Neurocognitive Growth Charting in Psychosis Spectrum Youths

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IMPORTANCE Psychosis-risk studies have examined help-seeking adolescents and young adults. Population-based studies evaluating psychotic symptoms and neurocognitive performance across childhood are needed for “growth charting” cognitive development. We hypothesized that psychosis spectrum youths have delayed neurocognitive age relative to chronological age. We expected larger lags with increased symptom severity and in late adolescence and early adulthood.

OBJECTIVES To examine neurocognitive age and compare typically developing participants with psychosis spectrum participants.

DESIGN, SETTING, AND PARTICIPANTS The Philadelphia Neurodevelopmental Cohort is a genotyped sample, with electronic medical records, enrolled in the study of brain behavior. In an academic and children’s hospital health care network, a structured psychiatric evaluation was performed and a computerized neurocognitive battery administered to evaluate performance in several domains. From 18 344 youths in the recruitment pool who were aged 8 to 21 years, physically and cognitively capable of participating, and proficient in English, participants were randomly selected with stratification for age, sex, and ethnicity. A total of 9138 participants were enrolled in the study between November 1, 2009, and November 30, 2011, and 2321 endorsed psychotic symptoms: 1423 significant (psychosis spectrum) and 898 limited (psychosis limited). They had no comorbid medical conditions. They were compared with 981 participants endorsing significant other psychiatric symptoms and with 1963 typically developing children with no psychiatric or medical disorders.

MAIN OUTCOMES AND MEASURES The computerized neurocognitive battery provides accuracy and speed measures on 12 tests and speed measures alone on 2, yielding 26 measures used in a regression analysis to predict chronological age. Prediction was performed on the entire set and separately for each domain (executive, episodic memory, complex cognition, social cognition, and sensorimotor speed).

RESULTS Throughout childhood and adolescence, the psychosis spectrum group had lower predicted age compared with the typically developing group and the group with other psychiatric symptoms. The psychosis spectrum group had a greater developmental lag than the psychosis limited group. The lags were most pronounced for complex cognition and social cognition and were smallest for sensorimotor speed.

CONCLUSIONS AND RELEVANCE Individuals who endorse psychotic symptoms are neurocognitively delayed across the age range; this delay relates to symptom severity and is not prominent in other psychiatric disorders. Combined clinical and neurocognitive assessment can facilitate early detection and targeted intervention to delay or ameliorate disease progression.

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A cross medicine, early identification of disorders is increasingly recognized as critical for optimizing therapeutic interventions. The schizophrenia prodrome is a prolonged phase of subthreshold symptoms and functional decline preceding diagnostic conversion.\(^1\)\(^,\)\(^2\) A growing literature has examined the clinical course of help-seeking individuals with prodromal presentation and gauged rates of conversion to schizophrenia.\(^3\)\(^,\)\(^4\) Because impaired cognition is a core feature of schizophrenia associated with disrupted functioning,\(^5\)\(^,\)\(^6\) prodromal investigations have incorporated neurocognitive tests sensitive to deficits in schizophrenia.\(^7\)\(^,\)\(^8\) Meta-analyses conclude that at-risk individuals show a similar deficit profile, albeit with less impairment than evident in first-episode and chronic schizophrenia.\(^9\)\(^,\)\(^10\) While longitudinal studies are limited, individuals who transition to psychosis manifest greater neurocognitive deficits at intake.\(^9\)\(^,\)\(^10\)

Epidemiologic studies report psychotic symptoms during childhood,\(^11\)\(^-\)\(^13\) with prevalence of 17% in children (aged 9-12 years) and 7.5% in adolescents (aged 13-18 years),\(^14\) but the link to cognition is unknown.\(^1\) One study examined psychosis and cognition\(^15\) in 212 children, aged 11-13 years, reporting 8% prevalence for the risk syndrome associated with processing speed and working memory deficits. Notably, the age range is lower than late adolescence and early adulthood examined in prodromal clinics.

Population-based studies combining clinical and neurocognitive assessment can help transcend symptom-based classifications and incorporate phenotypic biomarkers for integration with genomics. Because schizophrenia is a neurodevelopmental disorder, concomitant evaluation of psychosis and cognition is required for creating “growth charts” of cognitive development in psychosis spectrum (PS) individuals relative to typically developing (TD) individuals. Such charts can help integrate brain-behavior phenotypes in a developmental context and detect course characteristics related to psychosis vulnerability, providing tools for staging and intervention.

The developmental course of cognitive performance has been studied with diverse tests.\(^16\)\(^-\)\(^18\) We have implemented a computerized neurocognitive battery (CNB)\(^19\) in large-scale studies,\(^20\)\(^-\)\(^23\) measuring performance in executive, episodic memory, complex cognition, social cognition, and sensorimotor speed domains. Deficits prominent in schizophrenia are heritable and are milder in unaffected family members.\(^20\)\(^,\)\(^21\)\(^,\)\(^22\)\(^,\)\(^23\)\(^-\)\(^25\) The sensitivity and validity of the CNB was established in a developmental cohort of 3500 Philadelphia Neurodevelopmental Cohort participants in whom we documented age and sex effects on performance.\(^26\)

To generate neurocognitive age growth charts, indices are calculated reflecting predicted age based on performance. When neurocognitive age lags behind chronological age, there is a delay or below age-expected performance; conversely, when neurocognitive age surpasses chronological age, there is accelerated or above-expectation performance. Herein, we examine neurocognitive age in the Philadelphia Neurodevelopmental Cohort sample and compare TD participants with those who endorsed psychotic symptoms. We hypothesized that youths with psychotic features have lower neurocognitive age relative to chronological age. We expected a larger gap with increased symptom severity and in late adolescence and early adulthood, a dynamic maturational period associated with clinical presentation of schizophrenia. We preliminarily evaluated the specificity of the findings by comparing PS individuals with and without other psychiatric morbidity and by examining a group endorsing other psychiatric symptoms.

### Methods

#### Participants

The Philadelphia Neurodevelopmental Cohort included children (aged 8-21 years) recruited through a National Institute of Mental Health Grand Opportunity study characterizing clinical and neurobehavioral phenotypes in a genotyped, prospectively accrued community cohort. Participants initially provided written consent for genomic studies when they presented for pediatric services to the Children’s Hospital of Philadelphia health care network. They provided blood samples for genetic studies, authorized access to electronic medical records, and provided written informed consent or assent to be recontacted for future studies. Of the 50 540 genotyped subjects, 18 344 met the following entrance criteria and were randomly selected, stratified for age, sex, and ethnicity: (1) ambulatory in stable health; (2) proficient in English; (3) physically and cognitively capable of participating in an interview and performing the CNB; and (4) absence of a disorder that markedly impairs motility or cognition (eg, paresis or palsy, intellectual disability). Notably, participants were not recruited from psychiatric clinics and the sample is not enriched for individuals who seek psychiatric help. Eligible participants were contacted by letter, which was followed by a telephone call that provided an opportunity to ask questions and schedule the study. A total of 9138 participants enrolled between November 1, 2009, and November 30, 2011, and were available for this analysis. Medical comorbidity was established using interview and electronic medical records. Severity of medical conditions was quantified as the following: 1 indicates none, no ongoing conditions requiring sustained intervention or interference with functioning; 2, mild, conditions requiring pediatric visits and sometimes medications but mild in severity; 3, moderate, conditions requiring standing medications and monitoring; and 4, severe, conditions requiring procedures and monitoring and that can be life threatening. Participants provided written informed consent or assent after a description of the study. Institutional review boards at the University of Pennsylvania and the Children’s Hospital of Philadelphia approved the protocol.

Participants with medical ratings lower than 3 who endorsed psychotic symptoms were compared with TD youths without psychiatric symptoms. Following established criteria, we defined a PS group and a psychosis limited (PL) group. To address specificity, we included all participants with medical ratings lower than 3 meeting criteria for other psychiatric disorders (OP): mood, anxiety, attention-deficit, disruptive behavior, and eating disorders. Groups differed in race compa...
sition, parental education, and Wide Range Achievement Test (WRAT) scores (Table 1).

Clinical Assessment

The program GOASSESS computerizes the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL). Participants aged 11 to 21 years were interviewed individually; collateral information was obtained independently from a caregiver for children aged 8 to 17 years. GOASSESS records demographic characteristics, life events, school performance, updated medical history, and emotional symptoms of anxiety, mood, attention-deficit, disruptive behavior, and eating disorders. Psychosis was assessed with added emphasis on subthreshold symptoms. For children older than 11 years, a substance use scale was self-administered. The clinical assessment took about 2 hours. Assessors were trained extensively (by M.E.C.), observed, certified, and monitored.

Psychosis Spectrum

GOASSESS included 3 measures of psychotic symptoms: (1) subthreshold positive symptoms in the past year were assessed with the 12-item assessor-administered PRIME Screen-Revised (PS-R) items were read out loud and self-rated on a 7-point scale [0 indicates definitely disagree; 6, definitely agree], and endorsement is followed by indicating onset of each endorsed symptom rated ≥4; (2) lifetime threshold hallucinations and delusions were evaluated with the K-SADS-PL psychosis questions and structured follow-up probes (a positive psychosis screen required either proband or collateral endorsing hallucinations or delusions lasting ≥1 day outside the context of substance use, illness, or medication use and with significant impairment or distress [rating ≥5 on an 11-point scale ranging from 0-10]); and (3) negative and disorganized symptoms were evaluated using 6 assessor-rated items from the Structured Interview for Prodromal Syndromes (SIPS) (item N2, avolition; N3, expression of emotion; N4, experience of emotions and self; N6, occupational functioning; D3, trouble with focus and attention; and P5, disorganized communication). The SIPS focus and attention scale was rated based on responses to the attention-deficit/hyperactivity disorder items; expression of emotion was based on interviewer observations throughout the assessment; and the remaining items were based on specific open-ended questions from the SIPS. Participants were included as PS if they met at least 1 of the following criteria: (1) were rated at severity 2 SDs or greater above their age-matched peers on the PS-R or SIPS; (2) had at least 1 PS-R item rated 6 or at least 3 items rated 5 (somewhat agree); or (3) endorsed definite or possible hallucinations or delusions on the K-SADS-PL psychosis screen. The PL group included individuals who did not meet criteria for PS but endorsed more subpsychotic (PS-R) or subthreshold negative or disorganized (SIPS) symptoms than their age-matched peers (±1 SD of the mean). Note that the PL group is smaller than the PS group because it is based only on the age-normed PS-R and Scale of Prodromal Symptoms scores.

Neurocognitive Assessment

The 1-hour CNB includes 14 tests assessing 5 neurobehavioral domains: executive (abstraction and mental flexibility, attention, working memory), episodic memory (words, faces, shapes), complex cognition (verbal reasoning, nonverbal reasoning, spatial processing), social cognition (emotion identification, emotion intensity differentiation, age differentiation), and sensorimotor speed (motor, sensorimotor). Except for the tests designed exclusively for measuring speed, each test provides measures of both accuracy and speed. The reading subtest of the WRAT was administered first to determine participants’ ability to complete the battery and to provide an estimate of IQ.

Statistical Analysis

Raw CNB scores were standardized (z transformed) as previously detailed. For consistency of interpretation, higher z scores always reflect better performance; z scores where higher numbers reflected poorer performance (ie, response time) were multiplied by −1.

To develop the neurocognitive growth chart, we performed a regression analysis with 10-fold cross-validation (SAS PROC GLMSELECT), entering age in years, with (date of evaluation − date of birth)/365.25 as a dependent measure to be predicted from the 26 performance measures (12 tests of accuracy and speed, 2 tests of only speed). The regression procedure adds variables to the model until additional variables do not
contributesignificantlytothepredictedvariance ($R^2$) in age.

Variablesselectedbythelinearmodelweresubmittedtofurthexaminationofnonlinearcomponentsusingageneraladditivemodel (SAS PROC GAM). Variables with significant nonlinear trends were entered into the linear model to evaluate whether their squared values added to the ability to predict age. These procedures were applied for the entire set of scores and then separately for each domain (executive, episodic memory, complex cognition, social cognition, and sensorimotor speed), entering all the scores from that domain. Regressions were run separately for males and females, and weights were based on the TD sample. As an outcome of these procedures, we calculated the predicted neurocognitive age across domains and for each domain separately. A across domains indicates the variables entering into the overall age prediction, and within domains shows the calculation for each domain.

### Results

**Prediction of Chronological Age From Performance Across Neurocognitive Domains**

The GLMSELECT obtained a model that predicted about 63% of the variance in age. Adjusted $R^2$ was 0.635 using 16 of the 26 scores in males and 0.629 using 13 scores in females (Table 2). Follow-up general additive model procedures did identify several measures with significant quadratic components, but when entered into the model, they did not improve the $R^2$ appreciably. For simplicity in clinical contexts, we retained the initial model (without squared variables) as it was more easily interpretable for diagnosis and intervention. The correlations between chronological and predicted cognitive age were 0.798, 0.780, 0.705, and 0.669 for the TD, OP, PL, and PS groups, respectively.

The age group × sex × diagnosis (TD, OP, PS, PL) MANCOVA on predicted age showed the expected main effects for age group ($F_{2,5193} = 685.22; P < .001$), with higher predicted age associated with higher chronological age. The main effect of diagnosis was significant ($F_{3,5193} = 11.37; P < .001$), indicating that the groups differed on predicted age. The age group × diag-

### Table 2. Coefficients for Calculating Neurocognitive Age Across and Within Domains*

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Executive</th>
<th>Memory</th>
<th>Complex Cognition</th>
<th>Social Cognition</th>
<th>Sensorimotor Speed</th>
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<tr>
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<tr>
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<td></td>
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<td></td>
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<td></td>
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</table>

*To calculate neurocognitive age, β weights are multiplied by the standardized scores and added to the intercept. Across domains indicates the variables entering into the overall age prediction, and within domains shows the calculation for each domain.

Abbreviations: ABF, abstraction and mental flexibility; AGD, age differentiation; ATT, attention; EMD, emotion intensity differentiation; EMI, emotion identification; FMEM, face memory; LAN, verbal (language-mediated) reasoning; MOT, motor speed; NVR, nonverbal reasoning; SM, sensorimotor speed; SMEM, spatial memory; SPA, spatial processing; VMEM, verbal memory; WM, working memory.

To address specificity, we used MANCOVAs to compare PS participants with other psychiatric symptoms vs those without and to compare the OP participants with TD participants and with the PS groups.
Figure 1. Chronological Age Compared With Predicted Neurocognitive Age for Female and Male Psychosis Spectrum Participants and Typically Developing Participants

Analysis by Domains
The MANCOVAs contrasting PS with TD on predicted age for the 5 specific domains yielded significant interactions of domain. These included (significance by the Hotelling-Lawley trace) domain × diagnosis × sex ($F_{4,4177} = 2.43; P = .046$), indicating that the decrement in predicted age for PS differed by sex. A 3-way interaction of domain × sex × age group ($F_{48,12272} = 1.71; P = .002$) indicated that the sex difference in domain-predicted age was age group related, and a 4-way interaction of domain × sex × age group × diagnosis ($F_{48,12272} = 1.57; P = .007$) indicated that these effects differed between the TD and PS groups. As can be seen in Figure 1B-F, PS males showed an early decrement in memory, complex cognition, and social cognition, which remained stable across the age cohorts with some amelioration for complex cognition. The PS females showed minimal lag in memory across all age groups, while for complex cognition the lag appeared at a later age group but was more persistent.
Contrasting PS and PL Groups

The MANCOVA contrasting PS with PL groups on predicted age showed main effects for severity group ($F_{1,1397} = 15.07; P < .001$), with higher predicted age for the PL group compared with the PS group. The means are shown in Figure 2A. The MANCOVA on the domain-related age predictions additionally showed a severity group × domain interaction ($F_{4,2258} = 2.46; P = .04$), with lower predicted age for the PS group more pronounced for complex cognition and social cognition domains (Figure 2B–F).

Contrasting PS With and Without Other Psychiatric Comorbidity

The MANCOVA contrasting within the PS cohort those with other psychiatric comorbidities (n = 855) vs those without (n = 568) showed no main effect of group on predicted age ($F_{1,1397} = 1.29; P = .26$). It also did not show a group × age group interaction ($F_{2,1397} = 0.57; P = .87$).

Discussion

Prodromal studies in help-seeking youths do not provide data on cognition earlier in development. Cohort studies of adults with schizophrenia document cognitive deficits on testing during school age but limited contemporaneous data on psychotic features. In this largest population-based study to date evaluating psychotic symptoms and neurocognition, 15.5% of the sample endorses significant psychotic symptoms and 9.8% have milder symptoms, comparable to estimates from a meta-analysis in youths. The growth charts show that individuals who report psychotic symptoms are neurocognitively behind chronological age compared with TD youths. Furthermore, those with more significant symptoms show greater developmental lag than those with milder symptoms not meeting prodromal criteria. The growth charts suggest that the delay associated with endorsement of psychotic symptoms is across domains, ranges between 6 and 18 months, and is present already at age 8 years. After age 16 years, the departure from the normal growth curve becomes wider. These findings augment the literature documenting cognitive deficits in school-aged children eventually diagnosed as having psychosis. Our study demonstrates that both cognitive delay and psychotic symptoms co-occur and are detectable at an early age.

The developmental delay is more pronounced in some cognitive domains than others, with effect sizes ranging from small to medium. The New Zealand longitudinal cohort suggests that children who later develop schizophrenia already have deficits in verbal reasoning in childhood and deficits later evolve in working memory, attention, and processing speed.

Our cross-sectional data are consistent as complex cognition, including verbal reasoning, already lags in the psychosis groups at age 8 years and remains pronounced. We also documented a lag in social cognition already evident at that age, not evaluated in previous studies.

The lag is not constant across the age span, narrowing at age 12 years and again at age 16 years. In a cross-sectional study, these could reflect cohort effects (eg, placement of severe cases in special programs). However, the effects are consistent for males and females and across severity groups. They could reflect resilience or other factors. Only longitudinal studies can resolve such issues, and the age bands 11 to 13 years and 15 to 17 years seem especially important for longitudinal focus.

Notably, working memory and face memory do not contribute to predicting chronological age and show less age-related improvement than other domains, having a protracted developmental course. Sex differences in neurocognitive gap were domain specific, with PS females showing earlier and greater lag in complex and social cognition relative to their TD counterparts. Females with schizophrenia have a later onset and less severe symptoms, reflecting less vulnerability; perhaps greater neurocognitive dysfunction is needed for psychosis to occur.

While our ascertainment procedures differ from current clinical high-risk studies that recruit help seekers, we nonetheless capture an at-risk sample. The WRAT scores and parental education are lower in the psychosis groups, consistent with clinical high-risk samples and population-based studies of psychosis in adults. The current ascertainment strategy captures a broader continuum of psychotic experiences related to neurocognition in youths who are not help

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Table 3. Sample and Effect Sizes for Each Age Group on Average Neurocognitive Age by Domain

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<th>17</th>
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Abbreviations: NC, neurocognitive; PS, psychosis spectrum; TD, typically developing.
Important, a major feature of psychosis is limited insight and refrain from help seeking. While the focus of this article is on psychosis, the Philadelphia Neurodevelopmental Cohort dataset enabled examination of psychiatric comorbidities and specificity. We found that participants with other psychiatric disorders did not show a neurocognitive delay. Within PS, those who had other psychiatric disorders did not differ from those without such comorbidity. Furthermore, medical comorbidity could be excluded through the interview and electronic medical records. Thus, the neurocognitive delay seems firmly related to the presence and severity of psychotic symptoms.

An obvious limitation of this study is its cross-sectional nature, which precludes separating progression from cohort effects. However, participants have consented to be recontacted and we are following up with comprehensive assessment and neuroimaging in 300 PS and 200 TD individuals. Because it is likely that not all PS will develop into debilitating or distressing psychosis, follow-up will provide the opportunity to examine risk and protective factors. Another limitation is the lack of validation of the GOASSESS instrument. We have taken care to ensure reliable administration by highly trained and monitored assessors, and the majority of GOASSESS derived from the K-SADS-PL using similar probes and item wording. GOASSESS DSM-IV-TR disorder indices and National Comorbidity Survey–Adolescent Supplement DSM-IV-TR diagnoses exhibited very good concordance in the National Comorbidity Survey–Adolescent Supplement sample, providing support for their validity. However, the National Comorbidity Survey–Adolescent Supplement sample did not assess psychosis. The ratings of psychotic symptoms included in GOASSESS incorporate established instruments, which have shown predictive validity of clinical high-risk status. Initial evaluation of our follow-up data, which included blinded consensus review, indicates acceptable sensitivity and specificity. The ascertainment through pediatric clinics may affect generalizability, and we have taken steps to address this potential limitation. Electronic medical records were first
screened for significant disorders that may affect performance. Thus, we did not include children with physical or mental conditions that compromise performance. Indeed, all participants completed the CNB and were fully engaged. The WRAT scores also attest to the average cognitive abilities of the normative sample. We set a relatively low bar for inclusion to capture a diverse sample and further limited the analysis to children who do not have significant medical conditions. Another limitation is reliance on a 1-hour battery to assess neurocognitive performance. Although this duration is vastly shorter than that required by traditional batteries, it is still too long for routine screening. We are applying psychometric methods including item response theory to improve efficiency of testing and facilitate alternative methods of administration.

Conclusions

This study illustrates the utility of neurocognitive age in efforts to understand the developmental unfolding of psychosis. We demonstrated that individuals who endorse psychotic symptoms have a neurocognitive lag already at age 8 years, when they are almost a year behind. While this gap widens and narrows during the developmental span, its existence concomitant with psychotic symptoms at an early age should facilitate early detection and provide information necessary for designing intervention strategies. Although as a group PS individuals show greater lag in complex cognition than other domains, including executive functions, the lag pattern may differ for individuals and can form the basis for designing tailored intervention approaches. Furthermore, neurocognitive age provides a metric that can be used to examine other indices of maturation such as “brain age.” Structural and functional magnetic resonance imaging studies are applying the brain age concept to provide an estimate of neurobiological parameters in relation to chronological age during both childhood and senescence. Integration of brain measures with neurocognitive parameters provides phenotypes for genomics to achieve early and individualized prognostic profiles informing intervention.

REFERENCES


