest are dichotomized into High (1, 2, 3) and Low (4, 5).