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Symptom trajectories and psychosis onset in a clinical high-risk cohort: The relevance of subthreshold thought disorder

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ABSTRACT

Background: Prior studies have implicated baseline positive and negative symptoms as predictors of psychosis onset among individuals at clinical high risk (CHR), but none have evaluated latent trajectories of symptoms over time. This study evaluated the dynamic evolution of symptoms leading to psychosis onset in a CHR cohort.
Method: 100 CHR participants were assessed quarterly for up to 2.5 years. Latent trajectory analysis was used to identify patterns of symptom change. Logistic and proportional hazards models were employed to evaluate the predictive value for psychosis onset of baseline symptoms and symptom trajectories.
Results: Transition rate to psychosis was 26%. Disorganized communication (i.e., subthreshold thought disorder) presented an increased hazard for psychosis onset, both at baseline (Hazard Ratio (95% CI) = 1.4 (1.1–1.9)) and as a trajectory of high persistent disorganized communication (Hazard Ratio (95% CI) = 2.2 (1.0–4.9)). Interval clinical data did not improve the predictive value of baseline symptoms for psychosis onset.
Conclusions: High baseline disorganized communication evident at ascertainment tended to persist and lead to psychosis onset, consistent with prior behavioral and speech analysis studies in similar cohorts. Remediation of language dysfunction therefore may be a candidate strategy for preventive intervention.

1. Introduction

The clinical high-risk (CHR) state for psychosis is characterized by attenuated psychotic symptoms, i.e. subthreshold delusions (unusual thought content, suspiciousness, grandiosity), subthreshold hallucinations (perceptual disturbances) and subthreshold thought disorder (disorganized communication) (Miller et al., 2003). Individuals who meet CHR criteria also have profound negative symptoms, related to their poor function (Corcoran et al., 2011). Prior large (N > 100) CHR cohort studies have examined the predictive value of positive symptoms obtained at ascertainment for psychosis onset within 1–2 years (~15–25%), finding baseline severity of subthreshold thought disorder and subthreshold delusions, and variably negative symptoms, to be associated with later psychosis onset (Cannon et al., 2008; Lemos-Giraldez et al., 2009; Ruhrmann et al., 2010; Demjaha et al., 2012; Nelson et al., 2013).

The clinical high-risk state, however, is likely dynamic over time, and interval data may be informative in quantifying risk for psychosis outcome. As yet, two research groups have examined interval clinical data, finding correlations of symptoms with contemporaneous transition to psychotic disorder. One study (N = 138) assessed symptoms and potential psychosis onset at baseline, six months, and one year in CHR participants, finding that persistent negative symptoms were associated with the development of psychosis (15%) (Piskulic et al., 2012). Another study (N = 61) assessed symptoms and potential psychosis onset at baseline, one year and three years, finding that consistently elevated positive and negative symptoms were present at all three time points among CHR participants who developed psychosis (Lemos-Giraldez et al., 2009). We build on these prior studies, which had three assessment points, by increasing the number of assessments (quarterly for up to 2.5 years) in order to assess if there are

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heterogeneous trajectories of different "prodromal" symptoms (Fusar-Poli et al., 2014) associated with psychosis outcome.

For data analyses, we used latent trajectory analysis, which offers the opportunity to use interval clinical data between baseline characterization and psychosis onset (or censoring) to examine symptom trajectories as potential predictors of psychosis onset, i.e. latent groups that vary qualitatively by pattern of symptom change (Jones et al., 2001). For more trait-like symptoms of schizophrenia, such as thought disorder, latent trajectory analysis can determine whether there is any added predictive value of trajectories beyond that of baseline severity. In psychiatry, latent trajectory analyses have been used to evaluate the patterns of symptoms in autism onset (N = 52) (Ozonoff et al., 2011), in disparate types of mood episodes in bipolar disorder (N = 118) (M'Bailara et al., 2013), and in response to antipsychotic medications in first-episode psychosis patients (N = 161) (Pelayo-Teran et al., 2014).

Latent class cluster analysis has been used to identify baseline negative symptoms and baseline functional impairment as predictive of psychosis onset (N = 318) (Valmaggia et al., 2013). Latent trajectory analysis, however, has not yet been utilized previously in CHR cohorts. Herein, we evaluated prodromal symptom trajectories in CHR participants assessed on a quarterly basis for up to 30 months until psychosis onset or censoring, to assess the predictive value of clinical trajectories for psychosis. It was hypothesized that latent symptom trajectories exist that have predictive value for psychosis outcome, including time to onset.

2. Experimental/materials and methods

2.1. Participants

This prospective CHR cohort study was ascertained from 2004 through 2012 at the New York State Psychiatric Institute at Columbia University Medical Center. Participants were 100 English-speaking, help-seeking youths between the ages of 12 and 30 years (at study entry) who were referred from schools and clinicians, or self-referred through the research program website, and who were ascertained as at clinical high-risk for psychosis using the Structured Interview for Prodromal Syndromes/Scale of Prodromal Symptoms (SIPS/SOPS; Miller et al., 2003). Exclusion criteria included history of threshold psychosis or Axis I psychotic disorder, risk of harm to self or others incommensurate with outpatient care, any major medical or neurological disorder, and IQ < 70. Additionally, attenuated positive symptoms could not have occurred solely in the context of substance use or withdrawal, or have been better accounted for by another Axis I disorder (i.e. a mood disorder). All adult participants provided written informed consent; participants under the age of 18 provided written assent, with written informed consent provided by a parent. This study was approved by the Institutional Review Board at the New York State Psychiatric Institute at Columbia University.

Of note, participants were assessed quarterly in person for up to 2 1/2 years (defined specifically as fewer than or equal to 958 days, or 30 months + 1.5 month acceptable window for the final assessment), or until time of transition to psychosis. For those participants who did not develop psychosis or complete the full 2 1/2 years of assessments, their longitudinal symptom data were considered censored for survival analyses with their last in-person interview, but their outcome with respect to transition by 2 1/2 years was assessed through telephone interview, for the purposes of logistic regression analyses.

2.2. Measures

Demographic information (self-reported age, gender, ethnicity, and education/ employment status) was recorded at time of enrollment in the study, as was the use of medications (separate dichotomous variables indicating yes/no for use of antidepressants, yes/no for use of antipsychotics) and cannabis use (yes/no, determined using timeline follow-back procedures for the prior month). The use of other medications and other substances was reported too infrequently for consideration in data analyses.

The SIPS/SOPS was used for ascertainment, and for ratings of prodromal symptoms at baseline and then quarterly for up to 2.5 years, with transition to psychosis determined using its "presence of psychosis" criteria (at least one positive symptom at threshold level (i.e. rating = 6) present several times per week for one month, or for a full day if disorganizing or dangerous). The research design of quarterly clinical ratings was established to characterize symptom trajectories toward psychosis onset. The SIPS/SOPS was administered by trained masters-level clinicians, and ratings were achieved by consensus with the senior author (CMC), who was certified multiple times in its administration by investigators at Yale University, and who has maintained excellent inter-rater reliability with other clinical high-risk programs (intraclass correlation coefficients (ICCs) > 0.70 for individual scale items and 1.00 for syndrome ratings).

2.3. Data analyses

Demographics and baseline use of medications/cannabis were evaluated for association with transition to psychosis, using Student t-tests, χ^2 analyses and proportional hazards models; any identified as such were included as covariates in further analyses. Stepwise logistic regression and Cox proportional hazards models, with forward selection based on likelihood-ratio estimates, were then used to evaluate the association of any baseline positive symptoms with psychosis transition (yes/no and time to onset, respectively), as well as the predictive value of the sums of both positive and negative symptom scores. Odds ratios (OR) and hazard ratios (HR), with 95% confidence intervals (CI), were calculated using logistic regression and Cox regression analyses, respectively. Alpha (two-tailed) was set at 0.05 for all analyses.

Positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity were calculated for each of the baseline variables that were significantly associated with psychosis onset. Baseline symptom measures which presented a statistically significant hazard for psychosis onset were evaluated serially as dichotomous variables (i.e. low/high) divided at each possible score (from 1 through 5) in order to determine the optimal cutpoint to maximize the area under curve (AUC) for receiver operator characteristic (ROC) curves. The Youden Index was calculated as the maximal value for sensitivity + specificity − 1 (Ruopp et al., 2008) at this optimal cutpoint.

Trajectory analyses were used to identify clusters of participants following similar trajectories in symptoms over time using the "TRAJ" module of STATA (Jones et al., 2001). First, trajectory analyses were conducted for each symptom item that at baseline presented a statistically significant hazard for psychosis onset, with resulting trajectories evaluated for their own predictive power. Trajectories were fit using unadjusted censored normal models to account for clustering of scores at the scales' minima and maxima. The optimal number of trajectory groups and shape of each trajectory was selected using the Bayesian Information Criterion (BIC) (Schwarz, 1978), which penalizes complex models and thus attains a balance between model parsimony and fit to the data. Allowing for more than five trajectory groups did not improve any of the models and thus only models with five or fewer trajectory groups were considered. Additionally, the highest order polynomial considered for each trajectory was the cubic polynomial since higher order polynomials did not significantly improve model fit. All terms were significant with alpha set at 0.05 in the BIC-selected models. For exploratory analyses, STATA TRAJ was also used to examine trajectories for sum scores for positive and negative symptoms (Hawkins et al., 2004), and also for each SIPS/SOPS item.

Symptom trajectories evaluated for prediction of psychosis were also compared in terms of demographics and baseline use of medication/

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