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Early-onset schizophrenia is associated with impaired adolescent development of attentional capacity using the identical pairs continuous performance test[☆]

Emily Thaden, Joseph P. Rhinewine, Todd Lencz, Hana Kester, Kelly L. Cervellione, Inika Henderson, David Roofeh, Katherine E. Burdick, Barbara Napolitano, Barbara A. Cornblatt, Sanjiv Kumra^{*}

The Zucker-Hillside Hospital, Department of Psychiatry Research 75-59 263rd Street, Glen Oaks, NY, 11004, United States

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Abstract

The authors examined performance on the Continuous Performance Test-Identical Pairs “numbers” task in adolescents with schizophrenia ($n=59$) and healthy controls ($n=55$). Adjusting for an estimate of premorbid intelligence and socioeconomic status, patients performed worse than normal controls on all three d' conditions (2-digit, 3-digit, 4-digit). However, there was a significant group-by-age-by-condition interaction ($F[4, 100]=4.69, p<.01$) indicating an interaction between development and disease state. At the simplest level of the task (2-digit) the difference between patients with schizophrenia and controls was evident at all ages; while for the more difficult levels of the task (3-digit, 4-digit), differences between groups gradually increased across the tested age span (10 to 20 years of age). Premorbid social isolation was associated with worse attentional performance in patients, suggesting a relationship and continuity with negative symptoms. These data suggest that attentional differences in adolescents with schizophrenia are better captured by different tasks at different ages. The discrepant findings of attentional impairments reported in the literature for adolescents with schizophrenia could reflect the underlying etiological complexity of the disorder that may have a variable impact on involved brain regions and neurocognitive functioning.

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[☆] From the Department of Psychiatry Research, Zucker Hillside Hospital 75-59 263rd Street, Glen Oaks, NY, 11004, United States.

^{*} Corresponding author. Tel.: +1 718 470 4161; fax: +1 718 343 1659.

E-mail addresses: ethaden@lij.edu (E. Thaden),

jrhinewi@lij.edu (J.P. Rhinewine), tlencz@lij.edu (T. Lencz),

hkester@lij.edu (H. Kester), kcervellione@lij.edu

(K.L. Cervellione), droofeh@lij.edu (D. Roofeh), kburdick@lij.edu

(K.E. Burdick), barbara@NSHS.edu (B. Napolitano),

bcomblatt@lij.edu (B.A. Cornblatt), skumra@lij.edu (S. Kumra).

1. Introduction

A large generalized neurocognitive deficit has been consistently reported in adults with schizophrenia (Heinrichs and Zakzanis, 1998) and adolescents with early-onset schizophrenia (EOS defined as onset of psychotic symptoms by age 18 years) (Asarnow et al.,

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1994; Kenny et al., 1997; Kumra et al., 2000; Oie and Rund, 1999; Rhinewine et al., *in press*; Ueland et al., 2004). In schizophrenia, deficits in both sustained attention and working memory are thought to be reflective of the genetic vulnerability for the disorder (Cornblatt and Malhotra, 2001; Egan et al., 2000) and are also thought to embody fundamental cognitive processes upon which more complex functions depend (Asarnow et al., 1994; Goldman-Rakic, 1994; Silver et al., 2003). Significant impairments in sustained attention, as measured by the Continuous Performance Test (CPT), have been reported in adults with schizophrenia (see review Cornblatt and Keilp, 1994), healthy first-degree relatives of patients with schizophrenia (Cornblatt and Keilp, 1994; Nuechterlein et al., 1994), parents of probands with childhood-onset schizophrenia (Asarnow et al., 2002), and at-risk offspring of parents with schizophrenia (Erlenmeyer-Kimling et al., 2000; Nuechterlein, 1983).

Despite the consistent pattern of impairments in sustained attention in studies of adults with schizophrenia (Cornblatt and Keilp, 1994), studies of EOS have yielded conflicting results. Null findings have been reported in EOS patients compared to non-psychotic emotionally disturbed adolescents using the CPT (Erickson et al., 1984). Null findings have also been found in EOS patients compared to healthy adolescents using the Degraded Stimulus version of the CPT (DS-CPT: Nuechterlein, 1983) (Ueland et al., 2004) and using comparable measures of sustained attention (Kravariti et al., 2003; Oie et al., 1999). In contrast, significant differences in CPT-IP performance have been reported in two samples comparing adolescents with schizophrenia and healthy controls (Cosway et al., 2002; Rhinewine et al., *in press*). These discrepant results suggest that further investigation of attentional function in adolescents with schizophrenia is warranted.

Sample characteristics including premorbid intellectual ability, clinical presentation, and medication effects have been implicated to account for these inconsistencies; however, in studies that have employed adequate designs to assess the impact of clinical and demographic factors, these effects do not appear sufficiently robust to account for the discrepant results in the literature (Cosway et al., 2002; Erickson et al., 1984; Ueland et al., 2004). Also, the inconsistencies across samples of adolescents with schizo-

phrenia could be due to the varying task demands of different versions of the CPT. The DS-CPT produces its processing load on attention by burdening stimulus encoding and perceptual analysis, whereas the CPT-IP increases task difficulty by presenting increasingly complex stimuli and placing additional demands on working memory (Cornblatt and Keilp, 1994). In studies of adult patients with schizophrenia, parametric manipulations of stimulus difficulty have demonstrated dissociable effects of stimulus encoding versus maintenance in working memory (Lencz et al., 2003). Thus, in adolescents (Ueland et al., 2004) as compared to adults with schizophrenia (Cornblatt and Keilp, 1994; Nuechterlein, 1991), the DS-CPT may be relatively insensitive or not sufficiently demanding/complex to discriminate group differences (Rund et al., 1998).

The inconsistency of results across studies could also reflect an incomplete course of normative maturational events taking place during adolescence (Kravariti et al., 2003; Weinberger, 1987). Critical events of postnatal brain maturation, particularly of the glutamatergic systems (Olney et al., 1999) and prefrontal inhibitory circuits (Lewis et al., 2004), take place during late adolescence and coincide with the typical age of onset of prodromal and/or active symptoms for most adults with schizophrenia. If the pathophysiology of schizophrenia involves changes in these circuits during late adolescence, then attentional impairments and working memory dysfunction as evidenced by impaired CPT performance may become evident during this time period (Morey et al., 2005; Oie et al., 1999; Rund et al., 1998). Understanding of the evolution of cognitive impairments in adolescents with schizophrenia may contribute to effective rehabilitation interventions, as well as help identify adolescents who may be in the prodromal phase of the illness. Lastly, schizophrenia is thought to be a heterogeneous disorder that likely stems from complex variable etiologic factors (Cornblatt and Malhotra, 2001), and thereby, the illness would have a variable impact on involved brain regions and neurocognitive function across people with the disorder.

This study represents an extension of an earlier investigation in which we reported group differences in processing capacity on the most difficult processing load condition of the CPT-IP in adolescents with schizophrenia relative to healthy controls (Rhinewine

et al., in press). In this report, we examined data from two additional conditions that were less difficult in terms of processing load and employ two outcome measures. The present study investigated the pattern of CPT-IP performance in adolescents with EOS and healthy controls, as well as the correlates of sustained attention as measured by the CPT-IP. We hypothesized that 1) the EOS patients would show less improvement in attentional performance with increasing age relative to healthy controls and that this would be more pronounced as condition difficulty increased, and 2) CPT-IP performance would relate to premorbid adjustment and negative symptom severity (social avoidance), based on previous data collected from adolescents at genetic risk for schizophrenia (Cornblatt et al., 1992).

2. Methods and materials

2.1. Participants

The North Shore-Long Island Jewish Health System Institutional Review Board approved all procedures, including recruitment and consent. Written, informed consent/assent was obtained from participants and their legal guardians. Fifty-nine adolescents diagnosed with schizophrenia, schizoaffective, or schizophreniform disorder (EOS group) and 55 age and gender-matched normal controls (NC group) who completed the Early-Onset Schizophrenia: Neuroimaging Studies at the Zucker-Hillside Hospital in Glen Oaks, NY by March 2005 are included in this paper (Kumra et al., 2005). From the whole sample of 76 EOS and 78 NC participants, data was not available for 17 EOS and 23 NC subjects due to scheduling problems, machine failure, lack of cooperation/motivation during test administration due to severity of illness, and withdrawal of consent to participate in the study. The original sample did not differ from this study sample on age, sex, race, parental socioeconomic status, or handedness at the $p < .10$ level.

The recruitment, screening, and testing procedures for patients and healthy controls have already been described in detail (Kumra et al., 2004; Rhinewine et al., in press). In brief, healthy controls who reported prior psychiatric illness/treatment, past substance

abuse, and history of schizophrenia or bipolar disorder in first-degree relatives were excluded. An in-person screening for neurological impairments and DSM-IV psychiatric diagnoses (American Psychiatric Association, 1994) using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) was conducted. Healthy controls were matched to patients on the basis of age, gender, ethnicity and handedness but not on factors potentially related to effects of illness such as IQ (Meehl, 1970).

Patients with a history of mental retardation prior to onset of psychosis or neurological disorder were excluded. Diagnostic assessments were conducted by a research psychiatrist, psychologist, or a clinical nurse practitioner using a screening questionnaire for autistic symptoms (Lord et al., 1994) and a structured interview (K-SADS-PL; Kaufman et al., 1997). A best-estimate diagnosis was made from all available information including the structured interview, information from prior hospitalizations and outpatient treatment, and a review of the medical records.

2.2. Measures

The CPT-IP was given as part of a larger test battery (see Rhinewine et al., in press). Test sessions were conducted toward the end of hospitalization, at least two weeks after initiation of antipsychotics for subjects who were inpatients, and upon advice from hospital staff that the patient was stabilized.

In the Continuous Performance Test-Identical Pairs (CPT-IP), a target is defined as the second stimulus in any pair of identical stimuli; therefore, the participants must hold each stimulus in working memory to compare it with the stimulus immediately following it (Cornblatt and Keilp, 1994). To enhance feasibility of the testing procedure, only the “numbers” (i.e. not “shapes”) portion of the task was administered in three different processing-load conditions (2-digit, 3-digit, or 4-digit numbers). For each condition, 150 trials of numbers are presented at a rate of one trial per second: the stimulus is presented for 50 ms followed by a blank screen for 950 ms (Cornblatt et al., 1988). No breaks were given except after the completion of the 25 practice trials (all 3-digit), and the conditions were administered in the same order for each participant (practice

session, 2-digit, 3-digit, 4-digit). Participants were instructed to hold their finger down on the mouse button and to release the button briefly if and only if two numbers in a row were identical (i.e. “3674” followed by “3674”).

For the purposes of this study, the primary outcome variable for each of the three conditions was d' (d-prime), a signal detection index considered to measure discriminability. The greater the d' , or the proportion of hits (two trials in a row that are identical) to false alarms (two trials in a row that are similar but not identical), the better the performance. D' is seen as a measure of attentional capacity independent of differences in response rates (Bergman et al., 1995). Although the CPT is usually associated with processing capacity or vigilance, there is a general comparator function of the central executive in working memory that the CPT-IP assesses because information in working memory (i.e., a given CPT-IP stimulus) must be held “online” in order to determine when to respond (Pukrop et al., 2003).

The secondary outcome variable for each of the three conditions was β (transformed to the natural logarithm scale, $\ln\beta$). $\ln\beta$ measures shifts in response style or tendency to over-respond versus under-respond (the higher the value of $\ln\beta$ the more cautious the response style). Previous studies of adults suggest that patients with schizophrenia show a high rate of random responding that may reflect gross attentional dyscontrol (Cornblatt et al., 1989).

Measures of symptomatology that were obtained concurrently with the neuropsychological assessments for correlative analyses included: The Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1961), the Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1982), and the Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982). The Wide-Range Achievement Test, 3rd edition reading subtest (WRAT-3; Wilkinson, 1993) was administered to obtain an estimate of premorbid intelligence (Cosway et al., 2002). Parental socioeconomic status was assessed using the Hollingshead system and dichotomized so 1–3 qualified as ‘high socioeconomic status’ and 4–5 as ‘low socioeconomic status’ (Hollingshead and Redlich, 1958). Information regarding past and current antipsychotic treatment was obtained, and drug doses were converted into chlorpromazine equivalents for atypical (Woods, 2003) and typical

(Hales and Yudofsky, 2003) antipsychotics to estimate lifetime and current antipsychotic exposure.

2.3. Data analysis

Statistical analyses were performed using the SPSS version 11.0 or SAS 8.02. For demographic comparisons, t -tests and Chi-square tests were performed as appropriate. To distinguish attentional deficits from a generalized intellectual impairment, we included an estimate of premorbid intelligence (WRAT-3) as a covariate in our analyses (Cosway et al., 2002).

To test a hypothesis that there would be a differential performance pattern depending on processing load (i.e., across conditions) and age in normal controls versus early-onset schizophrenia adolescents, a Repeated Measures Analysis of Covariance (RM ANCOVA) was conducted. In this model, group status (EOS, NC) was the between-subject factor and condition (2-digit, 3-digit, 4-digit) was the within-subject repeated factor; the RM ANCOVA was conducted separately for d' and $\ln\beta$. The factors entered to predict the repeated measure were: group status, age at time of testing, parental socioeconomic status, premorbid intelligence, group-by-condition interaction, group-by-age interaction, and a group-by-age-by-condition interaction. A significant group-by-age-by-condition interaction would support this hypothesis. Subsequently, pairwise correlations were conducted to study the relationship between age and performance adjusting for premorbid intelligence in each group for each condition.

Spearman (for skewed variables) and Pearson correlations were conducted between clinical variables and each d' condition for the patient group. Clinical variables were selected based upon a developmental model relating poor attention to social skills in at-risk adolescents (Cornblatt et al., 1992). Backward conditional regressions were subsequently conducted, where factors significant at $p < .10$ level were retained in the model to examine the relative contribution of particular clinical variables on d' performance. Variable selection for the models was based on correlative analyses and considerations of parsimony and multicollinearity, meaning, that for measures tapping into the same underlying construct, only one factor was entered into the model.

3. Results

3.1. Sample

The EOS group and NC group did not differ on age, sex, race, or handedness (see Table 1). At a trend level, normal controls had a higher parental socioeconomic status than EOS patients. As expected, the groups also differed on a measure of premorbid intelligence wherein normal controls scored significantly higher than patients. Premorbid intelligence, parental socioeconomic status and age were retained as covariates in the remaining analyses.

For patients, the median age of the onset of psychosis was 14.00 years (range=7–18), and the median duration of psychosis was 1.90 years (range=.25–10.25). Almost all patients were receiving antipsychotics at time of testing ($n=55$).

3.2. CPT-IP performance

In the EOS group, the mean (standard deviation) for each d' condition was: 2-digit=2.2 (.92), 3-digit=1.57 (.87), and 4-digit=.75 (.72). In the NC group, the mean (standard deviation) for each d' condition was: 2-digit=3.33 (.51), 3-digit=2.79 (.95), and 4-digit=1.7 (.88).

Two RM ANCOVAs were conducted separately to test if CPT-IP performance on d' and $\ln\beta$ varied as a function of group status (EOS, NC) and/or age across the three conditions (2-digit, 3-digit, 4-digit), while adjusting for premorbid intellectual ability and parental socioeconomic status. A significant three-way interaction (age-by-group-by-condition) was revealed for d' ($F[4, 100]=4.69, p<.01$), in

which premorbid intelligence was also significant to the repeated measure ($F[1, 100]=15.07, p<.001$) but parental SES was not. Fig. 1 shows the influence of age and group status on the d' values across the three conditions.

To better characterize the three-way interaction, pairwise correlations examined the relationship between age and d' performance controlling for premorbid intelligence in each group for each condition. In normal controls, d' scores were positively correlated with age across all conditions. However, in the patient group, age was not significantly correlated to d' conditions, except 4-digit d' attained a trend ($p=.06$) (See Fig. 1). Therefore, for the 2-digit condition, main effects of group and age significantly plotted the data, while for the 3-digit and 4-digit conditions group-by-age interactions significantly plotted the data (confirmed using regression analyses predicting to each d' condition from age, group, age-by-group, parental SES, and premorbid intelligence; data not presented.). It was not possible to differentiate at what age the two groups differed for either the 3-digit and 4-digit levels of difficulty since the confidence intervals for both conditions were quite wide and overlapped across all ages for both conditions. Lastly, curve estimations were run to explore whether the relationship between age and each d' condition was a linear or quadratic fit; R^2 and p values revealed that both lines comparably fit the data (data not presented).

In the RM ANCOVA for $\ln\beta$ conditions, no factors remained in the model except condition (performance was significantly worse as conditions became more difficult); therefore, this performance measure was not examined in subsequent analyses.

Table 1

Characteristics of adolescent patients with schizophrenia-spectrum disorders and healthy control subjects

	Patient group ($N=59$)	Healthy control group ($N=55$)	Analysis		
	N	N	χ^2	df	p
<i>Characteristics</i>					
Sex (male/female)	35/24	27/28	1.20	1	.27
Ethnicity (white/not white)	24/35	18/37	.77	1	.38
SES (high/low)	49/10	52/3	3.72	1	.05
Handedness (right/not right)	56/3	51/4	.29	1	.86
	Mean (SD)	Mean (SD)	t	df	p
Age at testing	15.98 (2.10)	15.74 (2.21)	.61	112	.54
WRAT-3 scaled	95.23 (15.91)	108.40 (9.90)	-5.04	104	<.01*
Full-scale IQ	84.04 (15.53)	112.47 (13.35)	-9.85	104	<.01*

¹ Socioeconomic status, Hollingshead system (Hollingshead and Redlich, 1958), where 1–3="high" and 4–5="low".

² Wide Range Achievement Test (WRAT-3) Reading subtest (Wilkinson, 1993).

³ Full-scale IQ scores estimated from the Vocabulary, Similarities, Picture Completion, Block Design, Arithmetic and Coding subscales (Donders, 1997) of the Wechsler Intelligence Scale for Children—Third Edition (WISC-III; Wechsler, 1991), or the Similarities, Picture Completion, Block Design, Arithmetic, Coding, Information and Digit Span subscales (Axelrod et al., 2001) of the Wechsler Adult Intelligence Scale—Third Edition (WAIS-III; Wechsler, 1997) for subjects over the age of 16.

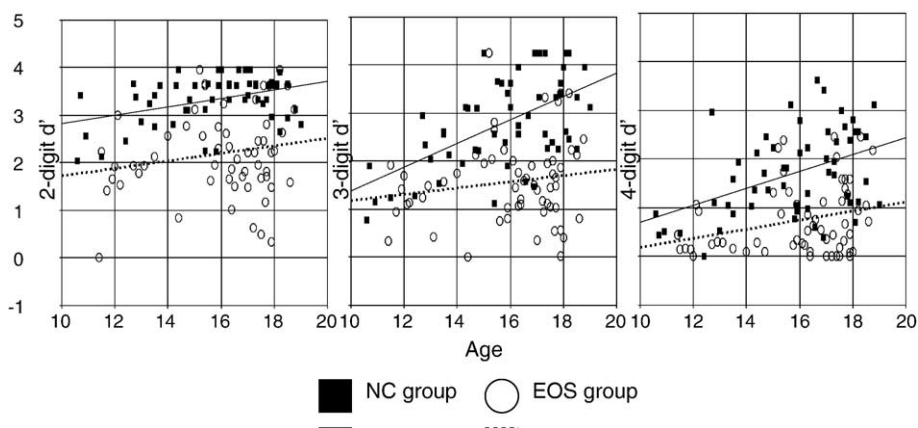


Fig. 1. CPT-IP d' values in relation to age in 55 normal controls (NC) and 59 adolescents with early-onset schizophrenia (EOS). Pairwise correlations adjusting for premorbid intelligence (WRAT-3 reading scores; Wilkinson, 1993) were conducted in the NC group for 2-digit d' ($r=.35, p<.05$), 3-digit d' ($r=.60, p<.001$), and 4-digit d' ($r=.42, p<.01$), and in the EOS group for 2-digit d' ($r=.21, p=.14$), 3-digit d' ($r=.18, p=.20$), and 4-digit d' ($r=.26, p=.06$).

3.3. Relationship of CPT-IP performance and clinical correlates in patients

Next, correlative analyses were conducted to explore what clinical variables related to CPT d' performance. Based upon the literature (Comblatt and Keilp, 1994), the variables explored for each d' condition were: lifetime antipsychotic exposure, duration of psychosis, premorbid IQ, SANS total and asociality subscores, and PAS total and social subscore (see Table 2).

Table 2
Correlations of clinical characteristics to d' performance in 59 adolescents with early-onset schizophrenia

Variable	2-digit d'	3-digit d'	4-digit d'
Duration of psychosis ¹	-.08	.01	-.07
Lifetime medication exposure ^{1,2}	-.26*	-.22	-.14
SANS total score ³	-.25	-.14	-.13
SANS asocial subscore ³	-.27*	-.12	-.13
PAS total score ⁴	-.43**	-.41**	-.42**
PAS social isolation subscore ⁴	-.34**	-.33*	-.37**
WRAT-3 reading scores ⁵	.51**	.44**	.24

¹ Spearman, rather than Pearson, correlations were conducted due to skewness.

² Chlorpromazine equivalents calculated for atypical (Woods, 2003) and typical (Hales and Yudofsky, 2003) antipsychotics.

³ Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1982).

⁴ Premorbid Adjustment Scale, social isolation subscale (Cannon-Spoor et al., 1982).

⁵ Wide Range Achievement Test (WRAT-3) Reading subtest (Wilkinson, 1993).

Subsequently, we examined what clinical correlates predicted to d' performance for each condition using backward conditional regressions where factors were retained in the model if $p<.10$. Based on the model of at-risk adolescents (Comblatt and Keilp, 1994) and correlative analyses, we created a model in which age, premorbid social isolation, premorbid diagnosis of ADHD, premorbid intelligence, current social avoidance, and lifetime antipsychotic exposure were included. Estimated premorbid intelligence, premorbid social isolation, and SANS asociality subscore predicted to 2-digit d' accounting for 45% of the variance ($F(3,45)=11.40, p<.001$). In addition, estimated premorbid intelligence and age predicted 3-digit d' values ($R^2=.35, F(2,45)=11.52, p<.001$), and estimated premorbid intelligence, premorbid social isolation, and age predicted 4-digit d' values ($R^2=.26, F(3,45)=4.81, p<.01$).

4. Discussion

After adjusting for substantial differences in estimated premorbid intelligence, patients were still noted to have significant attentional deficits relative to normal controls on all d' conditions. The observed attentional deficit appears to represent a true impairment in processing capacity rather than a group difference in response style or motivation, as patients did not differ from normal controls on $\ln\beta$, and the deficit between groups remained relatively equal across conditions. In light of the negative findings in a similar sample using the DS-CPT (Ueland et al.,

2004), which may have been due to insufficient task difficulty, we predicted that if the CPT-IP tapped into the same underlying construct as the DS-CPT, then we would find diminishing group differences as attentional demands declined across conditions. However, since we did not find any diminished group effect across conditions, our findings are consistent with a hypothesis that the CPT-IP is a measure of sustained attention that relies on working memory, in contrast to the DS-CPT, which relies on perceptual analysis. Alternatively, the differences in attentional impairments across different samples of adolescents with schizophrenia may simply reflect the underlying etiologic heterogeneity of the disorder.

In this sample of adolescents with EOS, we found that the 2-digit condition adequately captures attentional deficits, which is different from the standard used in adults with schizophrenia and adolescents at-risk for schizophrenia (i.e. 4-digit d'). However, as supported by the three-way interaction (group-by-age-by-condition), the more difficult conditions provide information about adolescent development of sustained attentional capacity. Healthy controls, but not patients, showed improved test performance with increasing age (range, 10 to 20 years) on each condition. For normal adolescents, performance on the CPT appears to progressively improve through adolescence (Fig. 1) and achieve performance commensurate with adults during late adolescence (Pukrop et al., 2003), the most common age of onset for schizophrenia (Lewis et al., 2004).

Group-by-age interactions were only present in the conditions that required a higher processing load (3-digit and 4-digit), supporting a hypothesis that the conditions requiring a higher attentional capacity may more clearly differentiate the developmental trajectory between healthy adolescents and adolescents with EOS. This idea was further supported when 3-digit d' was regressed on 2-digit d' and the residuals were explored: the slope for age increased in normal controls and decreased in patients as compared to the 3-digit results, reinforcing that the relationship between increased attentional capacity and age was a developmental effect (data not presented). Based upon the idea that the 3-digit and 4-digit conditions encapsulate all the skills necessary to accomplish the 2-digit condition (e.g., maintenance and updating), yet have a different relationship with group status and

age, the differing performance across conditions is most likely due to increased attentional capabilities and/or increased speed of encoding acquired with maturation (Elvevag et al., 2000). Therefore, these data support an interaction between development and disease state, such that for those with schizophrenia, pre- and young adolescents are best differentiated with the simplest version of the task; mid- and late adolescents with the intermediate version, and perhaps adults are best differentiated with the most difficult version. Less acutely ill individuals, including those at-risk with the disease, might require more difficult versions of the task for differentiation from early adolescence through adulthood.

We propose that abnormalities in the development of frontostriatal circuits that subserves working memory may be central to the pathophysiology of schizophrenia (Lewis et al., 2004; Manoach, 2003) and that these neurodevelopmental irregularities are perceptible via the CPT-IP in adolescents with EOS. White matter forms the structural basis of connectivity in the brain. We have shown a pattern of abnormal subcortical frontal white matter development in adolescents with schizophrenia using diffusion tensor imaging (Kumra et al., 2005) that are similar to the frontal subcortical regions that have been implicated in the performance of the CPT-IP in healthy adults using SPECT (Keilp et al., 1997). Furthermore, during working memory tasks significant hypoactivation in schizophrenic patients compared to normal controls was found in similar regions, including the dorsolateral prefrontal region and anterior cingulate, using voxel-based morphometry (Manoach et al., 2000; Salgado-Pineda et al., 2004). Thus, a pathophysiological process in EOS involving disruption of subcortical frontal white matter integrity may have an important role in the attentional deficits tapped by the CPT-IP (Cornblatt and Keilp, 1994).

We do not believe that exposure to antipsychotic medications accounted for age-by-group effects since this variable was not retained in our final models. The correlation between lifetime medication exposure and 2-digit d' performance may be attributable to severity of illness; for instance, those who are the most ill are most likely to have the highest medication exposure and worse performance. Furthermore, previous studies have suggested that exposure to antipsychotic medications does not substantially affect performance on the CPT (Bergman et al., 1995; Erickson et al.,

1984), and novel antipsychotics have generally been found to minimally improve sustained attention (Harvey and Keefe, 2001; Keefe et al., 1999).

Our results are congruent with findings from studies of adolescents at genetic risk for developing schizophrenia: premorbid intelligence (Cosway et al., 2002) and premorbid social isolation (Cornblatt and Keilp, 1994) were associated with d' performance. These data are consistent with a developmental model in which an impaired capacity to process attention-demanding information in the environment—especially subtle and highly complex interpersonal cues and communications—leads to symptom exacerbation (experiencing stress) or to social isolation and poor development of social skills (avoiding stress) (Cornblatt et al., 1992). Furthermore, the observed association of attentional problems and premorbid social deficits perhaps suggests a relationship and continuity with negative symptoms. Although we did not find a relationship between negative symptoms and attentional problems in this study, as we would have predicted from longitudinal data of children at genetic high-risk for the development of schizophrenia (Cornblatt et al., 1992), this may be a limitation of the cross-sectional design. Due to the relative rarity of early-onset schizophrenia (Cannon et al., 2002), it would be difficult to conduct a prospective study of adolescents pre- and post-onset of psychosis to establish the temporal sequence of these relationships.

It should be noted that the observed attentional deficits in this cross-sectional study occurred in the context of a large group mean difference in premorbid intellectual ability, and thus, the presence of attentional problems in the affected group was not surprising. Although in the current study the difference in premorbid intelligence between groups was slightly larger than what has been reported in previous EOS samples (Erickson et al., 1984; Ueland et al., 2004), we adjusted for premorbid intelligence in the analyses. Significance was not lost by controlling for premorbid intelligence, which indicates that attentional deficits are distinguishable from the generalized intellectual impairment present in similar samples of adolescents with EOS.

The relationship between attentional problems, which are thought to emerge early in the course of childhood schizophrenia (Cornblatt et al., 1992), and the severity of the global cognitive impairments in

adolescents with schizophrenia is unknown. Longitudinal studies are needed to assess whether childhood attentional disturbances, as reflected by tasks such as the CPT-IP, could broadly interfere with cognitive development and exacerbate the decline in cognitive function typically observed after the onset of psychosis in adolescents (Gochman et al., 2005). Our data would suggest that further examination of attentional deficits using the CPT-IP in a less cognitively impaired sample of adolescents with EOS is needed to further establish the importance of attentional impairments in adolescents with schizophrenia. Lastly, there were a significant number of recruited subjects in both the affected and control groups that did not complete the testing procedures. We were not able to obtain IQ testing for the majority of these subjects. Thus, we are not able to assess whether the inclusion of these data would have changed the findings of the study.

In summary, we found that impairments in attentional performance using the CPT-IP become more pronounced with increasing age in adolescents with schizophrenia. More severe attentional deficits were related to lower premorbid intelligence, increased premorbid social isolation, and to social avoidance at the time of testing. This pattern of findings is consistent with a developmental model that abnormalities in the development of frontostriatal circuitry during late adolescence (Kumra et al., 2005; Morey et al., 2005) may account for a broad range of cognitive and social deficits in EOS (Erlenmeyer-Kimling et al., 2000).

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