Trajectories of cognitive development during adolescence among youth at-risk for schizophrenia

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Background: Among adults with schizophrenia, evidence suggests that premorbid deficits in different cognitive domains follow distinct developmental courses during childhood and adolescence. The aim of this study was to delineate trajectories of adolescent cognitive functions prospectively among different groups of youth at-risk for schizophrenia, relative to their typically developing (TD) peers. **Method:** Using linear mixed models adjusted for sex, ethnicity, parental occupation and practice effects, cognitive development between ages 9 and 16 years was compared for youth characterised by a triad of well-replicated developmental antecedents of schizophrenia (ASz; $N = 32$) and youth with a least one affected relative with schizophrenia or schizoaffective disorder (FHx; $N = 29$), relative to TD youth ($N = 45$). Participants completed measures of IQ, scholastic achievement, memory and executive function at three time-points, separated by approximately 24-month intervals. **Results:** Compared to TD youth, both ASz and FHx youth displayed stable developmental *deficits* in verbal working memory and inhibition/switching executive functions. ASz youth additionally presented with stable *deficits* in measures of vocabulary (IQ), word reading, numerical operations, and category fluency executive function, and a slower rate of growth (developmental *lag*) on spelling from 9 to 16 years than TD peers. Conversely, faster rates of growth relative to TD peers (developmental *delay*) were observed on visual and verbal memory, and on category fluency executive function (ASz youth only) and on matrix reasoning (IQ) and word reading (FHx youth only). **Conclusions:** These differential patterns of deviation from normative adolescent cognitive development among at-risk youth imply potential for cognitive rehabilitation targeting of specific cognitive deficits at different developmental phases. **Keywords:** Psychosis; intelligence; academic performance; memory; executive function.

Introduction

Schizophrenia is preceded by childhood dysfunctions in multiple cognitive domains (Dickson, Laurens, Cullen, & Hodgins, 2012), but such dysfunction may follow different developmental trajectories. Among children who develop schizophrenia in adulthood compared to those who do not, prior research has distinguished a premorbid trajectory of developmental *deficit* from age 4 to 15 years on measures of general intelligence (IQ), scholastic achievement, and verbal abilities, in which premorbid cognitive impairments emerge early and remain stable (Cannon et al., 2000; Crow, Done, & Sacker, 1995; Jones, Rodgers, Murray, & Marmot, 1994; Reichenberg et al., 2010). Conversely, a developmental *lag* whereby cognitive growth increasingly lags behind that evidenced by healthy individuals has been reported between 7 and 13 years in measures of visual-spatial problem solving and arithmetic (Reichenberg et al., 2010), with further slowing (lag) in growth in working memory

during adolescence (after age 13 years) (Meier et al., 2014).

Evidence for *developmental deterioration* (premorbid decline) in cognitive functioning across development is limited, but a decline in verbal abilities that emerges during adolescence, from age 13 to 18 years, among individuals who went on to develop schizophrenia in adulthood has been reported (Fuller et al., 2002; Maccabe, 2008). If similarly differentiated developmental trajectories of cognitive functions could be distinguished prospectively among children and adolescents who are at high-risk of schizophrenia, this would signify potential for preventative interventions targeting specific cognitive dysfunctions at key phases of development.

This study aimed to extend prior research by mapping developmental trajectories of cognitive functioning from childhood to adolescence (9–16 years) in youth at high-risk for schizophrenia relative to typically developing youth, across a range of cognitive functions known to be affected in schizophrenia. In addition to the three developmental trajectories described above (*deficit, lag* and *deterioration*), the study further examined whether

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delayed development of cognitive functions may 'catch up' during adolescence. Because cognitive development among typically developing youth is characterised by periods of gradual change interspersed with periods of accelerated cognitive growth (Thatcher, 1991), deficits in cognitive functions among at-risk youth might wax and wane during development. Thus, early difficulties may be followed by periods in which cognitive ability apparently catches up to that of healthy peers.

Although derived from data collected at a single time point between childhood and early adulthood, there is also evidence for distinct patterns of cognitive functions among at-risk youth. A recent investigation of a large population-based cohort of youth aged 8–21 years evaluated differences in age-related neurocognitive performance among those reporting and not reporting psychotic-like experiences (PLEs), an established risk marker for schizophrenia (Gur et al., 2014). Relative to peers without PLEs, youth with PLEs had a lower predicted mental age (i.e. developmental *deficit*) in a range of cognitive domains, most particularly in complex cognition indexed by verbal and nonverbal reasoning, and spatial processing. Another cross-sectional study reported a developmental *deficit* from 7 to 22 years in IQ among youth with a family history of psychosis compared to youth without such history, but also, evidence of a *delay* in visual memory performance among these individuals (Maziade et al., 2011).

To date, there have been no longitudinal reports comparing developmental trajectories of cognitive development between different at-risk populations, which may help to establish the generalisability of any subsequent predictors of psychosis (Barch, Cohen, & Csernansky, 2013). A study using cross-sectional data indicated few group differences across eight cognitive domains, with the exception of a greater impairment in vocabulary (a measure of IQ) among family high-risk youth, while help-seeking youth at ultra high-risk (UHR) for psychosis exhibited greater impairment in verbal memory (Seidman et al., 2010). Thus, prospective longitudinal studies measuring cognitive function on multiple occasions within individuals, and using the same neuropsychological tests, are required to capture within-person change alongside between-person age differences among youth at-risk for schizophrenia.

However, these established at-risk strategies are not without limitations. The presence of PLEs among children/adolescents constitutes a nonspecific risk marker for a broad range of mental disorders including schizophrenia (Werbeloff et al., 2012) while a family history of schizophrenia can prospectively identify only a minority of individuals who will develop the disorder (Mortensen, Pederson, & Pedersen, 2010). Strategies identifying individuals based on UHR criteria identify only help-seeking adolescents or young adults who may be at imminent risk of developing psychosis. An alternative

approach which uses a combination of antecedents of schizophrenia (including PLEs) to identify at-risk children may maximise opportunities to prospectively examine the development of the disorder (Laurens & Cullen, 2016).

In this study, we compared developmental trajectories of cognitive function from age 9 to 16 years among three groups of youth, and determined whether the trajectories differed according to definition of risk. These groups included: (a) children characterised by a triad of well-replicated antecedents of schizophrenia (ASz) (Laurens et al., 2007); (b) children with at least one affected relative with schizophrenia or schizoaffective disorder (family history of schizophrenia; FHx) and (c) typically developing children (TD) without antecedents or family history of schizophrenia. Children were assessed on up to three occasions separated by approximately 24-month intervals. At the initial assessment, undertaken when participants were aged 9–12 years, ASz and FHx youth, relative to TD youth, showed cognitive impairments in IQ, scholastic achievement, verbal memory, verbal working memory and executive functioning tasks requiring cognitive flexibility (Cullen et al., 2010; Dickson et al., 2014). On the basis of findings from our previous cross-sectional studies, we hypothesised that, during adolescence, the early cognitive impairments shown by the at-risk groups would remain stable (developmental *deficit)* or catch up with performance of typically developing peers (developmental *delay*). On measures of visual memory and executive functioning (verbal fluency, and problem solving and planning), where no baseline differences between at-risk groups and TD peers had been observed previously, we anticipated possible developmental *lags,* or even, *deterioration.*

Methods and materials
Sample

One hundred and six children aged 9–12 years were recruited for repeated cognitive (and other biological and psychosocial) assessments using a school-based community screening procedure. The flow diagram in Figure 1 summarises participant recruitment. No participant had experienced a psychotic episode or taken antipsychotic medication, had a neurological disorder, learning difficulties (IQ < 70), or a diagnosis of autism/Asperger's disorder. Ethical approval of the study was obtained from the Joint South London and Maudsley (SLaM) National Health Service (NHS) Foundation Trust and Institute of Psychiatry Research Ethics Committee. Children provided written assent and caregivers provided written consent for participation in the study.

The school-based screening questionnaire assessed a triad of antecedents of schizophrenia. ASz children presented all three antecedents: (a) a child-reported 'certainly-true' response on at least one of nine PLE items assessing hallucination- and delusion-like experiences (Laurens et al., 2007); (b) a score in the clinical range (approximately top tenth percentile on UK population norms) on the child-reported emotional symptoms scale or the caregiver-reported conduct problems, hyperactivity-inattention, or peer relationship problems scales of the
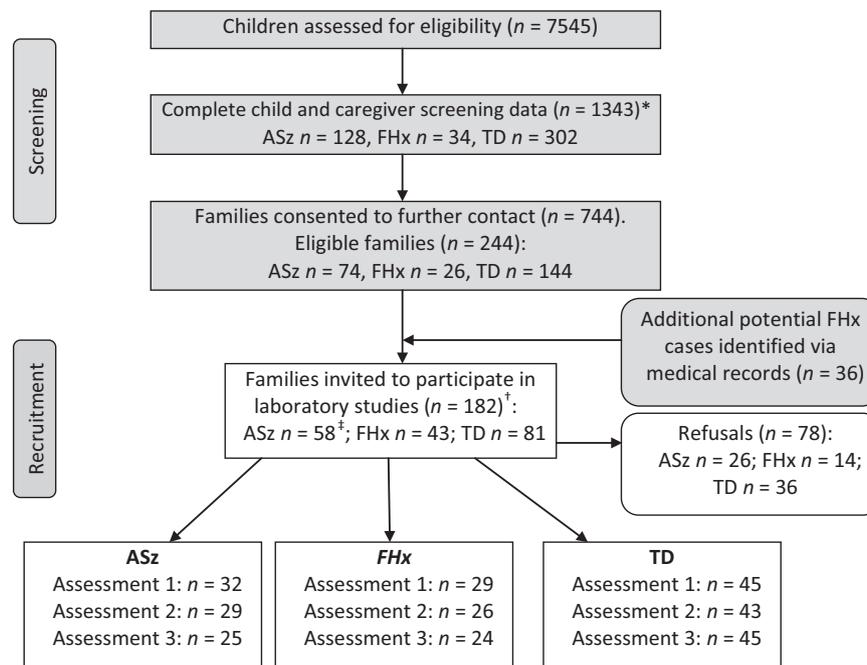
Figure 1 Flow diagram of participant recruitment and attrition within the study. *Notes*: ASz: triad of antecedents of schizophrenia; FHx: family history; TD: no antecedents or family history. *1,204 cases only were assessed for family history (questions not included in initial wave of screening); [†]62 eligible families were not contacted due to staff resourcing constraints (eligible but uncontacted children did not differ on demographic or antecedent characteristics from study participants); [‡]6 children meeting both ASz and FHx criteria were assigned to the FHx group for analysis

Strengths and Difficulties Questionnaire (Goodman, Ford, Simmons, Gatward, & Meltzer, 2000) and (c) a caregiver-reported motor and/or speech delay or abnormality (Laurens et al., 2007). TD children were defined as those who presented none of the three ASz criteria on screening questionnaires and who had no first-, second- or third-degree relative with a schizophrenia spectrum disorder, as confirmed via the Family Interview for Genetic Studies interview (FIGS) assessment with the child's primary caregiver (Maxwell, 1992).

To identify children with a family history of schizophrenia/schizoaffective disorder (FHx), the screening questionnaire also included items assessing family mental health problems (Laurens et al., 2007). Approximately 3.7% of 1,204 caregivers who completed these items indicated that their child had a relative with a schizophrenia spectrum disorder. In addition, medical records of mental health service users within the SLaM NHS Foundation Trust were reviewed to identify patients with a diagnosis of schizophrenia/schizoaffective disorder who had a relative aged 9–12 years. Identified families were approached following liaison with the patient's care worker. Just over half (55%) of the 29 FHx children in the present sample were identified via school screening questionnaires and the remainder via patient contacts. As confirmed by the FIGS with the child's caregiver (Maxwell, 1992), FHx children included: nine with a first-degree relative with schizophrenia; two with a first-degree relative with schizoaffective disorder; two with two second-degree relatives with schizophrenia; and 16 with one second-degree relative with schizophrenia.

The sample comprised 32 ASz, 29 FHx (six of whom also met ASz criteria) and 45 TD children. Table S1 presents comparisons of demographic characteristics of the three groups at initial assessment (age 9–12 years). Participants in the study did not differ from eligible children who did not take part on the prevalence of ASz triad components or demographic characteristics, with the exception that the proportion of ASz children presenting clinically-significant emotional problems was lower among those who completed cognitive assessments than among those who did not. All children completed their formal schooling in the United Kingdom and were fluent in English.

Procedure

Follow-up assessments spaced at approximately 2-year intervals were completed when children were aged between 11 and 14 years (assessment 2) and 13–16 years (assessment 3). Eligible children completed a battery of cognitive tasks at each of the three assessment phases, providing longitudinal data spanning ages 9–16 years. Caregivers reported children's ethnicity (according to the 2001 UK Census ethnic group categories) and parental occupational status (coded according to the UK National Statistics Socioeconomic Classification) (Office for National Statistics, 2010).

Measures

Cognitive assessments. Table S2 provides a brief description of the measures used to assess each domain, measuring general intelligence [IQ; Wechsler Abbreviated Scale for General Intelligence (Wechsler, 1999); using the vocabulary and matrix reasoning subtests], scholastic achievement [SA; Wechsler Individual Achievement Test (Wechsler, 2005); including word reading, numerical operations, and spelling], memory [Wide Range Assessment of Memory and Learning 2nd Edition (Sheslow & Adams, 2003); including verbal memory, visual memory, and verbal working memory], and executive function [EF; Delis-Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001); including multiple indices from verbal fluency, colour-word interference and the towers subtests]. To capture growth in cognitive abilities with age, we analysed raw cognitive scores rather than age-standardized scaled scores for all measures.

Statistical analyses

Univariate ANOVA, Fisher's exact test, and chi-square tests were used to compare groups on demographic variables. Longitudinal mixed models for repeated measures were fitted for each cognitive outcome to examine growth between 9 and 16 years of age using the Stata 14 statistical package

(StataCorp., 2015). The main predictors in all statistical models were group (ASz vs. TD; FHx vs. TD), fixed linear and quadratic effects of age, and interactions between linear and quadratic age and group. Any nonstatistically significant quadratic terms (at the $p > .05$ level) were subsequently removed. Exact age at each assessment was fitted as a continuous predictor, centred in statistical analyses to 11 years (the mean age of the total sample at assessment 1). To control for potential practice effects on the cognitive tests, an additional variable was created and entered into the models to indicate whether data were obtained from assessment one, two, or three.

For each domain, random-intercept and random-coefficients models were fitted. A random effect of participant was specified in each model to account for correlations between repeated measurements of individuals over time. The random-coefficients model additionally contained a random slope of age and an unstructured covariance matrix. Models were fit by maximum likelihood estimation (MLE). The simpler random-intercept model was retained unless a likelihood ratio test comparing the two models indicated that the random-coefficients model provided a better fit to the data. Analyses incorporated ethnicity, parents' occupation, sex, and practice effects as covariates, given their known associations with measurement of cognitive function (Waber, Forbes, Almli, & Blood, 2012). Details of normative adolescent cognitive development, and parameter estimates of linear mixed models for each cognitive measure, are presented in Table S3.

We interpreted results for both at-risk groups relative to TD youth in line with previous work examining cognitive growth premorbidly among individuals from a population-based cohort who later developed schizophrenia (Reichenberg et al., 2010). Developmental *deficit*, which emerged early and remained stable, was characterised by statistically significant estimated between-group differences at 11 years of age (mean intercept value) but no between-group differences in change per 1 year of age (rate of cognitive growth, or 'slope'). A significant negative slope value (or positive slope value for measures where the dependent variable was task completion time) indicated a developmental *lag* (a slower rate of cognitive growth over development). In contrast, a significant positive slope value (or negative slope value for task completion time outcome measures) indicating a faster rate of cognitive growth over development characterised developmental *delay*. Developmental *deterioration* was characterised by nonsignificant between-group differences in linear slope, but a significant negative quadratic slope (inverted U-shape).

Results

As detailed in Table S1, the groups did not differ on sex, laterality, or age on day of assessment 1, but differed on ethnicity and parents' occupation. Among the TD children, proportionately more were of white British ethnicity, and had parents with professional/managerial occupations. Results of significant group differences in trajectories of growth by cognitive domain are illustrated in Figure 2, panels A–K, and summarised by trajectory type in Table 1.

Developmental deficit

Relative to TD, both ASz and FHx demonstrated poorer performance on verbal working memory (panel H) at 11 years, but did not differ in their slope values, suggesting that these impairments emerged

early in childhood, and remained stable through age 16. Relative to the TD group, ASz individuals additionally displayed a stable deficit on IQ-vocabulary (panel A), SA-word reading (panel C), SA-numerical operations (panel D), and EF-inhibition/switching (panel K); and the FHx group displayed a stable deficit on EF-Inhibition (panel J).

Developmental lag

On SA-spelling (panel E), the ASz group had statistically significant negative linear slope values compared to TD youth, suggesting that their cognitive growth was slower.

Developmental delay

At 11 years, ASz relative to TD children obtained similar scores for verbal and visual memory (panels F and G) and EF-category fluency (panel I), with a statistically significant positive linear slope value indicating improvements with age. A similar pattern of developmental delay was observed for FHx relative to TD on IQ-matrix reasoning (panel B), SA-wording reading (panel C), and EF-inhibition/switching (panel K).

Developmental deterioration

No evidence was observed on any of the cognitive domains indicating a trajectory of deterioration for ASz or FHx youth.

No developmental differences

On measures of EF-letter fluency, EF-category switching accuracy, and EF-towers achievement, ASz and FHx youth showed development similar to that of TD youth, with no differences apparent in performance at 11 years, or in rate of cognitive growth with age. ASz youth, relative to TD, showed no differences in performance on IQ-matrix reasoning and EF-Inhibition. FHx youth only were similar to TD youth on measures of IQ-vocabulary, SA-numerical operations, SA-spelling, verbal and visual memory, and EF-category fluency.

Discussion

In this study, we used repeated, and identical, cognitive assessments, across ages 9–16 years, and identified distinct trajectories of cognitive development among youth at-risk for schizophrenia relative to typically developing youth. ASz youth demonstrated more widespread developmental *deficits* (i.e. impairments that emerged early and remained stable) than FHx youth. While both at-risk groups evidenced a stable *deficit* in verbal working memory, ASz youth additionally demonstrated *deficits* on measures of verbal functioning (IQ-vocabulary, SA-
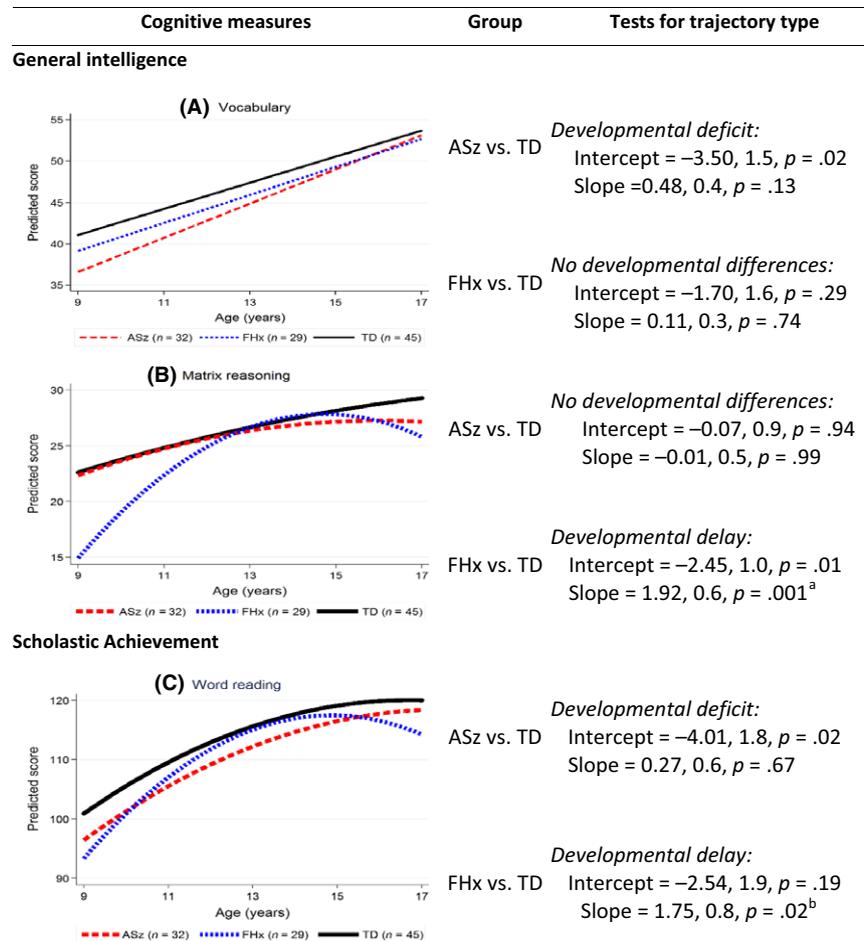
Cognitive measures	**Group**	**Tests for trajectory type**

General intelligence

| | **ASz vs. TD** | *Developmental deficit:* Intercept = −3.50, 1.5, *p* = .02 Slope =0.48, 0.4, *p* = .13 |
| | **FHx vs. TD** | *No developmental differences:* Intercept = −1.70, 1.6, *p* = .29 Slope = 0.11, 0.3, *p* = .74 |

| | **ASz vs. TD** | *No developmental differences:* Intercept = −0.07, 0.9, *p* = .94 Slope = −0.01, 0.5, *p* = .99 |
| | **FHx vs. TD** | *Developmental delay:* Intercept = −2.45, 1.0, *p* = .01 Slope = 1.92, 0.6, *p* = .001[a] |

Scholastic Achievement

| | **ASz vs. TD** | *Developmental deficit:* Intercept = −4.01, 1.8, *p* = .02 Slope = 0.27, 0.6, *p* = .67 |
| | **FHx vs. TD** | *Developmental delay:* Intercept = −2.54, 1.9, *p* = .19 Slope = 1.75, 0.8, *p* = .02[b] |

Figure 2 Line graphs of predicted values adjusted for sex, ethnicity, parental occupation and practice effects for General intelligence (panels A–B), Scholastic achievement (panels C–E), Memory (panels F–H), and Executive functioning (panels I–K) from 9 to 16 years for youth presenting with antecedents of schizophrenia (ASz), youth with a family history of schizophrenia (FHx), and typically developing youth (TD). *Notes*: Tests for trajectory type show fixed effects estimates with standard errors and significance values derived from random-intercept models; Intercept: Estimate of group differences at 11 years; Slope: Estimate of group differences in cognitive growth per 1 year of age; Developmental deficit trajectory type is characterised by a significant intercept and a nonsignificant slope estimate; Developmental lag is characterised by a significant negative slope estimate; Developmental delay is characterised by a significant positive slope estimate; Panels J and K: Dependent variable is task completion time measured in seconds, negative values indicate faster task completion time; and significant quadratic effects of age: [a]−0.34 (0.1), *p* = .005, [b]−0.38 (0.2), *p* = .04 [Colour figure can be viewed at wileyonlinelibrary.com]

word reading), SA-numerical operations, and EF-inhibition/switching, and developmental *delays* (i.e. early difficulties that caught up with performance of TD peers during adolescence) in verbal and visual memory measures, and a *lag* (i.e. slower cognitive growth relative to TD peers) in SA-spelling. Only FHx youth showed *delays* in IQ-matrix reasoning, SA-word reading, and EF-inhibition/switching. However, they showed a *deficit* in EF-inhibition (not observed in ASz), whereas ASz youth evidenced *delay* in EF-category fluency (not observed in FHx), highlighting the importance of administering a range of tests to differentiate specific impairments. Although these longitudinal findings are preliminary and require replication, we prospectively identified two patterns of cognitive growth in ASz and FHx youth (development *deficit* and *lag*) that have been described previously in premorbid assessments of individuals who later developed schizophrenia (Cannon et al., 2000; Crow et al., 1995; Jones et al., 1994; Reichenberg et al., 2010), and found evidence

for developmental *delays* in cognitive functions not previously identified in high-risk youth (Maziade et al., 2011). The observed differences in cognitive trajectories of the at-risk groups, if replicated, are potentially important for cognitive-rehabilitation interventions for at-risk children, and may reflect differences in structural and functional neural correlates.

We found no evidence for developmental *deterioration* on any cognitive subtest among at-risk youth, consistent with evidence from premorbid assessments during childhood and early adolescence in individuals who later developed schizophrenia (Reichenberg et al., 2010). However, these findings may reflect the restriction of assessments up to the age of 16 years in this study, as previous research has identified a decline in verbal abilities between 13 and 18 years among participants who later developed the disorder (Fuller et al., 2002; MacCabe et al., 2013).

Our finding that developmental *deficits* in aspects of scholastic achievement characterised only ASz but
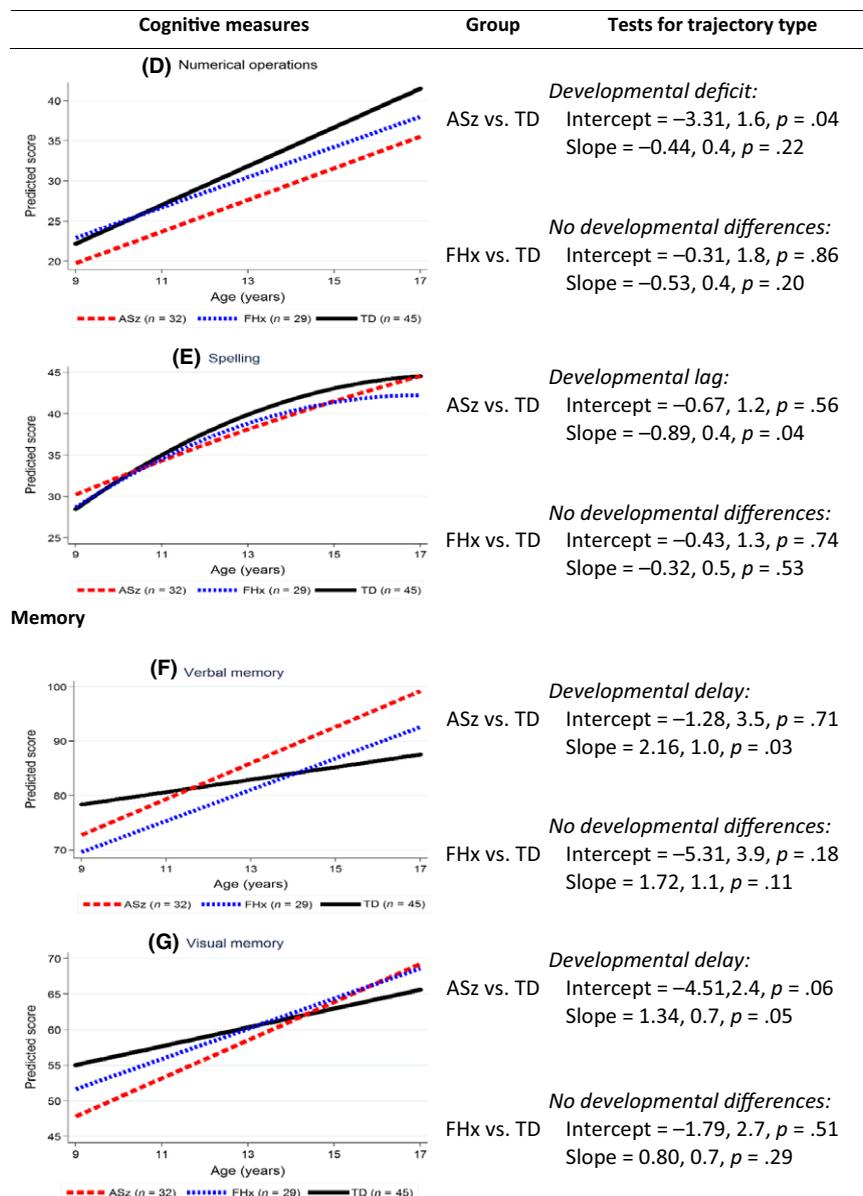
Cognitive measures	Group	Tests for trajectory type

(D) Numerical operations

Developmental deficit:
ASz vs. TD   Intercept = −3.31, 1.6, *p* = .04
Slope = −0.44, 0.4, *p* = .22

No developmental differences:
FHx vs. TD   Intercept = −0.31, 1.8, *p* = .86
Slope = −0.53, 0.4, *p* = .20

ASz (*n* = 32)   FHx (*n* = 29)   TD (*n* = 45)

(E) Spelling

Developmental lag:
ASz vs. TD   Intercept = −0.67, 1.2, *p* = .56
Slope = −0.89, 0.4, *p* = .04

No developmental differences:
FHx vs. TD   Intercept = −0.43, 1.3, *p* = .74
Slope = −0.32, 0.5, *p* = .53

ASz (*n* = 32)   FHx (*n* = 29)   TD (*n* = 45)

Memory

(F) Verbal memory

Developmental delay:
ASz vs. TD   Intercept = −1.28, 3.5, *p* = .71
Slope = 2.16, 1.0, *p* = .03

No developmental differences:
FHx vs. TD   Intercept = −5.31, 3.9, *p* = .18
Slope = 1.72, 1.1, *p* = .11

ASz (*n* = 32)   FHx (*n* = 29)   TD (*n* = 45)

(G) Visual memory

Developmental delay:
ASz vs. TD   Intercept = −4.51, 2.4, *p* = .06
Slope = 1.34, 0.7, *p* = .05

No developmental differences:
FHx vs. TD   Intercept = −1.79, 2.7, *p* = .51
Slope = 0.80, 0.7, *p* = .29

ASz (*n* = 32)   FHx (*n* = 29)   TD (*n* = 45)

Figure 2 Continued

not FHx youth contrasts with evidence from three population-based studies reporting poorer academic performance at 12 years and at 15–16 years among the children of parents with schizophrenia compared to the children of mothers with no mental disorder (Forsyth et al., 2012; Jundong et al., 2012; Lin et al., 2016). This might relate to greater heterogeneity in the familial loading for schizophrenia within the FHx group, which included individuals with first- or second-degree relatives (Dickson et al., 2014). Developmental *deficits* in reading and numerical operations among ASz youth compared to TD peers aligns with demonstrated associations between PLEs and poor general academic achievement and literacy (Bartels-Velthuis, van de Willige, Jenner, van Os, & Wiersma, 2011; Hameed, Lewis, Sullivan, & Zammit, 2013). The developmental *lag* in spelling observed among ASz compared to TD youth is also consistent with recent evidence that poor spelling at 12 years is associated with the later

development of schizophrenia (Lin et al., 2016), but diverges from our earlier work at 9–12 years which identified an impairment in the over-arching domain of scholastic achievement (i.e. averaged scores across word reading, spelling and numerical operations) among ASz and FHx youth relative to TD peers (Cullen et al., 2010; Dickson et al., 2014). Poor academic achievement during adolescence may represent an easily identifiable nonspecific marker of biological, psychological and social risk processes underpinning the development of schizophrenia.

The developmental *deficit* in verbal working memory characterising both at-risk groups relative to TD youth emerged early (9–12 years) and remained stable during adolescence, and may constitute a universal risk marker of schizophrenia. Poor premorbid verbal working memory has been reported in individuals with schizophrenia, and in individuals at familial and UHR for psychosis (Addington & Barbato, 2012; Agnew-Blais & Seidman, 2013; Reichenberg
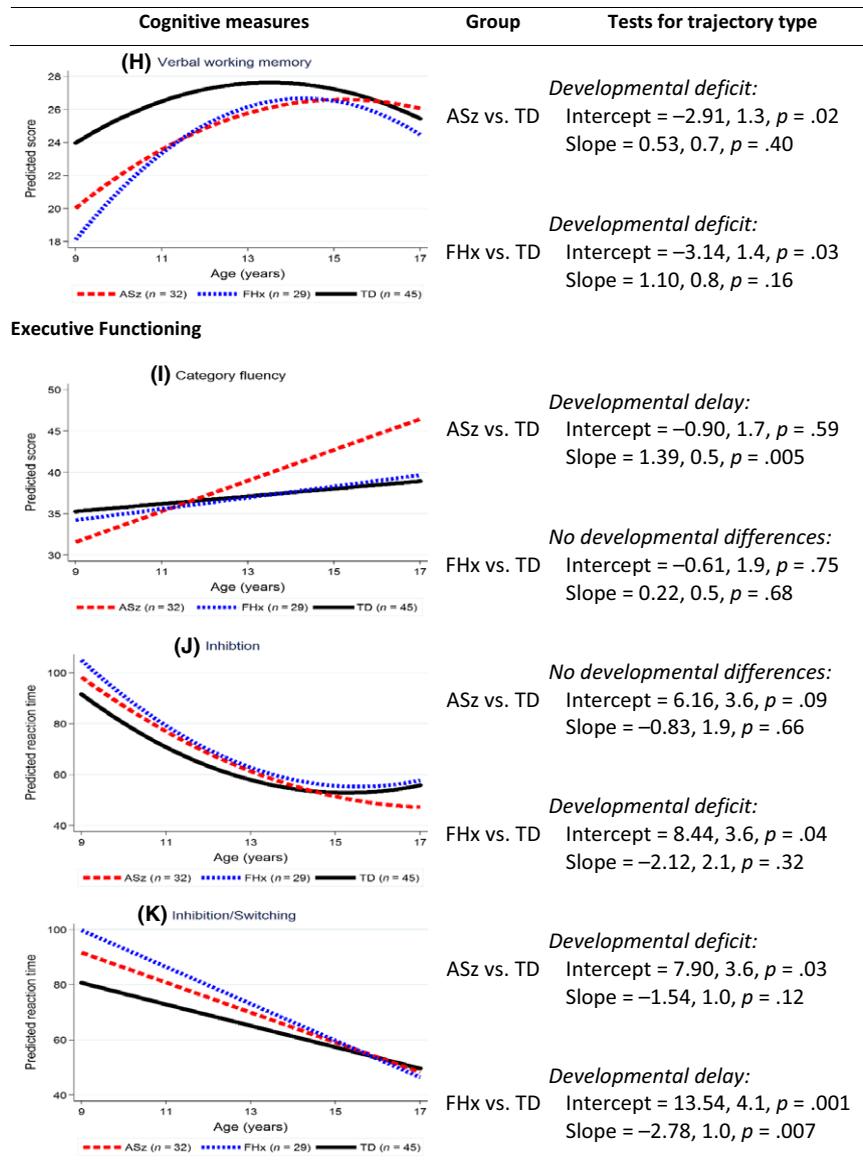
Cognitive measures	Group	Tests for trajectory type

(H) Verbal working memory

Developmental deficit:

ASz vs. TD   Intercept = −2.91, 1.3, *p* = .02
Slope = 0.53, 0.7, *p* = .40

Developmental deficit:

FHx vs. TD   Intercept = −3.14, 1.4, *p* = .03
Slope = 1.10, 0.8, *p* = .16

Executive Functioning

(I) Category fluency

Developmental delay:

ASz vs. TD   Intercept = −0.90, 1.7, *p* = .59
Slope = 1.39, 0.5, *p* = .005

No developmental differences:

FHx vs. TD   Intercept = −0.61, 1.9, *p* = .75
Slope = 0.22, 0.5, *p* = .68

(J) Inhibtion

No developmental differences:

ASz vs. TD   Intercept = 6.16, 3.6, *p* = .09
Slope = −0.83, 1.9, *p* = .66

Developmental deficit:

FHx vs. TD   Intercept = 8.44, 3.6, *p* = .04
Slope = −2.12, 2.1, *p* = .32

(K) Inhibition/Switching

Developmental deficit:

ASz vs. TD   Intercept = 7.90, 3.6, *p* = .03
Slope = −1.54, 1.0, *p* = .12

Developmental delay:

FHx vs. TD   Intercept = 13.54, 4.1, *p* = .001
Slope = −2.78, 1.0, *p* = .007

Figure 2 Continued

Table 1 Summary of the trajectories of cognitive development observed during adolescence among at-risk youth relative to typically developing youth

Cognitive domain	ASz trajectory	FHx trajectory
IQ-vocabulary	Deficit	
IQ-matrix reasoning		Delay
SA-word reading	Deficit	Delay
SA-numerical operations	Deficit	
SA-spelling	Lag	
Verbal working memory	Deficit	Deficit
Visual memory	Delay	
Verbal memory	Delay	
EF-category fluency	Delay	
EF-inhibition		Deficit
EF-inhibition/switching	Deficit	Delay

ASz, antecedents of schizophrenia; FHx, family history of schizophrenia.

et al., 2010), and is associated with childhood mental disorders (Willcutt, Sonuga-Barke, & Sergeant, 2008). Thus, it is likely a nonspecific cognitive deficit reflecting increased risk for multiple disorders including psychosis (McGorry et al., 2014). Training programs targeting working memory may benefit at-risk children, and has the potential to lead to broader improvements in cognitive and academic functioning, and improved mental health, even for those who do not go onto develop psychosis. Indeed, there is evidence that targeted cognitive training can elicit improvements at 4–6 month follow-up in mathematics and reading among typically developing children (Wexler et al., 2016), and in working memory among children with a diagnosis of Attention-deficit/Hyperactivity disorder (Klingberg et al., 2005). A recent systematic review of six studies reported preliminary evidence for the effectiveness of cognitive remediation to enhance cognition and improve functional outcome among UHR youth (Glenthøj, Hjorthøj, Kristensen, Davidson, & Nordentoft, 2017).

Only one prospective, population-based, cohort study has examined the developmental course of executive function among individuals with

schizophrenia. Participants who developed schizophrenia, relative to those who did not, showed a decline in performance on the Trails B test (measuring visual attention and task switching) from childhood to adulthood (Meier et al., 2014). Studies in high-risk cohorts offer important opportunities to examine changes in executive functions during critical (premorbid and prodromal) stages of the developing disorder. Both ASz and FHx youth presented difficulties in neuropsychological tasks requiring cognitive flexibility, which is associated with poor problem solving skills and compromised daily functioning among individuals with schizophrenia (Carrion et al., 2011).

Evidence of a *delay* in verbal memory in the ASz group was unexpected given that verbal memory is associated with transition to psychosis in clinical high-risk youth (Seidman et al., 2010). The finding of a *delay* in visual memory among ASz youth is inconsistent with previous work reporting a childhood *lag,* followed by adolescent *recuperation,* among FHx youth (Maziade et al., 2011). *Delay* might reflect waxing and waning in the relative prominence of particular impairments relative to the changes in normative growth during adolescence, and/or divergence in the pace of maturation in certain areas of the brain among youth at-risk for schizophrenia compared to TD peers (Roalf et al., 2014). It may be that youth who do not exhibit this spontaneous catch up are at greatest risk for developing schizophrenia in adulthood. Overall, our longitudinal findings demonstrate that cross-sectional investigations insufficiently capture the complex nature of cognitive development among at-risk youth. Indeed, further assessments of ASz and FHx children beyond 16 years may reveal only temporary recovery of functioning in midadolescence on measures such as verbal memory and EF-category fluency, which are characteristic of schizophrenia. Such deficits may re-emerge beyond the period of assessment in this study as youth approach the age typical of psychosis onset.

Findings from this study should be interpreted in light of three limitations. A relatively small sample, particularly by the third assessment, may have compromised our ability to detect subtle changes in cognitive development over adolescence. Nonetheless, functions characterised by the most robust impairments represent prime candidates for intervention. Drop-out rates were greater among ASz and FHx groups than TD, but due to the number of participants that declined to participate or who were noncontactable at the second and third assessments, it was not viable to statistically investigate this potential sample bias. A final limitation, is that we were unable to include pubertal age, and interactions between pubertal age and sex, as covariates in statistical models; puberty may play a role in cognitive development during adolescence (Blakemore, Burnett, & Dahl, 2010).

This study is characterised by two principal strengths. First, the longitudinal assessment of cognitive change was conducted prior to the age period of risk of onset of the prodromal phase of schizophrenia, and thereby delineates potential premorbid trajectories of cognition among at-risk youth. Second, our use of longitudinal mixed modelling affords greater statistical power than other procedures for analysing longitudinal data and is not limited by partially missing data or unequally spaced assessments (Curran, Obeidat, & Losardo, 2010).

Conclusion

Two groups of youth at-risk for schizophrenia, one with a family history of the disorder and one presenting well-documented antecedents of the disorder, showed distinct developmental trajectories of cognitive abnormalities during adolescence relative to TD youth. The type of trajectory (i.e. developmental *deficit* and/or *lag* vs. *delay*) could prove useful in discriminating between at-risk youth who do and do not go onto develop schizophrenia. Future research should explore whether cognitive training interventions among groups at-risk for schizophrenia, which have the potential to remediate difficulties contributing to the emergence of the disorder, should target cognitive impairments that emerge early and are stable across development, cognitive functions that develop at a slower rate than healthy peers, or those early cognitive delays that appear to exhibit plasticity and recuperation (Maziade et al., 2011).

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Supporting results information: Normative cognitive adolescent development.

Table S1. Comparisons of demographic characteristics at assessment 1 (aged 9–12 years) for each participant group.

Table S2. Description of the measures used to examine cognitive change from 9 to 16 years.

Table S3. Parameter estimates of fixed effects within longitudinal mixed models of cognitive performance adjusting for sex, ethnicity, parental occupational status and practice effects, describing developmental deficit (DD), developmental lag (DL), and developmental delay (DY) trajectories.

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Key points

- Adult schizophrenia is preceded by childhood dysfunctions spanning multiple cognitive domains, but different cognitive domains follow distinct developmental courses.
- In this prospective longitudinal study, we used repeated, and identical, cognitive assessments across ages 9–16 years, to examine trajectories of cognitive development among youth at-risk for schizophrenia compared to typically developing peers.
- We observed two patterns of cognitive growth (developmental *deficit* and *lag*) previously reported among individuals who later developed schizophrenia, and found evidence for developmental *delays* in cognitive functions not previously identified among high-risk youth.
- Type of trajectory may be useful in discriminating between at-risk youth who do and do not develop the disorder in adulthood.
- Findings highlight the potential for interventions that target specific cognitive dysfunction at key developmental phases.

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