

Altered Cognitive Development in the Siblings of Individuals With Schizophrenia

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Deanna M. Barch¹, Rachel Cohen², and John G. Csernansky³

¹Departments of Psychology, Psychiatry, and Radiology, Washington University in St. Louis; ²Department of Psychology, Washington University in St. Louis; and ³Department of Psychiatry, Northwestern University

Abstract

Our goal in the current study was to further investigate the late neurodevelopmental hypothesis of schizophrenia by examining cross-sectional, age-related changes in cognitive function among young adult (a) siblings of individuals with schizophrenia ($n = 66$), (b) healthy control subjects ($n = 77$), and (c) the siblings of healthy control subjects ($n = 77$). All subjects participated in a battery of tasks in four domains: verbal IQ, working memory, episodic memory, and executive function. We found significant group differences in the relationships between age and performance in working memory and episodic memory, with similar patterns for executive function and verbal IQ. The siblings of individuals with schizophrenia showed impaired performance in working memory, episodic memory, and executive function. In addition, healthy control subjects and their siblings showed age-related improvements in all four cognitive domains, whereas the siblings of individuals with schizophrenia showed this result for verbal IQ only.

Keywords

schizophrenia, cognition and emotion, developmental psychopathology

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For many years, researchers have conceptualized schizophrenia as a neurodevelopmental disorder. Theories of early neurodevelopmental aberration (Murray, Jones, & O'Callaghan, 1991; Rapoport, Addington, Frangou, & Psych, 2005) have focused on errors in brain development that occur during the pre- and perinatal period, which may be due to abnormalities in mechanisms such as neuronal migration (Fatemi & Folsom, 2009). Theories of late neurodevelopmental aberration (Karlsgodt et al., 2008) have focused on disruptions in the maturation of neural circuits during the peripubertal period, such as cortical synaptic pruning (Feinberg, 1982, 1990) and gray/white matter growth (Pantelis et al., 2005). In addition, 2-hit models have postulated that early neurodevelopmental events set the stage for, or create a vulnerability for, later irregularities in development (Keshavan, 1999; Keshavan & Hogarty, 1999). Our goal in the current study was to address questions primarily related to the late neurodevelopmental theory of schizophrenia by examining the developmental trajectory of cognitive function in the siblings of individuals with schizophrenia, who are at increased risk for developing schizophrenia (Gottesman, 1991).

Theories of early neurodevelopmental abnormalities in schizophrenia have predicted that cognitive, behavioral, and neuroanatomical antecedents of schizophrenia should be present from a very early age in individuals who develop schizophrenia and then remain static until the onset of the acute syndrome. Such theories are consistent with the large body of data, including the work of Walker, Savoie, and Davis (1994), that has shown subtle neuromotor deficits in toddlers who eventually develop schizophrenia. In addition, other researchers have reported cognitive deficits, in particular, disproportionate deficits in working memory and selective attention, in children who go on to develop schizophrenia (Cornblatt, Obuchowski, Roberts, Pollack, & Erlenmeyer-Kimling, 1999; Niendam et al., 2003).

Late neurodevelopmental theories of schizophrenia are more in keeping with the postpubertal onset of

Corresponding Author:

Deanna M. Barch, Departments of Psychology, Psychiatry, and Radiology, Washington University in St. Louis, Campus Box 1125, One Brookings Dr., St. Louis, MO 63130
E-mail: dbarch@artsci.wustl.edu

schizophrenia. Also, the literature on normative cognitive development during puberty has provided potential candidate mechanisms for disruptions that could presage the onset of schizophrenia. A wealth of researchers have pointed to the maturation of a range of cognitive functions across the course of puberty, including working memory, executive control, and specific aspects of attention and episodic memory function (e.g., Davidson, Amso, Anderson, & Diamond, 2006; Luna, Garver, Urban, Lazar, & Sweeney, 2004). It is important to note that these are all cognitive domains known to be impaired in schizophrenia (Barch, 2005). Human and nonhuman animal data have begun to elucidate the neural mechanisms that underlie the development of cognition during puberty. For example, research has shown that gray matter development is characterized by periods of growth followed by gray matter volume reductions driven by selective synaptic pruning (Huttenlocher & Dabholkar, 1997; Rakic, Bourgeois, & Goldman-Rakic, 1994). The timing of gray matter development varies across brain regions (Casey, Giedd, & Thomas, 2000; Lenroot & Giedd, 2006). Gray matter growth peaks relatively late in the dorsolateral prefrontal cortex (Giedd et al., 1999; Gogtay et al., 2004), a region thought to be critical for executive control, working memory, and many aspects of episodic memory as well.

In contrast, white matter growth is characterized by a relatively linear increase from childhood to adulthood (Giedd et al., 1999), with increases in white matter linked to improvements in cognitive function with age (Edin, Macoveanu, Olesen, Tegner, & Klingberg, 2007; Nagy, Westerberg, & Klingberg, 2004; Olesen, Nagy, Westerberg, & Klingberg, 2003). In addition, a number of studies have shown that functional activation in dorsolateral prefrontal regions, in response to working memory and cognitive control demands, increases with age (Brahmbhatt, McAuley, & Barch, 2008; Casey et al., 1995; Ciesielski, Lesnik, Savoy, Grant, & Ahlfors, 2006; Klingberg, 2006; Klingberg, Forssberg, & Westerberg, 2002; Schweinsburg, Nagel, & Tapert, 2005) such that activity is greater in adults than in children, although a few studies have shown greater activation in children than in adults (Klingberg et al., 2002; Schweinsburg et al., 2005; Tsujimoto, Yamamoto, Kawaguchi, Koizumi, & Sawaguchi, 2004).

Given this data on normative developmental mechanisms, late neurodevelopmental hypotheses of schizophrenia have postulated the occurrence of abnormalities of synaptic pruning (enhanced; Feinberg, 1982), abnormal white matter growth (e.g., impaired myelination; Bartzokis, 2002), and accompanying abnormalities in age-related improvements in cognitive function (Karlsgodt et al., 2008). It is logical that the critical test of late neurodevelopmental hypotheses of schizophrenia is to examine abnormalities in the longitudinal course of development. Giedd et al. (2008) have recently argued

elegantly for the need to examine such neurodevelopmental trajectories as indicators of risk for neuropsychiatric disorders. However, few researchers have examined trajectories of cognitive development in individuals at risk for schizophrenia. Cornblatt et al. (1999) found that attention deficits were present very early in children who went on to develop schizophrenia and that the severity of these deficits was stable across the measurement period. Furthermore, at least one other study has shown that IQ deficits present in high-risk offspring actually diminished with development, rather than increasing across the course of development (Goodman, 1987).

In contrast, Worland, Weeks, Weiner, and Schechtman (1982) found that verbal IQ showed a decline from age 8 to age 16 in the offspring of individuals with schizophrenia. In addition, Cosway et al. (2000) found that high-risk individuals whose symptoms increased also showed a decline in IQ. Moreover, Kremen et al. (1998) found that IQ decline from ages 4 to 7 predicted adult-onset psychosis, and MacCabe et al. (2013) found that decline in verbal ability from ages 13 to 18 predicted increased risk for psychosis. It is interesting that the Worland et al. study was consistent with a 2-hit model, given that the offspring of individuals with schizophrenia showed early IQ impairment followed by further decline across puberty. Thus, the literature on cognitive development in relationship to schizophrenia risk is mixed as best, with both positive and negative results, and with few studies focusing on more than a single cognitive domain. Furthermore, recent research has shown that decline in temporal lobe gray matter and verbal IQ across late childhood into adolescence predicted an increase in psychosis in individuals with 22q11 deletion syndrome (Kates et al., 2011), a syndrome associated with an enhanced risk of developing schizophrenia.

Providing further evidence for the late neurodevelopmental theory, research has shown that children with childhood-onset schizophrenia have deviant developmental trajectories, with both decreased white matter growth (Gogtay et al., 2008; Vidal et al., 2006) and increased frontal gray matter loss (Vidal et al., 2006). Similarly, first-episode patients with schizophrenia, as well as prodromal individuals, have been shown to have enhanced thinning of the dorsal surfaces of the frontal lobes (Sun, Stuart, et al., 2009). In addition, research has indicated that genetically high-risk subjects demonstrate greater reductions in right frontal lobe volumes over time, although this abnormality did not distinguish between high-risk subjects who did and did not develop schizophrenia (Job, Whalley, Johnstone, & Lawrie, 2005). Finally, Gogtay et al. (2007) examined cortical brain development in the nonpsychotic siblings of individuals with childhood-onset schizophrenia between the ages of 8 and 28. These researchers found evidence of gray matter loss in frontal and superior temporal regions that started at age 8 but disappeared by age 20 in frontal regions, particularly

among those with improved function. However, although the Gogtay et al. sample did contain some younger children, the mean age for the first scan was 16, and only healthy siblings (no psychosis or schizotypal personality disorder) were included, which could have led to a sample less saturated with risk for schizophrenia.

In the current study, our goal was to shed further light on early versus late neurodevelopmental hypotheses of schizophrenia by examining the developmental trajectory of cognitive function in the siblings of individuals with schizophrenia compared to control subjects and their siblings. We examined age-related changes in four cognitive domains (working memory, executive control, episodic memory, and verbal IQ) during puberty and early adulthood in the siblings of individuals with schizophrenia as compared to healthy control subjects and their siblings. An early neurodevelopmental hypothesis of schizophrenia would predict that we should see cognitive impairments even at our earliest ages among the siblings of individuals with schizophrenia, whereas it would not predict either altered age-related changes in cognitive function or a further enhancement of group differences in cognitive function with increasing age. In contrast, a late neurodevelopmental hypothesis of schizophrenia would predict abnormalities in the normal patterns of age-related improvement in cognitive function across the course of puberty into adulthood and an enhancement of group differences in cognitive function with increasing age. Finally, a 2-hit model would predict the presence of cognitive impairments prior to puberty as well as impaired age-related maturation of cognitive function and enhanced group differences in cognition as a function of increasing age.

Method

The subjects for this study were recruited through the Conte Center for the Neuroscience of Mental Disorders (CCNMD) at Washington University School of Medicine in St. Louis, tested at one time point (a cross-sectional design), and included: (a) nonpsychotic siblings of individuals with schizophrenia according to *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association, 1994) criteria ($n = 66$, age range = 11–27), (b) healthy control participants ($n = 77$, age range = 13–30), and (c) the siblings of healthy controls ($n = 77$, age range = 11–27). A subset of these subjects was included in a previous report on cognition and symptoms in the siblings of patients with schizophrenia (Delawalla et al., 2006). Siblings were full siblings, based on self-report. All subjects gave written informed consent for participation after being provided with a complete description of the risks and benefits of participating in the study.

The probands with schizophrenia (by which we recruited the siblings of individuals with schizophrenia) all had a confirmed diagnosis of schizophrenia or schizoaffective disorder, using the methods described in the next paragraph. Although the probands with schizophrenia completed all of the same cognitive and clinical assessments as the other three groups, they were not included in the current project because their age range was not sufficiently young enough to enable examination of developmental changes. We included healthy control subjects as well as their siblings to address confounds associated with differential recruitment and screening criteria for control subjects versus the siblings of patients. Our control subjects were required to have no family history of psychosis and no personal history of any Axis I disorder. However, we could not impose such a criterion on the siblings of individuals with schizophrenia because many have past depression or anxiety and to exclude such individuals would result in an unrepresentative sample. Thus, we also recruited the siblings of control subjects and allowed them to have the same personal history of nonpsychotic Axis I disorders as the siblings of individuals with schizophrenia. Thus, the two sets of siblings were recruited with the same methods and inclusion/exclusion criteria, other than the diagnosis of their sibling.

All subjects were diagnosed using *DSM-IV* criteria on the basis of a consensus between a research psychiatrist who conducted a semistructured interview and a trained research assistant who used the Structured Clinical Interview for *DSM-IV* Axis I Disorders (First, Spitzer, Gibbon, & Williams, 2001). Subjects were excluded if they (a) met *DSM-IV* criteria for substance dependence or severe/moderate abuse during the 6 months preceding assessment; (b) had a clinically unstable or severe medical disorder, or a medical disorder that confounded the assessment of psychiatric diagnosis or rendered research participation dangerous; (c) had a history of head injury with documented neurological sequelae or loss of consciousness; or (d) met *DSM-IV* criteria for mental retardation (mild or greater in severity).

The individuals with schizophrenia were all outpatients at the time of their assessment and were stabilized on antipsychotic medication for at least 2 weeks before participating in the study. Healthy control subjects were recruited using local advertisements in the same community and were required to have no lifetime history of Axis I psychotic or major mood disorders and no first-degree relatives with a psychotic disorder. Potential siblings of individuals with schizophrenia or siblings of healthy control subjects were excluded if they had a lifetime history of any *DSM-IV* Axis I psychotic disorder but no other *DSM-IV* Axis I disorders.

Clinical and cognitive assessments

Psychopathology and cognitive function were assessed as previously described (Delawalla et al., 2006; Harms et al., 2007). Briefly, psychopathology was assessed using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983a), the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1983b), the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 1999), and the Chapman psychosis proneness scales (Chapman, Chapman, & Kwapil, 1995). The raw scores from the clinical measures first were standardized by z scores, using the means and standard deviations computed across all subjects who have participated in research studies at the CCNMD, and then the z scores from specific measures were averaged to yield three clinical domains. The negative symptom domain consisted of the global scores from the SANS, the negative symptoms scores from the SIPS, and the Chapman Social and Physical Anhedonia Scales. The positive symptoms scores consisted of the global hallucinations and delusions SAPS scores, the positive symptom scores from the SIPS, and the Chapman Perceptual Aberration and Magical Ideation Scales. The disorganization symptom domain included the global scores for formal thought disorder and bizarre behavior from the SAPS and the disorganization symptoms from the SIPS.

Neurocognition was assessed using a battery of neuropsychological tests. The raw scores from the individual neuropsychological tests were first standardized by z scores, using the means and standard deviations computed on this sample, and the z scores from specific tests were then averaged to yield four cognitive domains—verbal IQ, which included only the Wechsler Adult Intelligence Test (WAIS-III; Wechsler, 1997a) and the Wechsler Abbreviated Scale of Intelligence Vocabulary measure (Wechsler, 1999); working memory; episodic memory; and executive function. The working memory domain ($\alpha = .75$) consisted of subtests from the Wechsler Memory Scale—Third Edition (WMS-III; raw scores on letter-number sequencing, digit span, and spatial span; Wechsler, 1997b), percentage correct on the 2-back version of the N -back task (Braver et al., 1997), and the 4-item d' score from the Continuous Performance Task (Nieuwenstein, Aleman, & de Haan, 2001). The episodic memory domain ($\alpha = .48$) consisted of raw scores on immediate recall on family pictures and logical memory (also subtests of the WMS-III) and the free recall score for Trials 1 through 5 on the California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 2000). The executive function domain ($\alpha = .66$) included time to completion on Part B of the Trail Making Test (Reitan, 1958), number of novel words generated on the category and verbal fluency tasks (Benton, 1968), raw score on the Matrix

Reasoning subtest from the WAIS-III, and the score for perseverative errors (reversed in sign) from the Wisconsin Card Sorting Test (Berg, 1948).

Results

As shown in Table 1, the three groups did not differ in age, $F(1, 217) = 2.26, p = .11, \epsilon^2 = .02$, personal education, $F(1, 217) = 0.43, p > .6, \epsilon^2 = .004$, parental education, $F(1, 217) = 0.04, p > .9, \epsilon^2 = .0001$, gender, $\chi^2(2, N = 220) = 4.67, p = .10, \phi = .15$, or race, $\chi^2(2, N = 220) = 3.6, p = .46, \phi = .13$.

Cognitive measures

We began by examining overall group differences in cognition across the three groups, using a multivariate analysis of variance (MANOVA) with the four cognitive domain scores as the dependent variables. The omnibus Wilks's Lambda was significant, $F(8, 424) = 2.57, p < .01, \epsilon^2 = .046$. As shown in Table 2, follow-up analyses of variance (ANOVAs) indicated that the groups differed in working memory, episodic memory, and executive function, all $ps < .01, .048 > \epsilon^2 < .058$, but not verbal IQ, $F(2, 215) = 1.72, p = .18, \epsilon^2 = .016$. As shown in Table 2, post hoc contrasts using Tukey's honestly significant difference test indicated that the siblings of individuals with schizophrenia demonstrated significantly impaired performance on working memory, episodic memory, and executive function compared to both the healthy control subjects and the siblings of healthy control subjects. There were no significant differences between healthy control subjects and their siblings on any measure (all $ps > .65$).

We next examined the relationship between age and cognition across the groups using hierarchical regressions, with one regression for each cognitive domain. In Step 1, we entered age and group status (siblings of individuals with schizophrenia vs. healthy control subjects and their siblings) to predict the cognitive domain score. In Step 2, we entered an interaction term between age and group status to determine whether there were group differences in the relationship between age and cognition. Step 1 was significant for all four domain scores, all $ps < .001$. Age predicted cognitive function for working memory, age $\beta = 0.28, p < .001$, executive function, age $\beta = 0.24, p < .001$, and verbal IQ, age $\beta = 0.43, p < .001$, but not for episodic memory, age $\beta = 0.64, p = .33$. Consistent with the MANOVA results presented in the previous paragraph, results showed that group status predicted cognitive function for working memory, group $\beta = -0.24, p < .001$, episodic memory, group $\beta = -0.25, p < .001$, and executive function, group $\beta = -0.26, p < .001$. However, in the regression, group also predicted verbal IQ, group $\beta = -0.16, p < .01$, although the effect

Table 1. Demographic and Clinical Characteristics of Study Subjects

Measure	Group					
	CON		SCN		SIB	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Age	20.79	3.72	20.16	3.94	21.51	3.63
Gender (% male)	51		35		47	
Race distribution (%)						
Caucasian	69		70		59	
African American	30		29		41	
Asian	1		1		0	
Education	12.81	2.72	12.42	3.01	12.45	2.84
Parental education	14.74	2.03	14.64	2.04	14.70	2.80
Symptom						
Negative ^a	-0.39	0.28	-0.30	0.40	-0.10	0.51
Positive ^b	-0.41	0.36	-0.31	0.36	-0.21	0.36
Disorganization ^c	-0.33	0.25	-0.29	0.29	-0.14	0.42

Note: Symptom scores are reported in *z* scores relative to the mean of a sample that included the probands with schizophrenia (see the Method section for details).

CON = healthy control subjects; SCN = siblings of healthy control subjects; SIB = siblings of individuals with schizophrenia.

^aSIB < CON, SCN at $p < .01$, CON = SCN. ^bSIB < CON, SCN at $p < .05$, CON = SCN.

^cSIB < CON at $p < .01$, CON = SCN.

size was smaller than for the other cognitive domains. In addition, Step 2 was significant for both working memory, $F_{\text{change}}(1, 216) = 3.84, p = .05$, and episodic memory, $F_{\text{change}}(1, 216) = 3.9, p < .05$, indicating a significant diagnostic group difference in the relationship between age and performance for working memory, $\beta = -0.74, p = .05$, and episodic memory, $\beta = -0.77, p < .05$. Step 2 was not significant for executive function, $F_{\text{change}}(1, 216) = 1.54, p > .2$, or verbal IQ, $F_{\text{change}}(1, 216) = 2.55, p > .1$.

The group differences in the relationship between age and working memory performance reflected the presence of the expected significant positive correlations in

both the healthy control subjects ($r = .38, p < .01$) and their siblings ($r = .36, p < .01$) but the absence of a significant correlation between age and working memory in the siblings of individuals with schizophrenia ($r = .08, p > .20$). For episodic memory, the healthy control subjects showed a significant positive relationship between age and episodic memory ($r = .27, p < .05$), whereas this correlation was nonsignificant in the siblings of control subjects ($r = .04, p < .20$) and even negative in the siblings of individuals with schizophrenia ($r = -.14, p > .10$). Although the interaction between age and group was not significant for executive function and verbal IQ, the

Table 2. Group Differences in the Four Cognitive Domains

Measure	Group					
	CON		SCN		SIB	
	<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>
Verbal IQ	.14	.11	.01	.11	-.17	.12
Working memory ^{a,b,c}	.13	.07	.04	.07	-.21	.08
Episodic memory ^{a,c}	.11	.08	.11	.08	-.25	.08
Executive function ^{a,c}	.13	.07	.07	.07	-.21	.08

Note: CON = healthy control subjects; SCN = siblings of healthy control subjects; SIB = siblings of individuals with schizophrenia.

^aSIB < CON at $p < .01$. ^bSIB < SCN at $p = .05$. ^cCON = SCN.

results indicated strong positive correlations between age and executive function and age and verbal IQ for both healthy control subjects and their siblings ($.53 < rs < .37$, all $ps < .01$). In contrast, the correlation between executive function and verbal IQ was not significant for the siblings of patients with schizophrenia ($r = .24$, $p > .10$), and the correlation between age and executive function was relatively weak in siblings of individuals with schizophrenia compared to the other groups ($r = .25$, $p < .05$). The pattern for all four cognitive domains is graphically illustrated in Figure 1.

Visual examination of the graphs in Figure 1 suggests relatively little difference between the groups in cognitive performance at younger ages but a greater difference at older ages. To examine this difference statistically, we categorized subjects as young if they were younger than 21 and as adult if they were 21 or older. We then conducted separate MANOVAs for the young and adult groups, examining group differences in the four cognitive domains. The Wilks's Lambda was not significant for group differences in the young group, $F(8, 200) = 0.59$, $p > .75$, $\epsilon^2 = .023$, but it was significant in the adult group, $F(8, 212) = 3.16$, $p < .005$, $\epsilon^2 = .11$, as illustrated in Figure 2. Follow-up ANOVAs for each cognitive domain in the adult group indicated significant group differences in working memory, $F(2, 109) = 8.08$, $p = .001$, episodic memory, $F(2, 109) = 9.30$, $p < .001$, and executive function, $F(2, 109) = 7.22$, $p = .001$, and a trend for verbal IQ, $F(2, 109) = 2.76$, $p = .05$. Post hoc contrasts indicated that the siblings of individuals with schizophrenia performed worse than the healthy control subjects and the siblings of control subjects on working memory, episodic memory, and executive function, all $ps < .05$.

Psychopathological measures

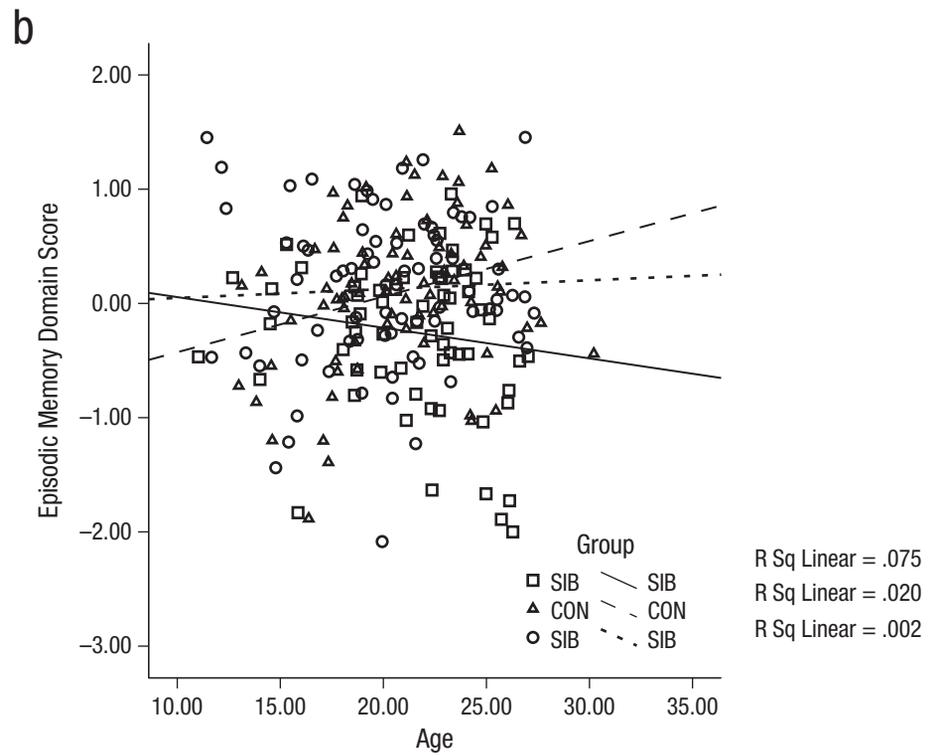
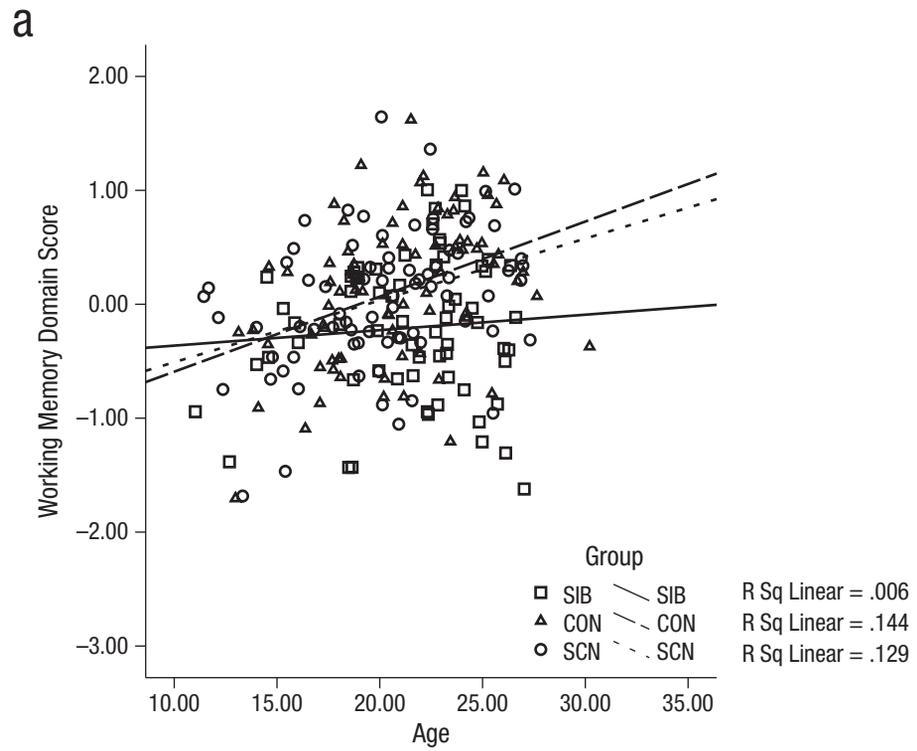
We examined overall group differences in symptoms across the three groups, using a MANOVA with the three symptom domain scores as the dependent variables. The omnibus Wilks's Lambda was significant, $F(6, 430) = 6.00$, $p < .001$, $\epsilon^2 = .07$. As shown in Table 1, follow-up ANOVAs indicated that the groups differed in all three symptom domains, all $ps < .005$, $.052 > \epsilon^2 < .11$. Post hoc contrasts using Tukey's honestly significant difference test indicated that the siblings of individuals with schizophrenia demonstrated greater negative and disorganization symptoms than both healthy control subjects and the siblings of healthy control subjects (all $ps < .05$) and demonstrated greater positive symptoms than healthy control subjects ($p < .01$) but not their siblings ($p = .17$).

Next, we conducted hierarchical regressions for the three symptom domains analogous to those conducted for the cognitive domains. Step 1 was significant for all three symptom domains (all $ps < .005$). However, only

group and not age predicted positive symptoms, age $\beta = -0.10$, $p > .15$, group $\beta = 0.21$, $p < .005$, negative symptoms, age $\beta = -0.09$, $p > .15$, group $\beta = 0.35$, $p < .005$, and disorganization symptoms, age $\beta = -0.05$, $p > .49$, group $\beta = 0.25$, $p < .005$. In addition, Step 2 was significant for negative symptoms, $F_{\text{change}}(1, 216) = 4.5$, $p < .05$, $R^2_{\text{change}} = .018$, indicating a significant diagnostic group difference in the relationship between age and performance for negative symptoms, $\beta = -0.81$, $p = .05$. However, follow-up within-group correlations indicated that this interaction was due to a positive but nonsignificant correlation between age and negative symptoms in the siblings of healthy control subjects group, $r = .14$, $p = .21$, but was due to negative and nonsignificant correlations in the healthy control subjects and the siblings of individuals with schizophrenia groups, $r = -.23$, $p = .06$ and $r = -.20$, $p = .09$, respectively. Step 2 was not significant for either positive symptoms, $F_{\text{change}}(1, 216) = 0.13$, $p > .7$, $R^2_{\text{change}} = .001$, or disorganization symptoms, $F_{\text{change}}(1, 216) = 0.01$, $p > .9$, $R^2_{\text{change}} = .0001$.

Furthermore, MANOVAs conducted separately for each age group indicated significant main effects of diagnostic group in both the young group, $F(6, 178) = 6.0$, $p < .001$, $\epsilon^2 = .15$, and the adult group, $F(6, 232) = 2.58$, $p < .05$, $\epsilon^2 = .07$. Follow-up ANOVAs indicated significant group differences across all three symptom domains in the adult group (all $ps < .05$, all $\epsilon^2s > .058$). However, in the young group, there was a significant group difference for negative symptoms, $F(2, 105) = 19.4$, $p < .001$, $\epsilon^2 = .27$, a trend for positive symptoms, $F(2, 105) = 2.6$, $p = .08$, $\epsilon^2 = .046$, and no significant difference for disorganization symptoms, $F(2, 105) = 2.0$, $p > .10$, $\epsilon^2 = .036$. Thus, unlike the cognitive domains, there was no evidence of age-related changes in any of the symptom domains, nor was there evidence of age-related changes in the magnitude of group differences in any of the symptom domains.

The difference in the results for the influence of age as a function of risk status for cognition versus symptoms led us to ask whether the relationship between symptoms and cognition varied as a function of age. To answer this question, we computed correlations between the three symptom domains and the four cognitive domains in the young (< 21) and adult ($21+$) subjects, controlling for group status, and compared them using Fisher's r -to- z transformations. As shown in Table S1 in the Supplemental Material available online, there were significant negative correlations between negative symptoms and verbal IQ, working memory, and executive function in both the young and adult subjects and no significant age differences in the magnitude of these correlations. In addition, there were significant negative correlations between positive symptoms and verbal IQ in both age groups as well as a negative correlation between positive symptoms and working memory in the young group and between



(continued)

Fig. 1. (continued)

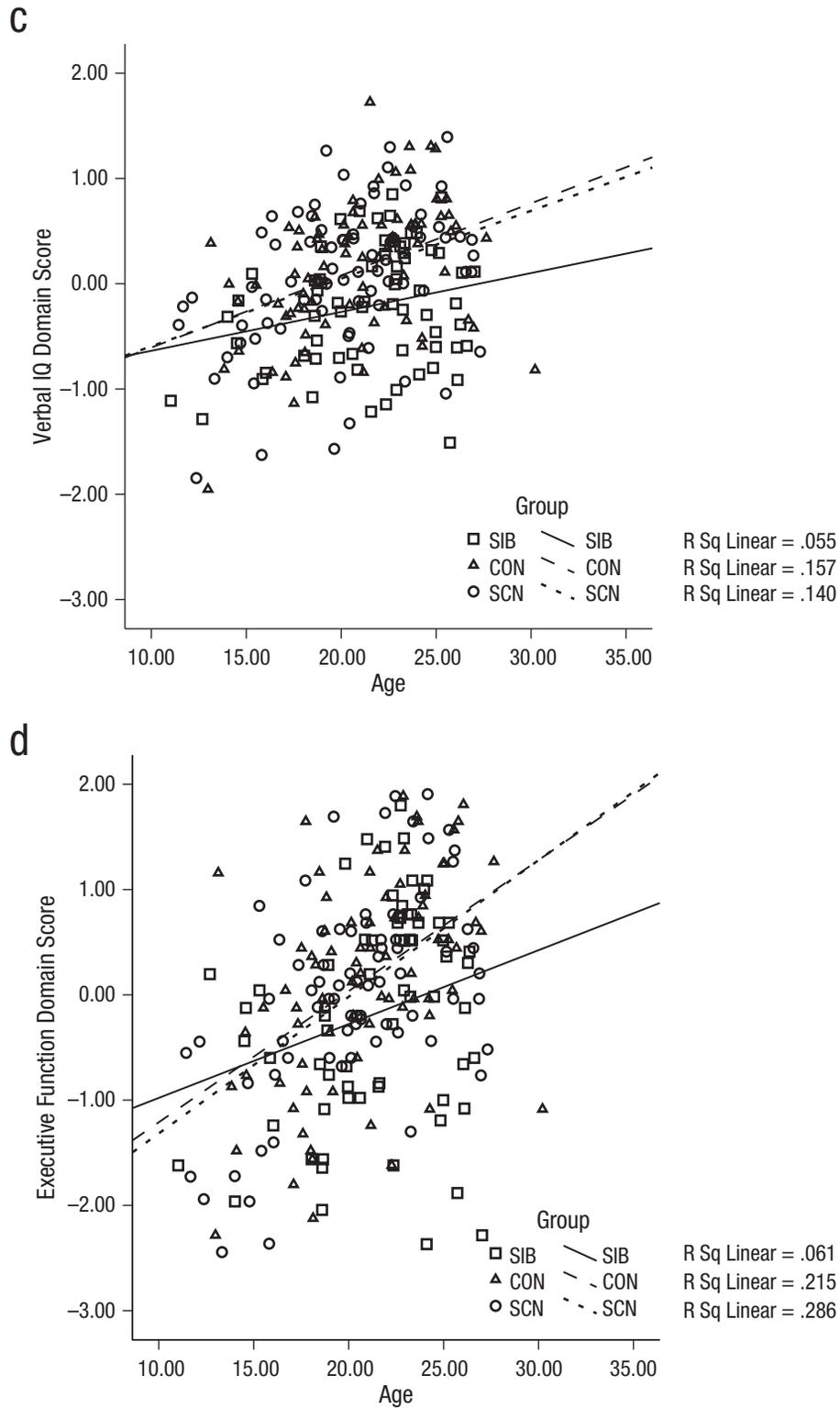


Fig. 1. Relationship between age and performance for (a) working memory, (b) episodic memory, (c) verbal IQ, and (d) executive function. CON = healthy control subjects; SCN = siblings of healthy control subjects; SIB = siblings of individuals with schizophrenia.

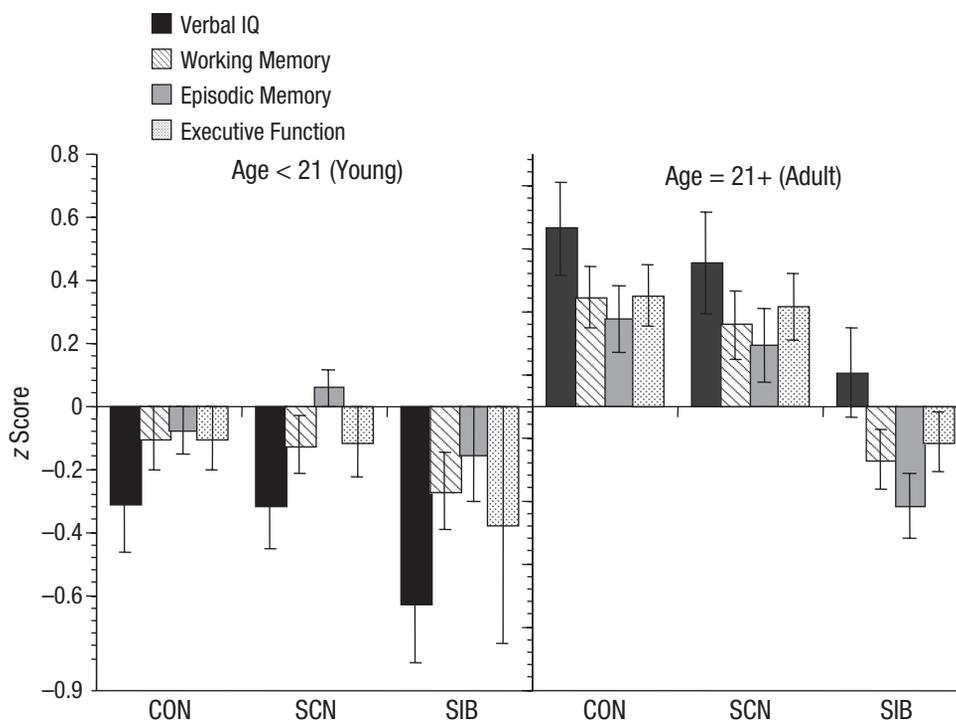


Fig. 2. Cognitive performance for verbal IQ, working memory, episodic memory, and executive function as a function of diagnostic group separately for young and adult age group. CON = healthy control subjects; SCN = siblings of healthy control subjects; SIB = siblings of individuals with schizophrenia. Error bars represent the standard error.

positive symptoms and episodic memory in the adult group. Moreover, disorganization symptoms were negatively correlated with verbal IQ, working memory, and executive function in both groups and negatively correlated with episodic memory in the adult group. Again, however, none of these correlations differed significantly as a function of age.

Discussion

The goal of the current study was to shed further light on the early and late neurodevelopmental hypothesis of schizophrenia by examining age-related changes in cognitive function among the siblings of individuals with schizophrenia, healthy control subjects, and the siblings of healthy control subjects. We found significantly impaired age-related development of cognitive function among the siblings of individuals with schizophrenia in both working memory and episodic memory, with similar patterns for executive function and verbal IQ. More specifically, both healthy control subjects and their siblings showed improvements in performance in each of these four domains as a function of increasing age (with the exception of episodic memory for the siblings of control subjects). However, the siblings of individuals with

schizophrenia did not show evidence of improvements as a function of age in working memory, episodic memory, or executive function, although they did show some evidence of improvement as a function of age for verbal IQ. Furthermore, we found that the siblings of individuals with schizophrenia showed impaired cognitive function in working memory, episodic memory, and executive function compared to healthy control subjects and their siblings in the adult age group but not in the young age group.

These results are consistent with a late neurodevelopmental hypothesis of schizophrenia in which normative neurobiological processes driving cognitive development through puberty are disrupted in those at risk for the development of schizophrenia. In addition, these results are consistent with prior studies showing altered development of white matter and gray matter (particularly in the frontal cortex) in individuals with childhood-onset schizophrenia (Vidal et al., 2006) and prodromal patients who develop psychosis (Sun, Phillips, et al., 2009). However, these results are not consistent with work by Cornblatt et al. (1999), who did not see evidence for enhanced cognitive impairment as a function of age in high-risk children who went on to develop schizophrenia. It is not clear why the results of the current study

differ from those of the New York High-Risk Project (Ott et al., 1998), although the most obvious difference is the selection of siblings versus children as high-risk subjects. Also, the current study used a more extensive battery of cognitive tasks than used in the Cornblatt et al. study, which might have allowed us to detect more subtle effects or a wider range of cognitive functions that could change as a function of development.

In contrast, our results provide little evidence consistent with either an early neurodevelopmental hypothesis or a 2-hit hypothesis, at least in terms of cognitive function. Specifically, we did not find that the younger siblings of individuals with schizophrenia demonstrated significantly impaired performance in any cognitive domain compared to healthy control subjects. This result is not consistent with prior research showing impairments in some cognitive domains (i.e., IQ and working memory) among children at risk for schizophrenia (de la Serna et al., 2010; Goldstein et al., 2000; Niendam et al., 2003; Sorensen, Mortensen, Parnas, & Mednick, 2006; Worland et al., 1982). Of note, however, the two domains with the largest effect size for a diagnostic group difference in our younger group were verbal IQ and executive function, which is somewhat consistent with the work of and other researchers suggesting that IQ impairments are important predictors of risk for psychosis (Kremen et al., 1998; MacCabe et al., 2013). It is important that in many of the prior studies examining cognitive function in young high-risk individuals, researchers have examined offspring rather than siblings. As such, it is possible that there are enhanced risk factors present in offspring (e.g., pre- or perinatal care issues) that might lead to enhanced evidence of cognitive impairment compared to samples such as ours that consist solely of siblings.

As noted earlier, researchers have replicated extensively a link between the severity of cognitive impairments and the severity of clinical symptoms, such as negative and disorganization symptoms, both in individuals with schizophrenia and in their siblings (Barch, Carter, & Cohen, 2003; Barch, Csernansky, Conturo, Snyder, & Ollinger, 2002; Delawalla et al., 2006; Nieuwenstein et al., 2001; Perlstein, Dixit, Carter, Noll, & Cohen, 2003). We replicated these findings in the current sample, showing consistent negative correlations between cognition and both negative and disorganization symptoms as well as some relationships with positive symptoms. Thus, we also examined whether the severity of subclinical symptoms varied as a function of age in the siblings of individuals with schizophrenia. It is interesting that we did not find age-related differences in any symptom domain, and both the younger and the older siblings of individuals with schizophrenia showed elevated subclinical schizotypal symptoms compared to healthy control subjects and their siblings, with increased negative

symptoms being most consistent across the age groups. Furthermore, we did not find any age differences in the magnitude of the relationship between clinical symptoms and cognition.

These results suggest one of two possibilities. One possibility is that subclinical schizotypal symptoms and cognitive impairment may be independent expressions of risk for psychosis, as some other researchers have found (Asarnow et al., 2002). However, this interpretation would not be consistent with studies that have shown a link between the severity of symptoms and the severity of cognitive impairments in individuals with schizophrenia and their relatives (Delawalla et al., 2006), as well as our data showing a significant relationship between clinical symptoms and cognitive function. Alternatively, although cognition and symptomatology may be linked, the emergence of subclinical symptoms may precede the emergence of cognitive impairments or may be a more sensitive indicator of risk. This interpretation would be consistent with the literature on the emergence of social difficulties—one aspect of negative symptoms—in children at risk for the development of schizophrenia (Cannon, Mednick, & Parnas, 1990; MacCrimmon, Cleghorn, Asarnow, & Steffy, 1980; Olin & Mednick, 1996; Sohlberg & Yaniv, 1985).

One of the major limitations of the current study is that it was cross-sectional rather than longitudinal; therefore, cohort effects or sample-selection issues could have biased the results. In a number of the early offspring high-risk studies, researchers did conduct repeated assessments throughout childhood and adolescence, although relatively few tools for noninvasive brain imaging were available for these studies, as they are today. In contrast, researchers in many sibling studies have been able to use a range of structural and functional neuroimaging tools but have not been able to study individuals prior to puberty (Munoz Maniega et al., 2008; Whalley et al., 2006). An additional limitation of the current study is that we studied a familial high-risk population that included a mixture of people who will and will not develop schizophrenia. Thus, it is not yet clear whether alterations in the development of cognitive function are a more general characteristic of familial risk or a specific predictor of psychosis onset.

Given the limitations of our own study and the extent literature we have described, an optimal study to test hypotheses about early, late, or 2-hit neurodevelopmental models would be a longitudinal design in one or more risk populations (e.g., offspring, siblings, and 22q11 deletion syndrome) that started at birth and had multiple waves of data collection prior to, during, and after puberty. It would be ideal to use several types of at-risk populations to determine the generalizability and replicability of any identified predictors. As noted by Giedd

et al. (2008), at least three assessment points are needed to characterize a trajectory, and ideally we would be able to determine trajectories of development prior to, during, and after puberty. Advances in modern imaging have made available many techniques for the noninvasive measurement of brain structure and function across the course of development, even making it feasible to assess such characteristics of brain development in newborn infants (e.g., resting-state brain connectivity during sleep; Smyser et al., 2010). Such a study should include detailed behavioral measures of cognitive, affective, and motor function and as many noninvasive measurements of brain integrity as possible (e.g., gray matter, white matter, resting-state functional connectivity, task-related activity when age appropriate, and perfusion). By including measures that are both more and less expensive, technically demanding, and invasive, we will be able to determine the relative utility of using more time-consuming and cost-demanding methods to clarify and identify predictors of psychosis. It is possible that less expensive/invasive measures may have as much utility (e.g., cognitive or motor function trajectories) as more expensive/invasive measures, yet we will ascertain this only by directly comparing them.

Furthermore, we should be careful not to think of full-blown psychosis as the only relevant outcome in such studies. In addition to full diagnostic outcomes that may not be evident until adulthood, it will be important to look at cognitive, social, or academic function during childhood and adolescence as outcomes that could be predicted by earlier measurements. In addition, we would need to examine subtle signs and symptoms of psychosis, including indicators of clinical high risk (Cannon et al., 2008; Woods et al., 2009) as intermediate outcome measures that can inform the developmental trajectory of psychosis risk. Given that adolescents and young adults with the clinical high-risk profile for psychosis already suffer significant distress and impairment in social, educational, and occupational function (Fusar-Poli, Yung, McGorry, & van Os, 2013), identifying neurodevelopmental trajectories that predict the onset of clinical high-risk symptoms and allow for targeted early intervention has significant public health benefits in and of itself, even if not all of those individuals will develop psychotic disorders that meet *DSM-5* criteria (Fusar-Poli, Bechdolf, et al., 2013; Fusar-Poli et al., 2012). Although we fully realize the practical limitations and constraints on the conduct of such a large-scale study, it is the only way we will be able to more adequately and definitively characterize and identify abnormalities in cognitive, affective, motor, and brain development as a precursor to psychosis.

Author Contributions

D. M. Barch designed the study, generated the hypothesis, analyzed data, and drafted the manuscript. R. Cohen generated the

hypothesis, analyzed data, and revised the manuscript. J. G. Csernansky designed the study, generated the hypothesis, and revised the manuscript.

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Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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Supplemental Material

Additional supporting information may be found at <http://cpx.sagepub.com/content/by/supplemental-data>

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