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Association of Age at Onset and Longitudinal Course of Prefrontal Function in Youth With Schizophrenia

Tara A. Niendam, PhD; Kimberly L. Ray, PhD; Ana-Maria Iosif, PhD; Tyler A. Lesh, PhD; Stefania R. Ashby, MS; Pooja K. Patel, BS; Jason Smucny, PhD; Emilio Ferrer, PhD; Marjorie Solomon, PhD; J. Daniel Ragland, PhD; Cameron S. Carter, MD

IMPORTANCE The extent of cognitive deterioration after schizophrenia (SZ) onset is poorly understood because prior longitudinal studies used small samples of older individuals with established illness.

OBJECTIVE To examine the association of age at onset and subsequent longitudinal course of prefrontal activity during the first 2 years of illness in youths with SZ and healthy control participants (HCs).

DESIGN, SETTING, AND PARTICIPANTS This naturalistic, longitudinal, functional magnetic resonance imaging (fMRI) study included patients with recent-onset SZ and HCs aged 12 to 25 years enrolled in an ongoing study of cognition in recent-onset psychosis in the Sacramento, California, area from October 13, 2004, through June 25, 2013. Participants completed clinical assessments and an established measure of cognitive control, the AX Continuous Performance Task (AX-CPT), during fMRI at baseline and at 6-, 12-, and 24-month follow-up. Whole-brain, voxelwise, and an a priori dorsolateral prefrontal cortex (DLPFC) region of interest analyses were performed. Group differences in developmental trajectories were examined by focusing on behavioral performance (d'-context) and cognitive control-associated brain activity. The association of antipsychotic medication and clinical factors were also examined. Data were analyzed from April 15, 2015, through August 29, 2017.

MAIN OUTCOMES AND MEASURES Primary outcomes included group differences (HC vs SZ) in behavioral performance (d'-context from AX-CPT) and brain activity for cue B-A trials of the AX-CPT in an a priori DLPFC region of interest at baseline and across the age span. Secondary analysis examined the influence of antipsychotics on behavioral performance and DLPFC activity.

RESULTS Among the sample of 180 participants (66.1% male; mean [SD] age at baseline, 19.2 [3.2] years), 87 patients with SZ (mean [SD] age, 19.6 [3.0] years) showed impaired performance compared with 93 HCs (mean [SD] age, 18.8 [3.4] years) across the age span (estimated difference [SE], −0.571 [0.12], d'-context; $P < .001$). Patients with SZ showed reduced activation in the DLPFC and parietal cortex (false discovery rate cluster corrected to $P < .05$) compared with HCs under conditions of high cognitive control at baseline. Region-of-interest analysis showed reduced activation in the DLPFC bilaterally for patients with SZ, with a trajectory that paralleled that of HCs across the age span (left DLPFC β [SE] estimates, 0.409 [0.165] for the HC group and −0.285 [0.130] for the SZ group [main effect of group, $P = .03$]; right DLPFC β [SE] estimates, 0.350 [0.103] for the HC group and −0.469 [0.157] for the SZ group [$P = .003$]). Antipsychotic medication, clinical symptoms, and global functioning were associated with SZ performance.

CONCLUSIONS AND RELEVANCE During the initial 1 to 2 years after illness onset, young individuals with SZ showed deficits in DLPFC activation and cognitive control, with developmental trajectories comparable to those of HCs. Younger age at onset was not associated with reduced cognition or activation. For individuals contributing to longitudinal analysis, results suggest that young patients do not show deterioration or disruption of ongoing brain development in the initial years after illness onset.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Tara A. Niendam, PhD, Department of Psychiatry and Behavioral Sciences, University of California, Davis, Imaging Research Center, 4701 X St, Ste E, Sacramento, CA 95817 (tniendam@ucdavis.edu).

Although neuroimaging provides insight into brain changes associated with schizophrenia (SZ), the field has struggled with 2 questions. First, whether schizophrenia is a neurodevelopmental or a neurodegenerative disorder is unclear. Early[1-3] and more recent structural imaging studies[4-9] showed increased ventricle size and reduced gray matter, supporting the concept of neurodegeneration introduced by Kraepelin and Robertson.[10,11] However, studies have not consistently shown neurodegeneration at the cellular level,[12,13] and some investigations suggest that a subset of changes in brain structure are associated with the effects of antipsychotic treatment.[14,15] In contrast, the neurodevelopmental hypothesis, proposed by Weinberger[16] and Murray and Lewis,[17] posits that prenatal central nervous system insults[18] and/or genetically based deviations during early brain development[19] interact with environmental risk factors,[20,21] leading to psychosis onset in late adolescence or early adulthood. This hypothesis is supported by evidence that differences in brain structure and/or function and cognition (1) are present in childhood before symptom onset,[22,23] (2) are present in individuals at clinical high risk for psychosis,[24-27] (3) worsen in individuals at clinical high risk who develop psychosis,[28] and (4) stabilize after psychosis onset.[29,30]

Second, clarity about the influence of age at psychosis onset on subsequent cognitive development is lacking. Earlier onset has been associated with poorer cognition[31] and reduced gray matter volume,[32] but this association is not consistently reported when patients are age matched to control individuals.[33,34] One longitudinal study in childhood-onset SZ showed normalization of cortical thinning in parietal regions, with continued reductions in frontal and temporal cortical thickness from late adolescence into early adulthood, leaving only the pattern of frontotemporal reductions that is typically observed in adult-onset SZ.[35] These findings suggest that early age at onset may be associated with a different pattern of disruption in brain structure and functioning than later-onset cases, serving as the basis of poor outcome in these individuals; however, lack of age-matched controls and/or comparisons of group means alone may obscure subtle age-related effects. Therefore, modeling dynamic changes in brain structure and function using functional magnetic resonance imaging (fMRI) during development to examine potential mechanisms that influence illness onset and course is critical.

To our knowledge, the utility of fMRI in elucidating age-related changes in brain function in SZ has not been fully explored.[36] Because structural and functional changes within the dorsolateral prefrontal cortex (DLPFC) are consistently replicated across all phases of SZ,[37,38] the DLPFC stands as a principal area worthy of developmental investigation. Previous fMRI studies demonstrated that changes in prefrontal activation during follow-up are associated with reductions in psychotic symptoms,[39,40] improved social functioning,[41] and treatment response.[42-45] These studies examined small samples, short follow-up periods, and adult patients with chronic illness. Larger-scale longitudinal studies following up young individuals through the earliest phases of illness—compared with age-matched healthy controls (HCs)—are needed to determine the age-related factors associated with early illness course and outcome.[46]

Consequently, this study examined the association of age at psychosis onset and developmental changes across the age span with prefrontal activation and associated behavior in young individuals early in the course of SZ spectrum disorders and demographically matched HCs. Individuals ranged in age from 12 to 25 years, covering the typical window for psychosis onset and the associated critical period of prefrontal brain development from adolescence into young adulthood. We used fMRI, an established measure of DLPFC-related cognition (AX Continuous Performance Task [AX-CPT][47-52]), and mixed-effects models[53] to investigate the longitudinal pattern of prefrontal activation and behavior during a 2-year follow-up within and between the 2 groups. Attrition is common in large-scale longitudinal studies, and our proposed statistical approach based on random effects capitalizes on all available data, including individuals with and without follow-up. This investigation examines (1) the association of age with prefrontal cognitive dysfunction present at baseline in SZ and (2) whether deterioration occurs across the age span. At baseline, we hypothesized that patients with SZ would show worse performance (as captured by d′-context on the AX-CPT) and reduced PFC activation under conditions of high cognitive control compared with age-matched HCs but that younger age at onset would not be associated with increased impairment.[33,34] Based on previous findings,[22,29,30] patients with SZ were not hypothesized to show deterioration in performance and brain activity across the age span, demonstrating that prefrontal functioning is already impaired at psychosis onset and does not deteriorate further. Based on findings from Lesh et al,[15] the association with use of antipsychotics was examined. Antipsychotic treatment was hypothesized to be associated with higher performance and prefrontal activity across the age span. Exploratory analyses examined the influence of time since baseline, sex, duration of untreated psychosis, symptoms, and global functioning on performance and brain activation within the SZ group.

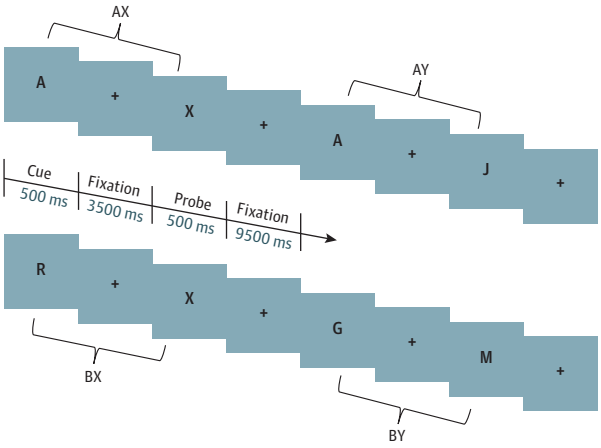
Key Points

Question Do young patients with recent-onset schizophrenia show a pattern of improvement or deterioration of prefrontal cognitive control processes during the first 2 years after illness onset compared with age-matched healthy controls?

Findings In this naturalistic, longitudinal, functional magnetic resonance imaging study, 87 young patients early in the course of schizophrenia showed stable behavioral and functional deficits in cognitive control that paralleled the pattern of 93 age-matched healthy control individuals across the age span.

Meaning In support of the neurodevelopmental hypothesis of schizophrenia, no evidence was found of (1) differential impairment related to earlier age at onset or (2) deterioration of cognitive control processes in young patients with recent-onset schizophrenia.

Figure 1. AX Continuous Performance Task Parameters and Timing



Rule:
Target response is an *X*, but only when it follows an *A*
Response:
1 = Target 2 = Nontarget
Trial Type
AX, 70%; AY, 10%; BX, 12.5%; and BY, 7.5%

Individuals make a target response to probe X only when it follows the cue A. Nontarget BX trials require increased cognitive control to prevent error.

Methods

Participants

Eighty-seven patients with SZ and 93 HCs aged 12 to 25 years were recruited from the University of California, Davis, Early Psychosis Program as part of a larger National Institute of Mental Health–funded study (principal investigator, C.S.C.). Participants completed fMRI and clinical assessments at baseline and after 6, 12, and 24 months. A subset of participants (32 [36.8%] with SZ and 58 HCs [62.4%]) had useable behavioral and fMRI data for at least 1 follow-up. Baseline data for some participants were reported in previous publications.[15,26,52,54,55] Details on inclusion and exclusion criteria are provided in the eMethods in the Supplement. This research was approved by the institutional review board of the University of California, Davis. All participants provided written informed consent; those younger than 18 years provided assent.

Clinical Measures

At each point, patient symptoms were rated on the 24-item Brief Psychiatric Rating Scale,[56] Scale for the Assessment of Positive Symptoms,[57] and Scale for the Assessment of Negative Symptoms.[58] Ratings were combined into the factors of reality distortion, disorganization, and poverty symptoms.[47,51,52] We obtained a Global Assessment of Functioning score.[59] Use of atypical antipsychotics was coded (present or absent) at each point. Duration of untreated psychosis was measured as the time from onset of psychotic symptoms (based on medical record review and retrospective clinical interview with the patient or collateral informants) to the initial evaluation date.

AX Continuous Performance Task

Participants completed the AX-CPT during fMRI (**Figure 1** and eMethods in the Supplement). Performance on the AX-CPT was measured using d′-context as Z AX hits (percentage correct) minus Z BX false alarms (percentage of errors),[60] which indexes the ability to use context to correctly respond to X probe in the context of a specific cue (A or B type).

Functional Imaging Methods and Data Analysis

Participants performed 4 blocks of event-related fMRI using the AX-CPT following the parameters in Figure 1 (eMethods in the Supplement). Data were collected on a 1.5-T scanner with a custom head coil (GE Healthcare). Functional MRI data were analyzed with Statistical Parametric Mapping–8 software (SPM8) (https://www.fil.ion.ucl.ac.uk/spm/software/spm8) and the FMRIB Linear Image Registration Tool[61,62] using all available scans. At baseline, whole-brain group-level random-effects analyses were conducted for the cue B minus cue A contrast (representative of high vs low cognitive demand), with a voxelwise threshold of $P < .001$ and cluster correction for false discovery rate set at $P < .05$.

In addition to baseline whole-brain analyses, a priori left and right DLPFC regions of interest (ROIs) associated with goal maintenance were selected for longitudinal analyses.[63,64] To model changes in brain activity across time, we extracted β values for each participant from the a priori ROIs for cue B minus cue A contrasts at each point. These ROI measures were used as described below to examine longitudinal changes.

Statistical Analysis

Data were analyzed from April 15, 2015, through August 29, 2017. Baseline group differences were assessed using 2-sample *t* tests for continuous variables and χ^2 tests (or Fisher exact tests when appropriate) for categorical variables. Mixed-effects linear models[53] were used to characterize the longitudinal trajectories of behavioral performance and blood oxygenation level–dependent signal and assess their associations with group and covariates. This approach is appropriate for repeated-measures data and accommodates missing and unequally spaced observations. Therefore, individuals with baseline information, as well as those with baseline and follow-up assessments, contributed data for the analyses. For each dependent variable, we first fitted a model to describe the course for HCs, with the linear and quadratic effect of age (centered at the mean age in the sample, 19.2 years) as fixed effects and a random effect for individual to account for the correlation due to repeated measures on the same individual. We removed the quadratic age effect if it was not significant. To this base model, we added and tested terms for group (SZ and HC) and its interaction with the linear and quadratic effect of age (where applicable) to examine group differences in the trajectories across the age span. Terms were retained if they added significantly to the core model. To evaluate whether time-varying characteristics, such as time since baseline, duration of untreated psychosis, clinical symptoms, global functioning, and antipsychotic use, were associated with the dependent variables, we tested each one individually by adding them to the core models as interactions with group. We

Table 1. Demographic and Clinical Characteristics of the Participants by Study Group

Characteristic	Study Group[a] Recent-Onset SZ (n = 87)	HC (n = 93)	*P* Value[b]
Age, mean (SD), y	19.6 (3.0)	18.8 (3.4)	.07
Male, No. (%)	73 (83.9)	46 (49.5)	<.001
Race, No. (%)			
Asian	7 (8.0)	25 (26.9)	.001
African American	15 (17.2)	3 (3.2)	
Native Hawaiian/Pacific Islander	1 (1.1)	1 (1.1)	
White	56 (64.4)	54 (58.1)	
Other	8 (9.2)	10 (10.8)	
Hispanic ethnicity, No. (%)	13 (14.9)	11 (11.8)	.54
Parental educational level, mean (SD), y	15.5 (2.8)	15.6 (2.6)	.88
GAF score, mean (SD)[c,d]	46.0 (9.5)	NA	NA
SCID diagnosis, No. (%)			
Schizophrenia	75 (86.2)	NA	NA
Schizoaffective disorder	6 (6.9)	NA	
Schizophreniform disorder	6 (6.9)	NA	
Medication use at baseline, No. (%)[e]			
Atypical only	61 (70.9)	NA	NA
Other medication	4 (4.7)	NA	
No medication	21 (24.4)	NA	
Duration of untreated psychosis, mean (SD), mo[c]	4.9 (4.5)	NA	NA
Symptom severity score, mean (SD)[f]			
Disorganization[g]	6.6 (3.5)	NA	NA
Reality Distortion[h]	15.5 (6.9)	NA	
Poverty[i]	13.9 (5.5)	NA	
Participation in study, No. (%)			
Baseline only	55 (63.2)	35 (37.6)	.001
1 Follow-up scan	19 (21.8)	27 (29.0)	
2 Follow-up scans	13 (14.9)	26 (28.0)	
3 Follow-up scans	0 (0)	5 (5.4)	
Time from baseline scan to last scan, mean (SD), mo	15.8 (6.8)	17.5 (6.6)	.26

Abbreviations: GAF, Global Assessment of Functioning; HC, healthy control; NA, not applicable; SCID, Structured Clinical Interview for *DSM-IV*; SZ, schizophrenia.

[a] Percentages have been rounded and may not total 100.

[b] Group characteristics were tested using 2-sample *t* tests for continuous and χ^2 or Fisher exact tests for categorical variables.

[c] Three patients were missing in the SZ group.

[d] Scores range from 1 to 100, with higher scores indicating better functioning.

[e] One patient was missing in the SZ group.

[f] Scores range from 3 to 41, with higher scores indicating more severe symptoms.

[g] Five patients were missing in the SZ group.

[h] Four patients were missing in the SZ group.

[i] Two patients were missing in the SZ group.

also investigated the effects of sex by adding a corresponding fixed effect in the model. Additional sensitivity analyses were conducted restricting the sample to the participants with at least 1 follow-up visit to confirm the longitudinal pattern from the primary analyses. Tests for all a priori hypotheses and exploratory analyses of clinical factors were 2-sided, with $P < .05$ considered statistically significant. All analyses were implemented using the PROC MIXED program in SAS software, version 9.4 (SAS Institute Inc).[65]

Results

Demographic characteristics are presented in **Table 1** for the entire sample of 180 participants (119 male [66.1%] and 62 female [34.4%]; mean [SD] age, 19.2 [3.2] years) and in eTable 1 in the Supplement for the subsample with at least 1 follow-up visit. Groups did not differ by age, duration of follow-up, or parental educational level. The HC group completed more follow-up scans (58 of 93 [62.4%]) than the SZ group (32 of 87 [36.8%]) ($P < .001$). The HC group was more often female (47 of 93 [50.5%] vs 14 of 87 [16.1%]; $P < .001$) and differed by race from the SZ group (eg, 7 of 87 [8.0%] vs 25 of 93 [26.9%] Asian; 15 of 87 [17.2%] vs 3 of 93 [3.2%] African American; 56 of 87 [64.4%] vs 54 of 93 [58.1%] white; $P < .001$).

Table 2 reports results of the mixed-effects models for behavioral performance and brain activation and for the effect of medication in the SZ group. eTables 2 to 4 in the Supplement report the exploratory results of the mixed-effects models examining the effect of covariates (sex, time since baseline, duration of untreated psychosis, clinical symptoms, and global functioning) on performance and activation in the SZ group.

Performance

As illustrated in Table 2 and **Figure 2**A, the model for behavioral performance (d′-context) included terms for linear and quadratic effects of age and group. The interaction terms for group with linear and quadratic age effects were not significant and therefore removed from the model, suggesting that the SZ group paralleled the pattern of performance of the HC group across the age span. The fixed effect for group was significant, indicating that the SZ group performed more poorly than controls across the age span (estimated difference [SE], −0.571 [0.12]; $P < .001$).

The association with medication use is summarized in Table 2 and Figure 2B. The SZ group not receiving medica-

Table 2. Parameter Estimates for the Core Mixed-Effects Regression Models of Behavioral Performance and Brain Activation in the Left and Right DLPFC ROI[a]

Model Term	β Estimate (SE)		
	Behavioral Performance, d'-Context	BOLD Activation	
		Left	Right
Core Models			
Estimated trajectory for HC group			
Baseline	3.485 (0.099)[b]	0.409 (0.165)[c]	0.350 (0.103)[b]
Linear age effect, y	0.093 (0.018)[b]	−0.007 (0.020)	−0.007 (0.024)
Quadratic age effect, y	−0.011 (0.005)[c]	–	–
Estimated difference between SZ and HC groups			
Baseline	−0.571 (0.122)[b]	−0.285 (0.130)[c]	−0.469 (0.157)[d]
Quadratic age effect, y	–	–	–
Linear age effect, y	–	–	–
Models Adjusting for Medication Use in the SZ Group			
Estimated trajectory for HC group			
Baseline	3.490 (0.100)[b]	0.361 (0.086)[c]	0.351 (0.103)[b]
Linear age effect, y	0.091 (0.018)[b]	−0.011 (0.020)	−0.011 (0.024)
Quadratic age effect, y	−0.011 (0.005)[c]	–	–
Estimated difference between nonmedication SZ and HC groups			
Baseline	−0.906 (0.195)[b]	−0.464 (0.234)[c]	−0.831 (0.281)[d]
Linear age effect, y	–	–	–
Quadratic age effect, y	–	–	–
Estimated difference between medication and nonmedication SZ groups	0.427 (0.195)[c]	0.216 (0.245)	0.460 (0.294)

Abbreviations: BOLD, blood oxygen level–dependent; DLPFC, dorsolateral prefrontal cortex; HC, healthy control; ROI, region of interest; SZ, schizophrenia.

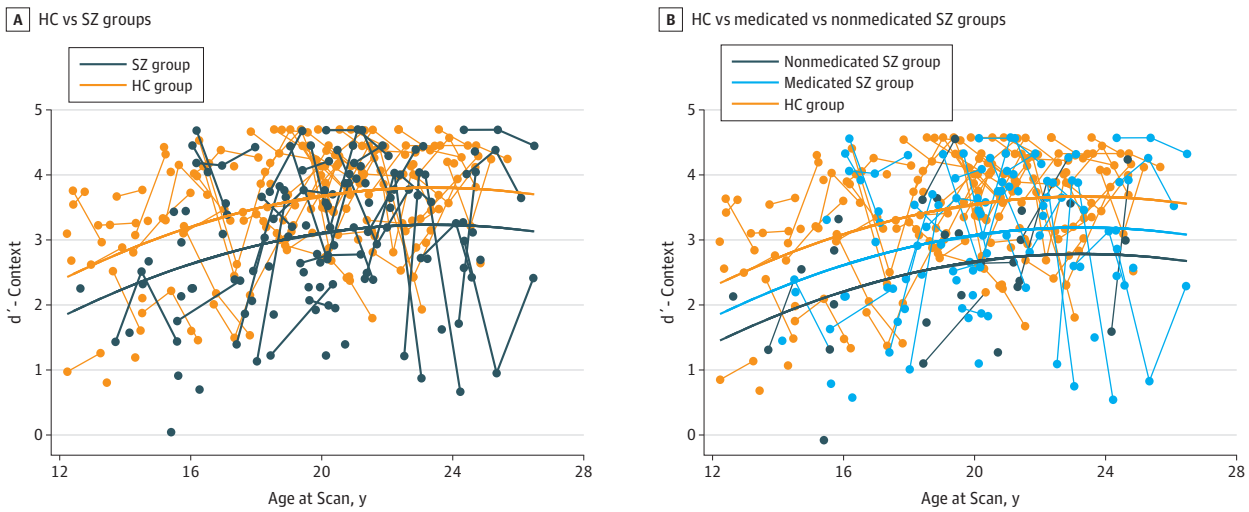
[a] Age was centered at 19.2 years (the mean age in the sample at baseline). One patient in the SZ group was missing medication information. Quadratic effect of time was not retained in the model if it was not significant (represented by minus signs); thus, it was only reported for d'-context.

[b] $P < .001$, corresponding 2-sample *t* tests of the fixed effects in the mixed-effects linear regression models.

[c] $P < .05$, corresponding 2-sample *t* tests of the fixed effects in the mixed-effects linear regression models.

[d] $P < .01$, corresponding 2-sample *t* tests of the fixed effects in the mixed-effects linear regression models.

Figure 2. Estimated Trajectories in Behavioral Performance (d'-Context) on the AX Continuous Performance Task



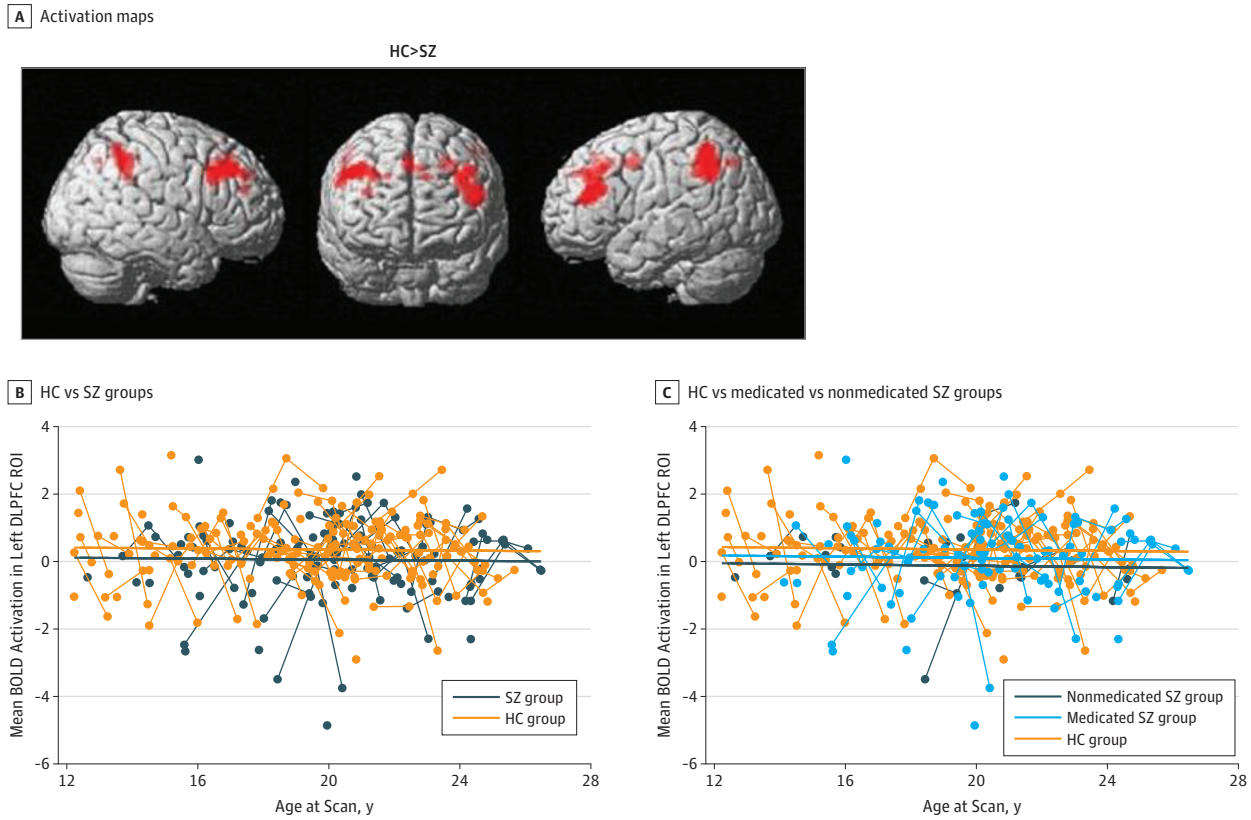
Dots and connected lines show the longitudinal sequence for as many as 3 follow-up visits (at 6, 12, and 24 months). A dot alone indicates the participant performed the test at baseline only. Patients with schizophrenia (SZ) are stratified between those who received (medicated SZ group) and did not receive (nonmedicated SZ group) medications. HC indicates healthy control.

tion (hereinafter referred to as the nonmedicated SZ group) performed 0.906 points (β estimate; SE, 0.195) lower than the HC group ($P < .001$). The SZ group receiving medication (hereinafter referred to as the medicated SZ group) performed significantly better than the unmedicated SZ group (estimated difference [SE], 0.427 [0.195]; $P = .03$) but significantly worse than the HC group (estimated difference, 0.480 [0.131]; $P < .001$).

Functional Activity

At baseline, whole-brain analysis revealed reduced activation bilaterally in the PFC-parietal cognitive control network under conditions of high cognitive control (cue B − A) in patients with SZ when compared with HCs of similar age (**Figure 3**A). Analyses using the a priori left DLPFC ROI showed lower blood oxygenation level–dependent activation in the SZ group for high control trials relative to the HC group (cue B − A

Figure 3. Functional Activity



A, Between-group whole-brain activation maps from baseline data contrast healthy controls (HCs) vs patients with schizophrenia (SZ) for conditions of high cognitive control (cue B − A), displayed at height threshold of $P < .001$ (false discovery rate cluster corrected to $P < .05$). B and C, Estimated trajectories of a prior left dorsolateral prefrontal cortex (DLPFC) activation for conditions of high cognitive control (cue B − A) between HC and SZ groups and among HCs and patients with SZ receiving (medicated SZ group) vs not receiving (nonmedicated SZ group) medication. Dots and connected lines show the longitudinal sequence for as many as 3 follow-up visits (at 6, 12, and 24 months). A dot alone indicates the participant performed the test at baseline only. BOLD indicates blood oxygenation level–dependent; ROI, region of interest.

β [SE] estimates, 0.409 [0.165] for the HC group and −0.285 [0.130] for the SZ group; main effect of group, $P = .03$) (Table 2). No change in activation with age and no group by age interaction was observed on the left side (shown in Figure 3B). The same patterns of significant group differences (β [SE] estimates, 0.350 [0.103] for the HC group and −0.469 [0.157] for the SZ group; $P = .003$) with no effect of age were also observed in the right DLPFC ROI (Table 2).

The nonmedicated SZ group showed lower activation in the left DLPFC than the HC group on high control trials (cue B − A for the nonmedicated SZ group, −0.464 [SE, 0.234]; cue B − A for the medicated SZ group, −0.249 [SE, 0.143]; $P = .08$) (Table 2 and Figure 3C). The medicated SZ group showed higher activation than the nonmedicated SZ group, but this difference did not reach significance. A similar pattern was observed in the right DLPFC. The nonmedicated and medicated SZ groups showed lower activation than the HC group on high control trials (nonmedicated SZ group, −0.83; medicated SZ group, −0.37 from HCs; both $P < .05$). The medicated SZ group showed higher activation than the nonmedicated SZ group, but this difference did not reach significance.

Exploratory Analysis of Covariates

Sex was not associated with the level or trajectory of performance or DLPFC ROI activation across the age span. Within the SZ group, duration of untreated psychosis was not associated with performance or activation. Higher clinical symptoms of reality distortion (−0.025 [SE, 0.011]; $P = .02$), disorganization (−0.115 [0.023]; $P < .001$), poverty (−0.031 [SE, 0.013]; $P = .02$), and lower global functioning (0.017 [SE, 0.007]; $P = .01$) were associated with significantly lower performance on the AX-CPT, regardless of age (eTable 2 in the Supplement; all $P < .05$). Clinical factors, however, did not affect the trajectory of performance or activation across the age span.

The SZ group with follow-up contributed data to estimates of the effect of time since baseline on cognitive control performance and associated activation. Although time in the study did not reach statistical significance as a covariate (except for left DLPFC ROI activation), all coefficients were positive, suggesting that performance did not worsen over time in patients with SZ and follow-up data (eTables 2 to 4 in the Supplement). eTable 5 in the Supplement reports results of sensitivity analyses restricted to the 90 participants with at least 1 follow-up. Results parallel those from the core models, with

the estimates of effect of time since baseline in the SZ group close to 0 (d′-context) or positive (DLPFC ROI activation), although relatively small with respect to SEs.

Discussion

To our knowledge, this study is the first to examine the longitudinal course of behavioral and functional deficits in cognitive control in young individuals with recent-onset SZ. Although typical cross-sectional studies only allow examination of age differences between groups, the current investigation used mixed-models analysis to examine (1) age-related differences between HCs and patients with SZ at baseline and (2) differences in the pattern of age-related changes within and between HCs and patients with SZ over time. In this large sample, deficits in cognitive control were observed in the SZ group relative to age-matched HCs at baseline using a well-validated paradigm, the AX-CPT.[47-52] We found no evidence for longitudinal deterioration of PFC functioning; rather, patients and HCs exhibited similar developmental trends in behavioral performance and brain function throughout adolescence and early adulthood.

Performance

Individuals with SZ showed impairments in cognitive control at illness onset regardless of age. This finding is consistent with previous behavioral studies of first-episode psychosis,[51] including those in the present cohort.[15,26,52,54,55] Onset of SZ coincides with critical periods of brain development during adolescence and early adulthood,[9] and cognitive functioning in healthy young adults improves during adolescence and early adulthood. Age at onset, however, was not associated with the extent of impaired behavioral performance in the SZ group because they showed a stable deficit at the point of onset, with a pattern of performance during follow-up that was comparable to that of the HCs.

Functional Activity

Consistent with previous studies,[15,26,38,52,54,55] patients exhibited significantly lower bilateral DLPFC activation during cognitive control-associated trials compared with the HCs. Paralleling our behavioral results, comparable DLPFC deficits were observed regardless of age at onset, and patients showed reduced yet stable bilateral DLPFC activation across the developmental age similar to that of the HCs. This finding supports the neurodevelopmental hypothesis of SZ,[16,17] in which deficits emerge before illness onset and remain relatively stable. Behavioral and functional activation results suggest prefrontal development is not arrested in SZ but rather that patients show ongoing brain development comparable to that of HCs, highlighting the possibility for plasticity and developmental capacity with therapeutic implications.

Association of Antipsychotic Medication

Individuals with SZ who were using antipsychotics at the time of assessment showed a tendency toward better performance than those who used no medication. Across the age span, the medicated SZ group showed greater left DLPFC activation compared with the nonmedicated SZ group. Consistent with previous studies,[66] medications did not account for the cognitive deficits observed in this SZ sample. Although consistent with previous publications,[15] we must acknowledge that our nonmedicated SZ group was small, and we did not examine the association of within-individual changes in medication dose between assessments or adherence owing to the naturalistic nature of the study. Therefore, these results should be considered preliminary and in need of replication.

Exploratory Analysis of Covariates

Neither sex nor duration of untreated psychosis was associated with performance or DLPFC activation, on average, across the age span. Symptom severity and poor global functioning were associated with worse cognitive control. These findings suggest that the clinical and functional state may be associated with an individual's mean prefrontal functioning but are not associated with their pattern of recovery or deterioration during follow-up. These results also suggest that pathologic changes in SZ may not affect the development of cognitive control processes after illness onset.

Limitations

This work is strengthened by inclusion of task-based functional neuroimaging analysis, bolstering links between brain and behavior in an established cognitive deficit in SZ. Longitudinal studies of the neuronal basis of cognition in psychiatric diseases are rare owing to the inherent challenges in performing such studies. Although this study was strengthened by the large sample size at baseline, significantly higher attrition was observed in the SZ compared with the HC groups, which may bias results. Our mixed-effects analysis yields valid estimates under the assumption of data missing at random, and valid estimates of group effects can often be obtained even when missing values are not completely random.[67] We conservatively estimated the association of time since baseline using only the patients with SZ with follow-up data. A second potential limitation is practice effects; however, a longitudinal study of AX-CPT performance[68] did not report practice effects in younger patients with SZ.

In general, this study was a treatment-engaged cohort with most participants showing clinical improvement during the relatively short follow-up period. These results might not generalize to a community-based sample or over a longer-term follow-up period. Future replication studies with additional follow-up are important next steps.

Conclusions

Results suggest that cognitive control deficits in SZ are present at onset and nondeteriorating, in agreement with the neurodevelopmental model of illness. Indeed, the observed pattern of performance for SZ across the age span suggests that these patients continue to benefit from ongoing brain maturation during the critical period of development from adolescence into young adulthood. Future research should examine the effects of specific interventions (eg, cognitive remediation, psychotherapy, medication, supported education, and employment) on the trajectory of cognitive control deficits in psychotic illness.

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Author Affiliations: Department of Psychiatry and Behavioral Sciences, University of California, Davis, Sacramento (Niendam, Ray, Lesh, Ashby, Patel, Smucny, Solomon, Ragland, Carter); Department of Psychology, The University of Texas at Austin (Ray); Division of Biostatistics, Department of Public Health Sciences, University of California, Davis, Sacramento (Iosif); Department of Psychology, University of Oregon, Eugene (Ashby); Department of Psychology, UCLA (University of California, Los Angeles), Westwood (Patel); Department of Psychology, University of California, Davis, Sacramento (Ferrer); MIND Institute, University of California, Davis, Sacramento (Solomon); Center for Neuroscience, University of California, Davis, Sacramento (Carter).

Author Contributions: Drs Niendam and Iosif had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Niendam, Lesh, Solomon, Ragland, Carter.
Acquisition, analysis, or interpretation of data: Niendam, Ray, Iosif, Lesh, Ashby, Patel, Smucny, Ferrer, Solomon, Carter.
Drafting of the manuscript: Niendam, Ray, Iosif, Lesh, Ashby, Smucny, Carter.
Critical revision of the manuscript for important intellectual content: Niendam, Ray, Iosif, Lesh, Patel, Smucny, Ferrer, Solomon, Ragland, Carter.
Statistical analysis: Niendam, Iosif, Ashby, Ferrer.
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Supervision: Lesh, Solomon, Ragland, Carter.

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REFERENCES

1. Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet*. 1976; 2(7992):924-926. doi:10.1016/S0140-6736(76)90890-4

2. Weinberger DR, Torrey EF, Neophytides AN, Wyatt RJ. Lateral cerebral ventricular enlargement in chronic schizophrenia. *Arch Gen Psychiatry*. 1979; 36(7):735-739. doi:10.1001/archpsyc.1979.01780070013001

3. Reveley AM, Reveley MA, Clifford CA, Murray RM. Cerebral ventricular size in twins discordant for schizophrenia. *Lancet*. 1982;1(8271):540-541. doi:10.1016/S0140-6736(82)92047-5

4. Arango C, Rapado-Castro M, Reig S, et al. Progressive brain changes in children and adolescents with first-episode psychosis. *Arch Gen Psychiatry*. 2012;69(1):16-26. doi:10.1001/archgenpsychiatry.2011.150

5. Kubota M, van Haren NE, Haijma SV, et al. Association of IQ changes and progressive brain changes in patients with schizophrenia. *JAMA Psychiatry*. 2015;72(8):803-812. doi:10.1001/jamapsychiatry.2015.0712

6. Lieberman J, Chakos M, Wu H, et al. Longitudinal study of brain morphology in first episode schizophrenia. *Biol Psychiatry*. 2001;49(6):487-499. doi:10.1016/S0006-3223(01)01067-8

7. Cahn W, van Haren NE, Hulshoff Pol HE, et al. Brain volume changes in the first year of illness and 5-year outcome of schizophrenia. *Br J Psychiatry*. 2006;189:381-382. doi:10.1192/bjp.bp.105.015701

8. Ho BC, Mola C, Andreasen NC. Cerebellar dysfunction in neuroleptic naive schizophrenia patients: clinical, cognitive, and neuroanatomic correlates of cerebellar neurologic signs. *Biol Psychiatry*. 2004;55(12):1146-1153. doi:10.1016/j.biopsych.2004.02.020

9. Lieberman JA. Is schizophrenia a neurodegenerative disorder? a clinical and neurobiological perspective. *Biol Psychiatry*. 1999;46(6):729-739. doi:10.1016/S0006-3223(99)00147-X

10. Kraepelin E, Robertson GM. *Dementia Praecox and Paraphrenia*. Huntington, NY: Robert E Krieger Publishing Co; 1971.

11. Kraeplin E. *Lehrbuch der Psychiatrie*. Vol 5. Leipzig, Germany: Barth; 1896.

12. Arnold SE. Neurodevelopmental abnormalities in schizophrenia: insights from neuropathology. *Dev Psychopathol*. 1999;11(3):439-456. doi:10.1017/S095457949900214X

13. Selemon LD. Increased cortical neuronal density in schizophrenia. *Am J Psychiatry*. 2004;161(9):1564. doi:10.1176/appi.ajp.161.9.1564

14. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S. Progressive brain changes in schizophrenia related to antipsychotic treatment? a meta-analysis of longitudinal MRI studies. *Neurosci Biobehav Rev*. 2013;37(8):1680-1691. doi:10.1016/j.neubiorev.2013.06.001

15. Lesh TA, Tanase C, Geib BR, et al. A multimodal analysis of antipsychotic effects on brain structure and function in first-episode schizophrenia. *JAMA Psychiatry*. 2015;72(3):226-234. doi:10.1001/jamapsychiatry.2014.2178

16. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry*. 1987;44(7):660-669. doi:10.1001/archpsyc.1987.01800190080012

17. Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? *BMJ (Clin Res Ed)*. 1987;295(6600):681-682. doi:10.1136/bmj.295.6600.681

18. Cannon TD, Rosso IM, Bearden CE, Sanchez LE, Hadley T. A prospective cohort study of neurodevelopmental processes in the genesis and epigenesis of schizophrenia. *Dev Psychopathol*. 1999;11(3):467-485. doi:10.1017/S0954579499002163

19. Pettegrew JW, Klunk WE, Panchalingam K, McClure RJ, Stanley JA. Molecular insights into neurodevelopmental and neurodegenerative diseases. *Brain Res Bull*. 2000;53(4):455-469. doi:10.1016/S0361-9230(00)00376-2

20. Walker E. Risk factors, and the neurodevelopmental course of schizophrenia. *Eur Psychiatry*. 2002;17(suppl 4):363s-369s. doi:10.1016/S0924-9338(03)00079-8

21. Walker EF, Diforio D. Schizophrenia: a neural diathesis-stress model. *Psychol Rev*. 1997;104(4):667-685. doi:10.1037/0033-295X.104.4.667

22. Niendam TA, Bearden CE, Rosso IM, et al. A prospective study of childhood neurocognitive functioning in schizophrenic patients and their siblings. *Am J Psychiatry*. 2003;160(11):2060-2062. doi:10.1176/appi.ajp.160.11.2060

23. Walker EF, Savoie T, Davis D. Neuromotor precursors of schizophrenia. *Schizophr Bull*. 1994; 20(3):441-451. doi:10.1093/schbul/20.3.441

24. Niendam TA, Bearden CE, Johnson JK, et al. Neurocognitive performance and functional disability in the psychosis prodrome. *Schizophr Res*. 2006;84(1):100-111. doi:10.1016/j.schres.2006.02.005

25. Niendam TA, Bearden CE, Zinberg J, Johnson JK, O'Brien M, Cannon TD. The course of neurocognition and social functioning in individuals at ultra high risk for psychosis. *Schizophr Bull*. 2007; 33(3):772-781. doi:10.1093/schbul/sbm020

26. Niendam TA, Lesh TA, Yoon J, et al. Impaired context processing as a potential marker of psychosis risk state. *Psychiatry Res*. 2014;221(1):13-20. doi:10.1016/j.pscychresns.2013.09.001

27. Mittal VA, Neumann C, Saczawa M, Walker EF. Longitudinal progression of movement abnormalities in relation to psychotic symptoms in adolescents at high risk of schizophrenia. *Arch Gen Psychiatry*. 2008;65(2):165-171. doi:10.1001/archgenpsychiatry.2007.23

28. Bartholomeusz CF, Cropley VL, Wannan C, Di Biase M, McGorry PD, Pantelis C. Structural neuroimaging across early-stage psychosis: aberrations in neurobiological trajectories and implications for the staging model. *Aust N Z J Psychiatry*. 2017;51(5):455-476. doi:10.1177/0004867416670522

29. Hedman AM, van Haren NE, van Baal CG, Kahn RS, Hulshoff Pol HE. IQ change over time in schizophrenia and healthy individuals: a meta-analysis. *Schizophr Res*. 2013;146(1-3):201-208. doi:10.1016/j.schres.2013.01.027

30. Bergh S, Hjorthøj C, Sørensen HJ, et al. Predictors and longitudinal course of cognitive functioning in schizophrenia spectrum disorders, 10 years after baseline: the OPUS study. *Schizophr Res*. 2016;175(1-3):57-63. doi:10.1016/j.schres.2016.03.025

31. Rajji TK, Ismail Z, Mulsant BH. Age at onset and cognition in schizophrenia: meta-analysis. *Br J Psychiatry*. 2009;195(4):286-293. doi:10.1192/bjp.bp.108.060723

32. Fraguas D, Díaz-Caneja CM, Pina-Camacho L, Janssen J, Arango C. Progressive brain changes in children and adolescents with early-onset psychosis: a meta-analysis of longitudinal MRI studies. *Schizophr Res*. 2016;173(3):132-139. doi:10.1016/j.schres.2014.12.022

33. White T, Ho BC, Ward J, O'Leary D, Andreasen NC. Neuropsychological performance in first-episode adolescents with schizophrenia: a comparison with first-episode adults and adolescent control subjects. *Biol Psychiatry*. 2006; 60(5):463-471. doi:10.1016/j.biopsych.2006.01.002

34. Holmén A, Juuhl-Langseth M, Thormodsen R, et al. Executive function in early- and adult onset schizophrenia. *Schizophr Res*. 2012;142(1-3):177-182. doi:10.1016/j.schres.2012.10.006

35. Greenstein D, Lerch J, Shaw P, et al. Childhood onset schizophrenia: cortical brain abnormalities as young adults. *J Child Psychol Psychiatry*. 2006;47 (10):1003-1012. doi:10.1111/j.1469-7610.2006 .01658.x

36. Luna B, Sweeney JA. Studies of brain and cognitive maturation through childhood and adolescence: a strategy for testing neurodevelopmental hypotheses. *Schizophr Bull*. 2001;27(3):443-455. doi:10.1093/oxfordjournals .schbul.a006886

37. Glahn DC, Ragland JD, Abramoff A, et al. Beyond hypofrontality: a quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. *Hum Brain Mapp*. 2005; 25(1):60-69. doi:10.1002/hbm.20138

38. Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Arch Gen Psychiatry*. 2009;66(8): 811-822. doi:10.1001/archgenpsychiatry.2009.91

39. Spence SA, Hirsch SR, Brooks DJ, Grasby PM. Prefrontal cortex activity in people with schizophrenia and control subjects: evidence from positron emission tomography for remission of "hypofrontality" with recovery from acute schizophrenia. *Br J Psychiatry*. 1998;172:316-323. doi:10.1192/bjp.172.4.316

40. Smee C, Krabbendam L, O'Daly O, et al. An fMRI study of prefrontal dysfunction and symptomatic recovery in schizophrenia. *Acta Psychiatr Scand*. 2011;123(6):440-450. doi:10.1111 /j.1600-0447.2010.01632.x

41. Lee KH, Brown WH, Egleston PN, et al. A functional magnetic resonance imaging study of social cognition in schizophrenia during an acute episode and after recovery. *Am J Psychiatry*. 2006; 163(11):1926-1933. doi:10.1176/ajp.2006.163.11.1926

42. Davis CE, Jeste DV, Eyler LT. Review of longitudinal functional neuroimaging studies of drug treatments in patients with schizophrenia. *Schizophr Res*. 2005;78(1):45-60. doi:10.1016 /j.schres.2005.05.009

43. Wolf RC, Vasic N, Höse A, Spitzer M, Walter H. Changes over time in frontotemporal activation during a working memory task in patients with schizophrenia. *Schizophr Res*. 2007;91(1-3):141-150. doi:10.1016/j.schres.2006.12.001

44. Reske M, Kellermann T, Habel U, et al. Stability of emotional dysfunctions? a long-term fMRI study in first-episode schizophrenia. *J Psychiatr Res*. 2007;41(11):918-927. doi:10.1016/j.jpsychires.2007 .02.009

45. Blasi G, Popolizio T, Taurisano P, et al. Changes in prefrontal and amygdala activity during olanzapine treatment in schizophrenia. *Psychiatry Res*. 2009;173(1):31-38. doi:10.1016/j.pscychresns .2008.09.001

46. Pantelis C, Yücel M, Wood SJ, et al. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophr Bull*. 2005;31(3):672-696. doi:10.1093/schbul/sbi034

47. Cohen JD, Barch DM, Carter C, Servan-Schreiber D. Context-processing deficits in schizophrenia: converging evidence from three theoretically motivated cognitive tasks. *J Abnorm Psychol*. 1999;108(1):120-133. doi:10.1037/0021-843X .108.1.120

48. MacDonald AW III, Carter CS. Event-related fMRI study of context processing in dorsolateral prefrontal cortex of patients with schizophrenia. *J Abnorm Psychol*. 2003;112(4):689-697. doi:10.1037/0021-843X.112.4.689

49. Barch DM, Carter CS, Braver TS, et al. Selective deficits in prefrontal cortex function in medication-naive patients with schizophrenia. *Arch Gen Psychiatry*. 2001;58(3):280-288. doi:10.1001 /archpsyc.58.3.280

50. Barch DM, Mathews JR, Buckner RL, Maccotta L, Csernansky JG, Snyder AZ. Hemodynamic responses in visual, motor, and somatosensory cortices in schizophrenia. *Neuroimage*. 2003;20(3): 1884-1893. doi:10.1016/S1053-8119(03)00449-X

51. Barch DM, Carter CS, MacDonald AW III, Braver TS, Cohen JD. Context-processing deficits in schizophrenia: diagnostic specificity, 4-week course, and relationships to clinical symptoms. *J Abnorm Psychol*. 2003;112(1):132-143. doi:10.1037 /0021-843X.112.1.132

52. Yoon JH, Minzenberg MJ, Ursu S, et al. Association of dorsolateral prefrontal cortex dysfunction with disrupted coordinated brain activity in schizophrenia: relationship with impaired cognition, behavioral disorganization, and global function [published correction appears in *Am J Psychiatry*. 2008;165(10):1359.]. *Am J Psychiatry*. 2008;165(8):1006-1014. doi:10.1176/appi.ajp.2008 .07060945

53. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982;38(4):963-974. doi:10.2307/2529876

54. Lesh TA, Westphal AJ, Niendam TA, et al. Proactive and reactive cognitive control and dorsolateral prefrontal cortex dysfunction in first episode schizophrenia. *Neuroimage Clin*. 2013;2: 590-599. doi:10.1016/j.nicl.2013.04.010

55. Yoon JH, Nguyen DV, McVay LM, et al. Automated classification of fMRI during cognitive control identifies more severely disorganized subjects with schizophrenia. *Schizophr Res*. 2012; 135(1-3):28-33. doi:10.1016/j.schres.2012.01.001

56. Lukoff D, Nuechterlein KH, Ventura J. Manual for the Expanded Brief Psychiatric Rating Scale (BPRS). *Schizophr Bull*. 1986;12:594-602.

57. Andreasen N. *The Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City: University of Iowa; 1984.

58. Andreasen N. *The Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City: University of Iowa; 1983.

59. Hall RC. Global Assessment of Functioning: a modified scale. *Psychosomatics*. 1995;36(3):267-275. doi:10.1016/S0033-3182(95)71666-8

60. Servan-Schreiber D, Cohen JD, Steingard S. Schizophrenic deficits in the processing of context: a test of a theoretical model. *Arch Gen Psychiatry*. 1996;53(12):1105-1112. doi:10.1001/archpsyc.1996 .01830120037008

61. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002;17(2):825-841. doi:10.1006/nimg.2002.1132

62. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal*. 2001;5(2):143-156. doi:10.1016/S1361-8415(01)00036-6

63. MacDonald AW III, Cohen JD, Stenger VA, Carter CS. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*. 2000;288(5472):1835-1838. doi:10.1126/science.288.5472.1835

64. Snitz BE, MacDonald A III, Cohen JD, Cho RY, Becker T, Carter CS. Lateral and medial hypofrontality in first-episode schizophrenia: functional activity in a medication-naive state and effects of short-term atypical antipsychotic treatment. *Am J Psychiatry*. 2005;162(12):2322-2329. doi:10.1176/appi.ajp.162.12.2322

65. *SAS/STAT* [computer program]. Version 9.4. Cary, NC: SAS Institute Inc; 2002-2012.

66. Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Arch Gen Psychiatry*. 2011;68(2):128-137. doi:10.1001/archgenpsychiatry .2010.199

67. Newgard CD, Lewis RJ. Missing data: how to best account for what is not known. *JAMA*. 2015; 314(9):940-941. doi:10.1001/jama.2015.10516

68. Strauss ME, McLouth CJ, Barch DM, et al. Temporal stability and moderating effects of age and sex on CNTRaCS task performance. *Schizophr Bull*. 2014;40(4):835-844. doi:10.1093/schbul /sbt089