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Twelve-Month Cognitive Trajectories in Individuals at Ultra-High Risk for Psychosis: A Latent Class Analysis

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Understanding longitudinal cognitive performance in individuals at ultra-high risk for psychosis (UHR) is important for informing theoretical models and treatment. A vital step in this endeavor is to determine whether there are UHR subgroups that have similar patterns of cognitive change over time. The aims were to: i) identify latent class trajectories of cognitive performance over 12-months in UHR individuals, ii) identify baseline demographic and clinical predictors of the resulting classes, and iii) determine whether trajectory classes were associated with transition to psychosis or functional outcomes. Cognition was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS) at baseline, 6- and 12-months (*N* = 288). Using Growth Mixture Modeling, a single unimpaired improving trajectory class was observed for motor function, speed of processing, verbal fluency, and BACS composite. A two-class solution was observed for executive function and working memory, showing one unimpaired and a second impaired class. A three-class solution was found for verbal learning and memory: unimpaired, mildly impaired, and initially extremely impaired, but improved ("caught up") to the level of the mildly impaired. IQ, omega-3 index, and premorbid adjustment were associated with class membership, whereas clinical variables (symptoms, substance use), including transition to psychosis, were not. Working memory and verbal learning and memory trajectory class membership was associated with functioning outcomes. These findings suggest there is no short-term progressive cognitive decline in help-seeking UHR individuals, including those who transition to psychosis. Screening of cognitive performance may be useful for identifying UHR individuals who may benefit from targeted cognitive interventions.

Key words: cognition/longitudinal/growth mixture modeling/schizophrenia/omega-3 index

Cognitive impairments emerge prior to first-episode psychosis and are a reliable risk factor for psychotic disorders.[1–5] On average, individuals at ultra-high risk (UHR) for psychosis[6] have poorer cognitive functioning at ascertainment than healthy controls, and those who later transition to psychotic disorder have significantly greater cognitive impairments than UHR individuals who do not transition.[1,2,4] However, the longitudinal course of cognitive functioning in UHR individuals and its relationship with the onset of psychotic disorder and other clinical, sociodemographic and functional characteristics is poorly understood. This is an important area of investigation for theoretical and treatment reasons.

Figure 1 shows five hypothetical trajectories of cognitive functioning in early-stage psychosis. Relative to the normative course of cognitive functioning, the early trajectory of cognitive functioning in psychotic disorders (particularly schizophrenia) could reflect a stable *deficit*, developmental *lag* (slower rate of improvement, indicated by increasing deficit over time), or *deterioration*.[7] Evidence supporting each of these cognitive trajectories has come from large cohort studies that have examined cognitive performance longitudinally in people prior to and after being diagnosed with schizophrenia or other psychotic disorders.[7–11] Different cognitive trajectories have been observed depending on the cognitive domain assessed, the stage of life (e.g., childhood, adolescence, adulthood) and stage of illness (e.g., prodromal, first-episode) examined, and the length of follow-up period.

Within UHR samples specifically, current evidence suggests that while deficits are evident at ascertainment, longitudinal performance in most cognitive domains remains relatively stable or improves, including in the period following transition to psychotic disorder.[12–16] These trajectories could reflect developmental *deficit* or *lag*, although improvement suggests the possibility of an initial *delay* with "catch-up"[15,17] (Figure 1), perhaps within the context of effective treatment. It is also noteworthy that some longitudinal studies have observed *no deficit* in some cognitive domains (Figure 1),[16,18] and one recent study observed a *deterioration* in verbal learning and memory over 10 years in UHR individuals,[12] a finding consistent with an earlier 1-year longitudinal study.[16] A limitation of UHR studies published to date is that cognitive assessments have only been conducted at two time-points, which restrains modeling the dynamic course of cognitive performance. Furthermore, analyses have been based on whole UHR samples versus healthy controls or pre-defined sub-groups (e.g., transition versus non-transition), which are known to be cognitively heterogeneous.[19] Latent subgroups with similar cognitive trajectories may exist within UHR cohorts, and through their identification improved prognostication and personalized treatment may be possible.

An extensive body of cross-sectional research has parsed the cognitive heterogeneity observed in psychosis using data-driven cluster analytic approaches; recent reviews suggest between 2–5 latent cognitive subgroups across the psychotic-bipolar disorder spectrum.[20,21] To our knowledge, only one study has applied cluster analysis to cognitive performance in UHR individuals, finding four cognitive clusters.[19] Membership of the most impaired cognitive cluster at baseline was associated with a higher likelihood of transition to psychotic disorder, a diagnosis of schizophrenia, and poorer 1-year functional outcome.[19]

An open question is whether there are UHR subgroups with different latent class cognitive *trajectories* (Figure 1). Identifying subgroups that show different patterns of cognitive change over time is important for understanding associations with illness progression or recovery, as well as non-illness factors, and identifying subgroup(s) in need of tailored treatment. Latent class cognitive trajectories have been identified in established schizophrenia[22–24] using Growth Mixture Modeling or Group-Based Trajectory Modeling. These are flexible, data-driven within-subject methods that classify individuals who have similar patterns of change over time into subgroups. To the best of our knowledge, no previous study has used a data-driven approach to determine whether latent subgroups with comparable trajectories in separate cognitive domains exist in UHR populations, and how these trajectories relate to premorbid/baseline illness and non-illness factors and outcome. The aim of the current study was to i) identify latent classes with different trajectories of cognitive performance over 12-months in UHR individuals, ii) identify demographic and baseline clinical predictors of the resultant classes, and iii) determine

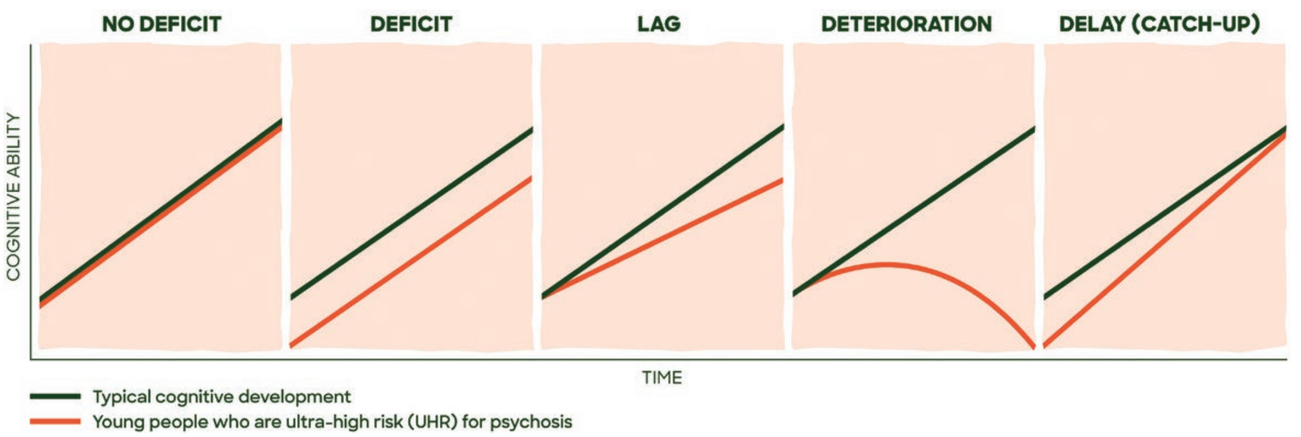

Figure 1. Hypothetical cognitive trajectories in people at risk of psychosis. Adapted and reprinted with permission from the American Journal of Psychiatry (Copyright ©2010). American Psychiatric Association. All Rights Reserved.

whether identified classes are associated with transition to psychosis and functional outcomes.

Materials and Methods

Design, Procedure, and Participants

This study involved secondary analysis of data from an international multi-site randomized controlled trial ("Neurapro"; ACTRN: 12608000475347).[25] Comprehensive details of the study methodology are provided elsewhere.[25] Briefly, UHR individuals were randomly allocated to either long-chain omega-3 polyunsaturated fatty acids plus cognitive behavioral case management (CBCM), or placebo plus CBCM for 6-months. Cognitive assessment was conducted at baseline, 6-months, and 12-months. There were no significant group differences on the primary (transition to psychosis) or secondary (clinical, functioning) outcomes of the trial,[26,27] but cell membrane markers (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA], omega-3 index [EPA+DHA]) were associated with functional and symptomatic outcomes.[28] Treatment groups were therefore combined for the current study[29] and omega-3 index included in the analysis. Participants provided informed written consent. Ethics approval was received from the Melbourne Health Human Research Ethics Committee (HREC#:2008.628).

Measures

Cognitive Functioning. Cognition was assessed with the Brief Assessment of Cognition in Schizophrenia (BACS).[30] The BACS examines six cognitive domains, including verbal learning and memory (Verbal Memory task), working memory (Digit Sequencing task), motor function (Token Motor task), verbal fluency (Semantic Fluency and Letter Fluency tasks), speed of processing (Symbol Coding task), and executive function (Tower of London task). T-scores (M = 50, SD = 10) derived from the BACS normative sample were calculated for each cognitive domain and a BACS Composite T-score was calculated by averaging the six standardized domain scores.

Baseline Independent Variables. Demographic variables included age, sex, years of education, and premorbid adjustment. Premorbid adjustment was assessed using the Premorbid Adjustment Scale (PAS).[31] The average subscale score from the Childhood, Early Adolescence, and Late Adolescence items was used; higher scores indicate poorer premorbid adjustment. A two-subtest short-form (Vocabulary/Matrix Reasoning) of the Wechsler Adult Intelligence Scale–3rd Edition[32,33] was administered at baseline to estimate IQ.

Clinical variables included omega-3 index (fasting cell membrane levels of EPA+DHA assessed by gas chromatography),[34] substance use, symptoms, and functioning. Substance use (specifically alcohol and cannabis) was assessed with the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST).[35] The Brief Psychiatric Rating Scale (BPRS)[36] assessed total and positive symptom (suspiciousness, unusual thought content, hallucinations, conceptual disorganization) severity. The Scale for the Assessment of Negative Symptoms (SANS)[37] assessed total negative symptom severity and the Montgomery-Åsberg Depression Rating Scale (MADRS)[38] measured depressive symptom severity. Higher scores indicate higher levels of substance use and symptomatology. The Social and Occupational Functioning Assessment Scale (SOFAS)[39] assessed global functioning; higher scores indicate better functioning.

Transition and Functioning Outcomes. Transition to psychosis was defined and assessed according to the operationalized criteria of the Comprehensive Assessment of the At-Risk Mental State.[40] Functioning was assessed with the SOFAS[39] at 12-month and medium-term follow-up.[27]

Statistical Analysis

Identifying Cognitive Trajectories. Growth mixture modeling (GMM) was used to identify subpopulations with comparable growth trajectories over time ("latent classes"). T-scores of all cognitive domains at all three time-points (baseline, 6-months, 12-months) were included in the GMM. Participants with at least one cognitive assessment were included in the analyses with missing values handled using Full Information Maximum Likelihood, assuming missingness at random. Variance around the growth parameters (i.e., intercept and slope) was allowed to vary within the latent classes. To identify the optimal number of latent classes, unconditional models with cumulative number of classes ranging from 1-4 were fitted. Number of classes was selected based on interpretability of classes, including sufficient number of cases per class (≥5%, i.e., 15 participants) and common fit information criteria: Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC), sample size adjusted BIC (aBIC), entropy values, Vuong-Lo-Mendall-Rubin, Lo-Mendall-Rubin Adjusted and bootstrap likelihood ratio test. Lower values of AIC, BIC, aBIC, and higher entropy indicate better fitting models.[41] Likelihood ratio tests provide a quantitative comparison between the model of interest with C and C-1 classes. A significant test ($P < .05$) indicates the model with C-1 classes should be rejected and the model with C classes should be favored.[41,42] Recommendations based on simulation studies prefer BIC/aBIC and Likelihood-based indices over AIC.[41,43] Moreover, entropy is used as a decisive indicator only when selecting among models with very similar fit indices.[43,44]

It would have been preferable to estimate trajectory classes and their predictors/outcomes within the one model, but due to the small number of cases per class, the class membership of each participant was saved and merged with the original data for separate analyses of predictors and outcomes.

Baseline Predictors of Cognitive Trajectories. Differences between trajectory classes for each cognitive domain on the baseline variables of interest were examined using Fisher's exact test for categorical variables and Analysis of Variance (ANOVA) for continuous variables. Class membership of each cognitive domain was then entered as dependent variables in separate logistic regression (2 classes) or multinomial regression (3 classes) analyses. Baseline predictors included: age, sex, years of education, premorbid adjustment (PAS average), IQ, omega-3 index, alcohol, and cannabis use (ASSIST), symptoms (BPRS total and psychotic, SANS total, MADRS), and functioning (SOFAS).

Cognitive Trajectories and Relationship to Transition and Functioning. Cognitive trajectory classes were determined using cognitive data collected at set time-points from baseline to 12-months, but the known psychosis transitions occurred at variable times, including before and *after* 12-months; thus, there was temporal incompatibility between the measurement of cognitive trajectory classes and transition to psychosis. In order to resolve this incompatibility, only transition status (yes/no) within 12-months from baseline (i.e., the same timeframe for cognitive trajectory class determination) was examined. As our aim was to determine whether transition *affects* trajectory (and not whether trajectory predicts later transition), transition status was recorded as "no" for those who transitioned after 12-months (i.e., transition times >365 days; n = 10). Additionally, for those whose transition times were censored before 12-months (i.e., they dropped out before 12-months and could not have their 12-month transition status determined; n = 51) we could either assume their 12-month transition status was "no" or exclude them from analysis. We ran the analyses using both scenarios using Fisher's exact test and then repeated the logistic/multinomial regression analysis with 12-month transition status (yes/no) added as an independent variable.

Differences in functioning (SOFAS) at 12-month and medium-term follow-up (3.4 years) among the cognitive trajectory classes were examined using ANOVA and Cohen's d effect sizes. Analyses were conducted using Mplus (Version 8.1), SPSS (Version 25), and R.[45]

Results

Sixteen of the original N = 304 Neurapro participants did not complete any cognitive assessments; thus, 288 participants were included in the current study (n = 287 completed baseline, n = 226 completed 6-month and n = 188 completed 12-month cognitive assessments) (Table 1). There were no significant differences in baseline demographic and clinical variables between individuals who completed a baseline assessment only and those with follow-up cognitive data (data not shown).

Latent Class Trajectories

Figure 2 shows the latent class trajectories identified through GMM and Table 2 shows the parameter estimates of the latent growth classes (Supplementary Table 1 shows fit indices). A single class was most appropriate for verbal fluency, speed of processing, motor function, and BACS composite (Figure 2a-d). For verbal fluency, the single-class solution had the lowest AIC-, BIC-, and aBIC-values, while the Likelihood-based indices did not suggest a distinct class-solution. For speed of processing, the single-class solution had the lowest BIC-value (two- and four-class solutions included classes with small participant numbers per class, 2.0% and 1.5%, respectively). The same applied to motor function, which had the smallest BIC-value (AIC/aBIC suggested a four-class solution, but lowest class frequency = 0.5%; entropy/Likelihood-tests a two-class solution, but lowest class frequency = 1.1%). For the BACS composite, contrary to the information fit criteria, a single-class solution was selected as all other class solutions produced class frequencies between 1.4 and 3.8%. Each single class was characterized by age-typical (average) performance (T-scores 45–50) with significant slight improvement over the 12-month period (Table 2).

Table 1. Baseline Characteristics of the Sample (N = 288)

	Mean/ Number	SD (Min-Max)/ Proportion
Demographic variables		
Age	19.1	4.6 (13–39)
Sex (Female)	158	54.9%
Country of birth (Native)	263	91.3%
Education (Years)	10.3	3.3 (2–21)
Premorbid Adjustment	0.29	0.14 (0–0.69)
Estimated IQ	102.8	14.7 (63–145)
Clinical variables		
BPRS Total	41.4	9.9 (24–86)
BPRS Psychotic	8.2	2.6 (4–16)
SANS Total	18.4	13.1 (0–63)
MADRS Total	19.4	9.0 (0–45)
ASSIST Alcohol Use	5.7	5.4 (0–26)
ASSIST Cannabis Use	4.0	6.8 (0–26)
SOFAS	53.5	11.9 (25–85)
Omega-3 index	7.3	1.8 (1.1–14.9)

Note: SD, Standard Deviation; BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; MADRS, Montgomery-Åsberg Depression Scale; ASSIST, Alcohol, Smoking and Substance Involvement Screening Test; SOFAS, Social and Occupational Functioning Assessment Scale.

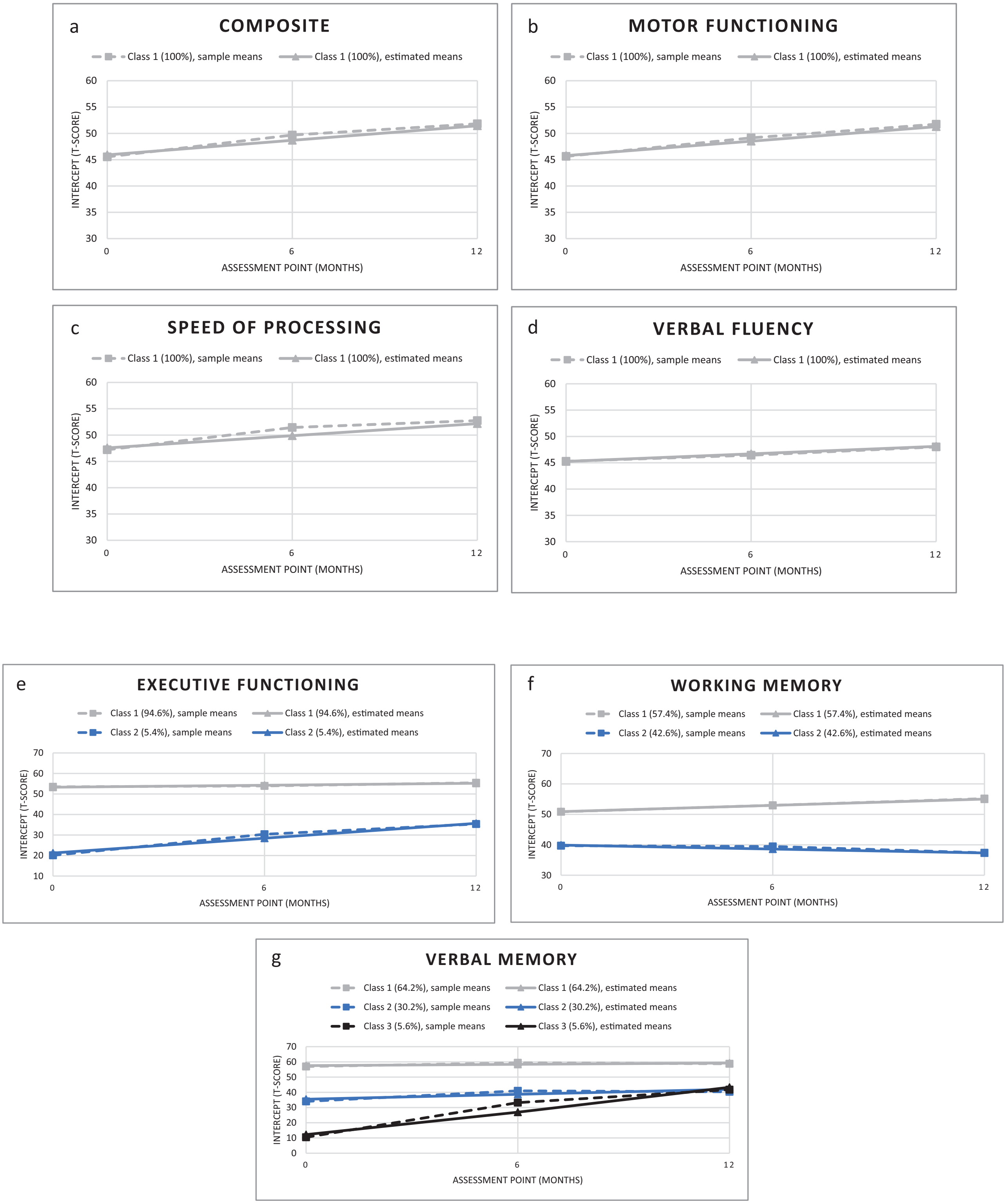

Figure 2. Twelve-month latent class trajectories for each cognitive domain.

A two-class solution was observed for executive function and working memory (Figure 2e-f). For executive function, this was based on the Likelihood-based indices and entropy and small class frequency for a four-class solution (2.4%). Class 1 (n = 272; 94.4%) was characterised by unimpaired (average) mildly improving performance (T-score >50) and class 2 (n = 16; 5.6%) was extremely impaired at baseline (T-score ~21) and significantly improved over the 12-month period, but remained impaired relative to class 1 (T-score ~35). For working

Table 2. Unstandardised Parameter Estimates of Latent Growth Classes

Cognitive domain	Class	Intercept	Slope
		Mean (SD)	Mean (SD)
BACSComposite	Class 1	45.91 (0.80)***	0.46 (0.05)***
Motor function	Class 1	45.77 (0.64)***	0.46 (0.06)***
Speed of processing	Class 1	47.56 (0.72)***	0.39 (0.05)***
Verbal fluency	Class 1	45.25 (0.70)***	0.24 (0.05)***
Executive function	Class 1	53.27 (0.48)***	0.16 (0.06)**
	Class 2	21.24 (3.98)***	1.20 (0.41)**
Working memory	Class 1	50.90 (1.25)***	0.34 (0.06)***
	Class 2	39.89 (1.22)***	-0.22 (0.11)
Verbal learning and memory	Class 1	57.56 (0.93)***	0.14 (0.07)*
	Class 2	35.47 (2.06)***	0.54 (0.13)***
	Class 3	12.21 (2.68)***	2.46 (0.73)**

Note: *$P < .05$, ** $P < .01$, *** $P < .001$

memory, class 1 (n = 170; 59.0%) showed an unimpaired (average) performance (T-score ~50), with significant mild improvement over time, and class 2 (n = 118; 41.0%) showed a mildly impaired performance (T-score ~40) that remained stable over time.

Finally, a three-class solution with significant improvement in all classes was found for verbal learning and memory (Figure 2g) based on the BIC and entropy; class 1 (n = 185; 64.2%) was unimpaired (average; T-score >55), class 2 (n = 86; 29.9%) was mildly impaired (T-score ~35), and class 3 (n = 17; 5.9%) was extremely impaired at baseline (T-score <15), but improved to the level of class 2 (mildly impaired) at 12-months.

Association Between Baseline Variables and Latent Cognitive Trajectories. Table 3 shows baseline demographic, premorbid, and clinical information according to latent trajectory classes for executive function (2 classes), working memory (2 classes), and verbal learning and memory (3 classes). The unique contribution of these variables to class membership was determined using logistic (executive function, working memory) and multinomial (verbal learning and memory; the "average" class set as the reference class) regression analyses. For executive function, IQ was the only significant predictor of class membership. Higher IQ was associated with lower likelihood of belonging to the "impaired" class (OR = 0.90, 95% CI = 0.84–0.95, $P < .001$). For working memory, IQ was again the only significant predictor of class membership, where higher IQ was associated with lower likelihood of belonging to the "impaired" class (OR = 0.94, 95% CI = 0.92–0.96, $P < .001$). For verbal learning and memory, the omega-3 index, IQ, and premorbid adjustment were significantly associated with class membership. Specifically, a higher omega-3 index was associated with a higher likelihood of belonging to the "extremely impaired" compared with the "average" class (OR = 1.61, 95% CI = 1.10–2.35, $P = .016$). Higher IQ was associated with lower likelihood of belonging to either of the impaired classes compared with the "average" class (Ors = 0.93–0.94, 95% Cis = 0.90–0.96/0.90–0.99, $P < .001$). Finally, lower premorbid adjustment was associated with higher likelihood of belonging to the "extremely impaired" class compared with the "average" class (OR = 200, 95% CI = 11–3663, $P < .001$). See Supplementary Table 2 for full details. Given baseline symptom variables were not associated with cognitive class membership, we checked whether changes in symptoms over 12-months differed between the trajectory classes. Executive function, working memory, and verbal learning and memory trajectory classes did not significantly differ in symptom change over the 12-months (Supplementary Table 3).

Transition Status and Functioning Outcomes in Relation to Cognitive Trajectories. Of the included participants, 28 (9.7%) were known to transition to psychosis within the 12-month period (i.e., period determining class membership; n = 16 transitioned before and n = 12 after 6-months). Supplementary Table 4 shows the differences between trajectory classes in relation to 12-month transition rates and Supplementary Table 5 shows mean time to transition within each class, which shows minimal difference between them. Only the working memory classes differed in transition rates, with a significantly higher number of transition cases in the "impaired" compared with the "average" class. When the previous logistic and multinomial regression analyses were repeated with transition status added as an additional independent variable, results remained similar to the previous analyses. Transition status was not significantly associated with cognitive trajectory class membership in any of the three cognitive domains (Supplementary Tables 6 and 7).

Supplementary Table 8 shows the differences between classes in functioning (SOFAS) at 12-month and medium-term follow-up. The working memory classes differed significantly, where the "average" class had significantly higher functioning than the "impaired" class at both 12-months (d = 0.42) and medium-term follow-up (d = 0.40). The verbal learning and memory classes also differed significantly, where the "average" class had significantly higher functioning than the mildly impaired class

Table 3. Baseline Characteristics of the Latent Class Trajectories for Verbal Learning and Memory, Working Memory and Executive Function

		Verbal learning and memory			Working memory		Executive function	
		Average (n = 185)	Mildly Impaired (n = 86)	Extremely Impaired (n = 17)	Average (n = 170)	Impaired (n = 118)	Average (n = 272)	Impaired (n = 16)
Sex	% male	52.4	33.7	23.5	51.8	35.6	46.0	31.2
	P-value[1]	.003			.008		.307	
Age	mean	19.5	18.0	20.7	19.5	18.5	18.9	21.9
	SD	4.4	4.4	5.6	4.6	4.4	4.4	6.0
	P-value[2]	.014			.070		.012	
Education (Years)	mean	10.6	9.8	9.8	10.6	9.8	10.3	10.2
	SD	3.5	2.6	3.0	3.3	3.2	3.3	2.6
	P-value[2]	.213			.042		.953	
Premorbid Adjustment	mean	0.26	0.35	0.33	0.27	0.33	0.29	0.36
	SD	0.14	0.14	0.14	0.13	0.14	0.14	0.15
	P-value[2]	<.001			<.001		.098	
Estimated IQ	mean	107.6	94.4	93.2	107.8	95.3	103.8	85.2
	SD	13.4	13.0	13.9	14.4	11.9	14.3	10.4
	P-value[2]	<.001			<.001		<.001	
BPRS Total	mean	40.6	42.5	44.1	41.1	41.8	41.3	42.4
	SD	9.5	9.7	13.8	9.6	10.3	9.5	14.8
	P-value[2]	.167			.528		.658	
BPRS Psychotic	mean	7.9	8.8	8.6	8.0	8.5	8.3	8.1
	SD	2.5	2.7	3.3	2.5	2.9	2.6	3.3
	P-value[2]	.031			.126		.771	
SANS Total	mean	18.2	18.1	21.1	18.1	18.8	18.3	19.3
	SD	13.7	11.4	14.7	13.3	12.8	13.1	13.9
	P-value[2]	.670			.673		.766	
MADRS Total	mean	18.7	20.7	20.6	19.1	19.9	19.4	19.7
	SD	8.5	9.8	10.3	8.5	9.7	8.9	11.0
	P-value[2]	.197			.458		.904	
ASSIST Alcohol Use	mean	5.8	6.1	2.4	5.8	5.6	5.7	4.9
	SD	5.2	5.9	3.3	5.2	5.5	5.4	5.3
	P-value[2]	.027			.687		.557	
ASSIST Cannabis Use	mean	4.4	3.9	0.4	4.0	4.0	4.0	3.4
	SD	7.1	6.8	1.0	6.6	7.2	6.8	7.6
	P-value[2]	.072			.975		.712	
SOFAS	mean	53.6	53.9	49.2	54.0	52.7	53.7	50.0
	SD	12.5	10.7	11.7	12.1	11.8	11.9	12.2
	P-value[2]	.345			.386		.232	
Omega-3 index	mean	7.3	7.2	8.6	7.3	7.4	7.3	8.4
	SD	1.8	1.7	2.0	1.9	1.8	1.8	2.1
	P-value[2]	.013			.656		.023	

Note: [1]Fisher's exact test[2];ANOVA.
SD, Standard Deviation; BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; MADRS, Montgomery-Åsberg Depression Scale; ASSIST, Alcohol, Smoking and Substance Involvement Screening Test; SOFAS, Social and Occupational Functioning Assessment Scale.

at 12-months ($d = 0.42$) and higher functioning than both impaired clusters at medium-term follow-up ($d = 0.38$ and 1.15, respectively). Though, the extremely impaired class was very small ($n = 4$) due to missing SOFAS data.

Discussion

These findings extend previous UHR studies of longitudinal cognitive performance through the first application, to our knowledge, of data-driven analyses for identifying latent cognitive trajectories in a relatively large sample. The finding of longitudinal improvement in cognitive performance across several cognitive domains and most latent classes is consistent with some previous studies.[12–14] Our findings suggest that individuals with unimpaired cognitive functioning at UHR ascertainment can be expected to remain unimpaired for at least 12-months while receiving treatment, regardless of transition status. Furthermore, in the case of working memory and verbal learning and memory, unimpaired cognition over time was associated with better functioning outcomes. This finding concurs with previous studies.[19,46–48] Thus, brief cognitive screening is likely to be helpful for guiding clinical prognostication and treatment decision-making, such that interventions specifically targeting cognitive functioning should only be offered to individuals with impaired cognition at ascertainment. To date, most clinical trials of cognitive remediation in UHR included participants with unimpaired cognition, which may partly explain their small effects (e.g.,[49, 50]).

Impaired cognitive trajectory classes were identified in the working memory, executive functioning, and verbal learning and memory domains. The impaired working memory class reflected a subtle *lag*, given it remained stable and the unimpaired class significantly improved. While both executive functioning classes improved, Figure 2 suggests a *delay* in the impaired class, as there is evidence of some degree of “catch-up”. For verbal learning and memory, the mildly impaired class showed a stable *deficit* relative to the unimpaired class (as they both improved), whereas the extremely impaired class showed “catch-up” to the mildly impaired class. These findings suggest that screening for deficits in working memory, executive functioning, and verbal learning and memory may be especially useful for guiding targeted early intervention.

As we did not recruit a demographically-matched healthy comparison group (i.e., age, sex, geographically-matched sample), nor a clinical comparison group, we cannot determine the degree of practice effects evident in each class or whether the cognitive class trajectories observed in the current study are *specifically* associated with UHR status. Indeed, transdiagnostic research in youth with early-stage mental illness has shown cognitive cluster membership to be independent of diagnosis and more strongly associated with functional outcome.[51,52] Further, a previous data-driven study found 6-year cognitive class trajectories in people with schizophrenia and healthy controls were very similar, suggesting that cognitive heterogeneity is not entirely explained by illness-related factors.[24] In the current study, baseline symptoms and substance use were not associated with the observed classes, nor was change in symptoms over 12-months. The lack of longitudinal association between cognition and symptomatology is consistent with previous UHR research,[12] but contrasts with full-threshold stages of psychotic illness, where higher negative symptoms especially, are associated with membership within impaired cognitive clusters cross-sectionally[53–55] and longitudinally[22,23] (relative to unimpaired). Possibly, the relationship between poorer cognition and psychosis becomes progressively stronger with stage of illness; an association that may be indicative of illness severity.

Although the proportion of individuals who transitioned to psychosis differed between the two working memory classes in univariate analysis, when transition status was considered alongside other demographic and clinical variables, it was not associated with trajectory class membership. While poorer cognitive functioning at UHR ascertainment is a well-established predictor (i.e., risk factor) of later transition to psychotic disorder,[1,4,19,56–58] the current weight of evidence suggests that transition to psychosis is not associated with the cognitive *course* over the short-term.[14] Nevertheless, it is possible that the number of people who transitioned over 12-months was too small for transition status to become uniquely associated with working memory trajectory class membership, suggesting caution in interpreting this finding. It might also be that transition to psychosis is less relevant to long-term outcome than persistent negative symptoms[59,60] or cognition.[61] In the current study, 12-month cognition class membership was significantly associated with medium-term functional outcome.

The most consistent predictor of cognitive trajectory class membership for the domains of working memory, executive functioning, and verbal learning and memory was baseline estimated IQ, with a higher IQ being associated with a lower likelihood of belonging to the impaired classes in all three cognitive domains. Several cross-sectional cluster analytic studies have shown that both premorbid and current IQ contribute to the prediction of cognitive class membership in first-episode[53–55,62] and persistent psychosis.[54,63,64] Our findings fit with a 6-year longitudinal study of people with schizophrenia and their siblings, where IQ was significantly lower in patients and siblings who belonged to a cognitive trajectory class characterized by persistent mild to severe impairment, compared with those who had persistently unimpaired cognitive function.[23]

Baseline omega-3 index was significantly associated with verbal learning and memory trajectory class membership, which is a novel finding. A higher baseline omega-3 index was associated with a higher likelihood of membership in the extremely impaired class relative to the average class. Notably, the extremely impaired class showed the steepest rate of improvement over the 12-month period. We might speculate that the omega-3 index confers longer-term protective effects for memory function, specifically in those who initially present with extreme impairment. Further investigation of omega-3 polyunsaturated fatty acids as useful biomarkers for cognitive course seems warranted.

Another novel finding was that premorbid adjustment also contributed significantly to prediction of verbal learning and memory trajectory class membership in UHR individuals. Previous studies have shown significant associations between poorer premorbid adjustment and deficits in learning and memory and global cognition in first-episode psychosis[62,65,66] and processing speed and general cognitive performance in established schizophrenia.[67,68] This lends support for neurodevelopmental origins of cognitive trajectory,[7] where the likely path of cognitive performance may be evident early on and more strongly associated with premorbid, rather than illness-related factors. Still, persistent symptoms or treatment may impart cumulative impacts (positive or negative) on cognitive functioning over time. Negative symptoms and institutionalization were found to increase one's risk for belonging to a cognitive deterioration trajectory class in older people with schizophrenia.[22,23] While background treatment during the trial was relatively controlled and no one received antipsychotics or mood stabilizers,[26] future research is needed to better delineate the early effects of different treatments on cognition.

Several limitations warrant mention. A 12-month follow-up is relatively short, limiting more precise modeling of the shape of the trajectories (e.g., by piecewise modeling) and detecting deterioration as in some previous studies.[10,12,69] Due to low case numbers per class, it was necessary to estimate trajectory class predictors/outcomes separately, whereas simultaneous modeling is preferable. Absence of demographically-matched healthy or clinical controls limits the ability to examine practice effects or the specificity of cognitive trajectory classes to UHR. As the assessments of cognition and transition to psychosis did not occur over exactly the same period, we could not consider the association between transition to psychosis between the 12-month and medium-term follow-up (3.4 years) on cognitive trajectory. The number of transitioned cases within the 12-month period was relatively low, perhaps reducing power to detect an association between transition status and cognitive trajectory class membership and also limiting statistical power to include time to transition in the analysis.

In conclusion, data-driven modeling is useful for identifying subgroups with similar cognitive trajectories in help-seeking young people at increased risk for psychosis, where the nature of cognitive trajectory is highly complex during this significant period of neurodevelopment. We found evidence for discrete 12-month latent class trajectories in the domains of working memory, executive function, and verbal learning and memory, which mostly differed in their intercept (baseline severity) and most classes showed significant improvement. IQ, premorbid adjustment, and omega-3 index were associated with trajectory class membership, but symptoms and transition to psychosis status were not. Working memory and verbal learning and memory latent class trajectory membership was associated with functional outcome. These findings require replication in independent UHR samples and their specificity should be determined through comparison to healthy and clinical control samples. Further research should aim to precisely delineate the relationship between cognitive course and treatment effects. Nevertheless, cognitive screening is likely to guide treatment decision-making in UHR individuals.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

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Conflict of Interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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