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Are factors that predict conversion to psychosis associated with initial transition to a high risk state? An adolescent brain cognitive development study analysis

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ABSTRACT

Objective: Previous work suggests that cognitive and environmental risk factors may predict conversion to psychosis in individuals at clinical high risk (CHRs) for the disorder. Less clear, however, is whether these same factors are also associated with the initial emergence of the high risk state in individuals who do not meet current threshold criteria for being considered high risk.

Method: Here, using data from the Adolescent Brain Cognitive Development (ABCD) study, we examined associations between factors previously demonstrated to predict conversion to psychosis in CHRs with transition to a "high risk" state, here defined as having a distress score between 2 and 5 on any unusual thought content question in the Prodromal Questionnaire-Brief Child version. Of a sample of 5237 children (ages 11–12) studied at baseline, 470 transitioned to the high-risk state the following year. A logistic regression model was evaluated using age, cognition, negative and traumatic experiences, decline in school performance, and family history of psychosis as predictors.

Results: The overall model was significant ($\chi^2 = 100.89$, $R^2 = 0.042$, $p < .001$). Significant predictors included number of negative life events, decline in school performance, number of trauma types, and verbal learning task performance.

Conclusions: These results suggest that factors that predict conversion in CHR teenagers are also associated with initial emergence of a "high-risk" state in preadolescents. Limitations regarding the degree to which model factors and outcome in this study parallel those used in previous work involving psychosis risk in older teenagers are discussed.

1. Introduction

Although the average age of onset of psychotic disorders such as schizophrenia is typically 18–25, it is now generally accepted that full-blown illness is often preceded by a prodromal, clinical high-risk (CHR) state characterized by attenuated symptomatology, functional decline, and a greatly-exacerbated risk of conversion to psychosis (20–35 %; 100× the rate in the general population) (Fusar-Poli, 2017; Fusar-Poli et al., 2013). Furthermore, researchers have developed risk calculators that use a set of cognitive, clinical, and environmental risk factors to predict which CHR individuals will convert to psychosis (Cannon et al., 2016; Kotlicka-Antczak et al., 2019; Malda et al., 2019; Studerus et al., 2020). The ability to predict which at-risk individuals are likely to convert to illness as well as a transition to a high-risk state in preadolescents may help identify those who may most strongly benefit from early interventions (e.g., cognitive behavioral therapy (CBT), which has shown promise in preventing conversion to psychosis (Addington et al., 2020)). Indeed, early interventions are also known to improve overall clinical outcomes in psychotic illness (Marshall et al., 2005). In the calculator by Cannon et al. (2016), the included risk factors were age, performance on a verbal learning and attention/processing speed test, the number of negative life experiences, the number of different types of traumas experienced, the degree to which functioning has declined over the past year, family history of psychosis, and current level of symptomatology (unusual thought content and suspiciousness). Using these factors, prior studies suggest conversion to psychosis can be

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predicted with 67–68 % balanced accuracy (using regression) in CHRs (Koutsouleris et al., 2021; Smucny et al., 2023).

Given the success of these factors at predicting conversion to psychosis in CHRs, one might ask a similar question in children and preadolescents that have yet to convert to a CHR state. Specifically, can these same premorbid factors predict transition to CHR status from a subthreshold prodromal state? If so, it may have major implications for designing preventative strategies that can identify early premorbid risk factors and ultimately reduce the rate of symptom progression.

To seek an answer to this question we used data from the Adolescent Brain Cognitive Development (ABCD) study. The ABCD is a large scale study that includes a host of clinical, environmental, and cognitive instruments (including others) that are measured in children starting at age 8–9 and continuing annually (or bi-annually, depending on the measure) for 10 years (https://abcdstudy.org). The current release, 5.0, includes complete data up through the 3rd follow-up year (i.e., ages 12–13). As the prodromal stage of psychosis may begin as early as age 12 (Cannon et al., 2016; Miller et al., 2003), the current release is well-suited to answer the clinical question outlined in this study. Notably, we chose to base our predictive model from that developed by Cannon et al. (2016) (as opposed to other models, e.g., (Kotlicka-Antczak et al., 2019; Malda et al., 2019; Studerus et al., 2020)) because the Cannon et al. (2016) model incorporated predictors beyond demographics and clinical measures (i.e., cognition and life experiences).

2. Methods

2.1. Participants

The ABCD data used in this report came from release 5.0 (Digital Object Identifier (DOI):10.15154/8873-zj65). DOIs can be found at https://nda.nih.gov/abcd/abcd-annual-releases.html. This release includes study waves 3 (2nd year follow-up, >99 % were ages 11–12) and 4 (3rd year follow-up, ages 12–13). The present study primarily used data from wave 3 as baseline predictors and wave 4 as the outcome measure in logistic regression. Potential participants were excluded from ABCD study participation for the following reasons: child not fluent in English, magnetic resonance imaging contraindication (e.g., irremovable ferromagnetic implants or dental appliances, claustrophobia, pregnant), major neurological disorder, gestational age <28 weeks or birthweight <1200 g, history of traumatic brain injury, or had a current diagnosis of schizophrenia, autism spectrum disorder (moderate, severe), mental retardation/intellectual disability, or alcohol/substance use disorder.

2.2. Outcome

The outcome measure was calculated using the Prodromal Questionnaire-Brief Child Version (PQ-BC), a 21-item self-report psychotic-like experience (PLE) questionnaire that includes a distress level scale (range 1–5) to indicate the severity of each PLE item ("how much did the experience bother you?") (Loewy et al., 2011). Of these, 11 were considered unusual thought content questions (Karcher et al., 2020b) (Supplementary Table 1). Distress scores (1 to 5) were extracted for these questions with the highest distress score used to define clinical high risk thresholds; specifically, preteens with a maximum score of 0 or 1 were considered non-risk, and scores 2–5 considered high risk. This threshold is consistent with clinical high risk definitions based on the Structured Interview for Prodromal Symptoms (SIPS) (Miller et al., 2003), although it should be noted that the SIPS is based on symptom severity (and not level of distress). As the PQ-BC does not include a symptom severity score, distress level was used as the closest available proxy.

Using these definitions, only individuals with a highest distress score of 0 or 1 at baseline were used for analysis. We then examined the significance of a regression model that predicted which individuals would transition to a "high risk" state at follow-up (i.e., a maximum distress score of 2–5).

2.3. Logistic regression features

Features for logistic regression were selected based on the North American Prodrome Longitudinal Study (NAPLS) risk calculator (age, Hopkins Verbal Learning Test-Revised (HVLT-R) total raw score, Brief Assessment of Cognition in Schizophrenia (BACS) Symbol Coding raw score, number of negative life events, number of trauma types, having a first degree relative with psychosis, and decline in global functioning over the past year) (Cannon et al., 2016). As the ABCD does not include the HVLT-R or BACS, the Rey Auditory Verbal Learning Test (RAVLT) and National Institutes of Health Toolbox Pattern Comparison Processing Speed Test raw scores were used instead (Thompson et al., 2019). Briefly, in the RAVLT participants are asked to listen to and recall a list of 15 unrelated words over five learning trials. A distractor list of 15 words is then presented, from which the individual is asked to recall as many words as possible. Next, the participant is tested on recall of the initially learned list. Finally, recall of the initial list is tested following a 30-min delay (Thompson et al., 2019). In the Pattern Comparison test, participants identify whether two visual patterns are the "same" or "not the same." Patterns were either identical or varied on one of three dimensions: color, adding/taking something away, or one versus many (Carlozzi et al., 2015). Number of negative life events was summed using the Life Events scale from ABCD year 2 and year 3 data; example events included, "Someone in the family died" and "Was a victim of crime/violence/assault" (see https://nda.nih.gov/data-structure/abcd_yle01 for full list of questions) (Grant et al., 2004; Hoffman et al., 2019; Tiet et al., 1998). Number of trauma types was determined using year 1 and year 3 data from the Kiddie Schedule for Affective Disorders and Schizophrenia Post-Traumatic Stress Disorder scale (Chambers et al., 1985). For this questionnaire participants provided yes/no answers if they experienced each of the following traumatic events: car accident, other accident, fire, witness of a disaster, witness of a violent crime, confronted with traumatic news, terrorism-related trauma, war zone trauma, witness to domestic abuse, physical abuse, sexual abuse, and "other." Decline in functioning was determined using a yes/no question asking the parent if the child showed a significant decrease in school grades over the prior year. Notably, unlike the NAPLS we did not include a baseline measure of unusual thought content severity as a predictor as the sample was designed to only include children who had low/absent (maximum distress scores 0–1) symptoms at baseline.

2.4. Logistic regression

Logistic regression was performed in SPSS v.28 (IBM), with the binary (yes/no) dependent variable being transition to a high risk state based on PLE unusual content score severity (see Outcome, above) and predictor independent variables as described above. The overall model was considered significant if $p < .05$. Significance of individual predictors was determined by the change in log-likelihood (if the term was removed; threshold $p < .05$). Individuals with missing data were excluded.

2.5. Clinical validation

To examine the validity of our outcome measure, we examined relationships between scores on the Child Behavior Checklist (CBCL) Thought Disorder scale and the PQ-BC-based outcome (although the measures are not equivalent, the CBCL Thought Disorder scale is the measure that is most closely related to the PQ-BC in the ABCD Study). Specifically, we 1) compared percent change (between baseline and follow-up) in CBCL Thought Disorder T score (rescaled to a lowest score of 1 (from 50) between converters and non-converters, and 2) examined the Pearson's correlation between percent change in CBCL Thought

Disorder T score (rescaled) and change in the highest PLE unusual content distress score. Significance for these tests was set to $p < .05$.

3. Results

Of the entire ABCD sample ($n = 11,868$), 8972 children reported a highest unusual thought content PQ-BC distress score between 0 and 1 at baseline. Of these, 656 individuals did not have available PQ-BC outcome data (year 3 scores), leaving 8316 individuals who both met baseline criteria and had outcome data. Of these 8316 participants, 727 did not have RAVLT data, 1985 did not have Pattern Comparison task data, 114 did not have negative life events data, 381 did not have number of trauma types data, 296 did not have family history of psychosis data, 492 did not have data re: school grades.

After removing individuals with missing data, 5237 children were available for the primary analysis (predicting the PQ-BC-based outcome). Of these, at follow-up one year later 470 became "high-risk" (showed a highest PQ-BC unusual thought content distress score > 2) and the remaining 4767 remained "low-risk."

Summary data are presented in Table 1, and logistic regression statistics are presented in Table 2. For examining the association with transition to a high-risk state, the overall logistic regression model was significant ($p < .001$). In decreasing order of importance ($\Delta - 2$ log-likelihood), significant features associated with transition were the total number of negative life events, showing a significant drop in grades vs. the previous year, the number of trauma types, and the total number of correct answers on the RAVLT (negative association).

To validate our definition of transition to a high-risk state, we compared change in CBCL Thought Disorder score between converters and non-converters. Of the sample of 5237 children in the primary analysis, an additional 343 did not have complete CBCL Thought Disorder information, leaving 4894 participants for the CBCL analysis. As shown in Table 1, children who converted showed significantly higher percent increases in CBCL Thought Disorder vs. children who did not ($t = 6.19$, $p < .001$). A significant association was also observed between change in unusual highest unusual thought content distress score and change in CBCL thought disorder score ($r = 0.086$, $p < .001$).

4. Discussion

In this study, we demonstrate that risk factors previously shown to predict transition to psychosis in CHR individuals are also associated with conversion to a prodromal-like state in preadolescent individuals. The baseline features that were most strongly associated with the follow-up outcome measure were the number of negative life events, recent drop in functioning (school grades), verbal learning performance, and the number of trauma types. Individuals that transitioned to the high-risk state also showed significantly greater increases in CBCL Thought Disorder score over the follow-up period, providing additional clinical validation of the PQ-BC-based distress score threshold used to define conversion. These results suggest that the same set of risk factors that predict conversion to psychosis in CHR (with minor differences due to the data collection instruments being utilized) are also associated with the initial transition to a CHR state in pre-adolescents.

Consistent with research predicting conversion to psychosis in CHRs (Cannon et al., 2016), decline in functioning and poorer verbal learning were two of the strongest predictors of transition to the CHR state. A significant positive association between traumas/negative life experiences and CHR status is also consistent with prior studies (Loewy et al., 2019; Mayo et al., 2017). Somewhat surprisingly, however, family history of psychosis was not a significant feature in this study. Several factors may explain this negative finding, including non-specificity of psychosis symptoms (as they are prominent in several disorders) and relatively low genetic risk (only ~10 % of people with a parent with schizophrenia also have the illness (Rasic et al., 2014)). It should also be noted that the extent to which family history predicts psychosis conversion or symptomatology in CHRs is controversial, with some studies showing significant relationships (Cannon et al., 2008; Santesteban-Echarri et al., 2022) and others not (Cannon et al., 2016; Georgopoulos et al., 2019). It is also possible that including schizophrenia polygenic risk scores in future work will enhance model performance, as previous work in CHRs suggest these scores significantly improve psychosis prediction (Perkins et al., 2020).

The findings in this study are in conceptual agreement with previous work in the ABCD that have examined relationships between these factors (among others) and psychotic-like experiences (PLEs) as measured by the PQ-BC. For example, Karcher et al. (2020b) found a significant relationship between adverse childhood experiences and PQ-BC scores in the first wave (ages 9–10) of the study. A later longitudinal analysis across the first three ABCD waves (i.e., through the baseline timepoint of the present work) found that cognition, poor school performance, and negative life experiences predicted the development of persistently distressing PLEs over the three year study period (Karcher et al., 2022). The present study expands upon this work by examining an older age range (that corresponds to the age when psychosis prodrome begins) and using a model that parallels previous work in CHRs.

To be consistent with the NAPLS-2 calculator (Cannon et al., 2016),

Table 1
Summary data. All data are from baseline and are mean (SD) unless otherwise specified. CBCL scores were set to a lowest score of 1 (i.e., CBCL score used = CBCL T score - 49).

Measure	Entire sample	Converters	Non-converters
N	5237	470	4767
Age in years[a]	11.50 (0.60)	11.47 (0.50)	11.50 (0.61)
N sex M/F (%M)	2816/2421 (54 %)	183/287 (39 %)	2633/2134 (55 %)
RAVLT sum correct trials[a]	69.72 (14.07)	67.26 (14.51)	69.97 (14.00)
NIH Toolbox Pattern Comparison raw score[a]	45.61 (7.10)	44.90 (7.43)	45.68 (7.07)
N negative life events[a]	4.23 (3.39)	5.56 (3.85)	4.10 (3.32)
N trauma types[a]	0.67 (1.07)	0.89 (1.33)	0.65 (1.04)
N has family history of psychosis Y/N (%Y)[a]	529/4708 (10 %)	54/416 (12 %)	475/4292 (10 %)
N showed drop in grades last year Y/N (%Y)[a]	678/4559 (13 %)	92/378 (20 %)	586/4181 (12 %)
CBCL Thought Disorder score	4.14 (5.16)	5.08 (5.99)	4.05 (5.06)
CBCL Thought Disorder score at follow-up	4.22 (5.23)	5.90 (6.29)	4.05 (5.09)
CBCL Thought Disorder Score percent change	0 (4)	113 (298)	50 (19)

[a] Used for logistic regression models.

Table 2
Logistic regression results. Predictors are listed in order of descending Δ-2 log-likelihood (LL).

Full model			
χ^2	−2 LL	R^{2a}	*p*
100.89	3061.73	0.042	<.001

Predictors	Δ-2 LL if term removed	Beta	*p*
Negative life events	51.85	0.093	<.001
Showed drop in grades last year	10.56	0.427	<.001
Trauma types	7.84	0.105	.003
RAVLT sum correct trials	7.70	−0.010	.005
Age in years	0.69	−0.066	.39
NIH Toolbox Pattern Comparison raw score	0.61	−0.006	.43
Has family history of psychosis	0.004	0.010	.95

[a] Nagelkerke R^2.

sex was not included as a feature in any models. Notably, however, a greater percentage of participants who transitioned to the prodromal-like state were female. This may be surprising given that schizophrenia onset is known to occur later in women vs. men (Angermeyer and Kuhn, 1988; Li et al., 2016). Why might such a discrepancy have occurred? First, the self-report nature of the PQ-BC may have induced sex effects, as males and females may differ in their interpretation of the level of distress induced by a PLE (i.e., girls may report the "same" PLE as being more distressing than boys). Second, it is important to distinguish transition to the pseudo-prodromal state from actual CHR status and full-blown psychotic illness. It is possible that although girls may be more likely to transition to the prodromal-like state, neuroprotective factors (e.g., estrogen (Grigoriadis and Seeman, 2002)) may help protect against further illness progression.

These findings may have implications for early intervention programs. It is now well-known that early intervention is associated with improved outcomes in after psychosis onset (Marshall et al., 2005). Although less clear, some evidence suggests that some forms of treatment (e.g., CBT or CBT combined with group counseling and cognitive remediation) during the CHR state may also reduce the risk of conversion to psychosis (Addington et al., 2020). As negative life events, recent drop in school grades, verbal learning performance, and the number of trauma types were the most significant factors when predicting transition to the prodromal-like state (as defined in this study), it is possible that these questions may be used as screening tools by clinicians to identify those individuals most at risk for worsening PLEs and thus the most likely to show clinical benefit for such interventions.

Our study had several limitations. As SIPS data were unavailable, our CHR definition was based on the PQ-BC. Although the PQ-BC has demonstrated construct validity in prior work (Karcher et al., 2018, 2020a) as well as the present study (based on associations with CBCL Thought Disorder score) it is still not used in the clinic to diagnose an individual as having CHR status (which typically requires a structure clinical interview rather than self-report). Indeed, self-report measures may be more likely to be biased and unreliable, due to several factors such as: 1) a desire to provide "socially acceptable" answers, 2) a desire to exaggerate or downplay effects to influence interpretation, and 3) confusion/misunderstanding/individual differences in how questions are interpreted (Rosenman et al., 2011). The latter may be particularly problematic in young populations when asked to rate the level of PLE "distress" in the PQ-BC, as this level may be subjective. Secondly, although the predictors used in this study were chosen as proxy measures for those in the NAPLS risk calculator, the measures available in the ABCD were not identical to those used by the NAPLS. For example, because an equivalent to a Global Assessment of Functioning score (First et al., 2002) was not available in the ABCD, recent drop in school grades was used as a proxy for general functioning. This measure may have been influenced by other predictors (e.g., cognition). Finally, the participant age range in this study represented the youngest age range associated with the psychosis prodrome, and our result requires replication in older samples as additional ABCD study releases become available as the sample proceeds through adolescence.

Despite these limitations, the results of the present study support our hypothesis that an initial transition to a CHR-like state is associated with features extracted from a set of readily administered instruments that are comparable to those used to predict conversion to psychosis in CHR individuals. As the logit function-based manifold used in logistic regression may limit its predictive capability, the ability of more sophisticated machine learning and deep learning approaches to predict this transition will be examined in future work.

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CRediT authorship contribution statement

Jason Smucny: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Funding acquisition, Formal analysis. **Avery Wood:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Ian N. Davidson:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Methodology. **Cameron S. Carter:** Writing – review & editing, Supervision, Resources, Project administration.

Declaration of competing interest

The authors declare no conflicts of interest.

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