Latent Profile Analysis and Conversion to Psychosis: Characterizing Subgroups to Enhance Risk Prediction

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Background: Groups at clinical high risk (CHR) of developing psychosis are heterogeneous, composed of individuals with different clusters of symptoms. It is likely that there exist subgroups, each associated with different symptom constellations and probabilities of conversion. Method: Present study used latent profile analysis (LPA) to ascertain subgroups in a combined sample of CHR (n = 171) and help-seeking controls (HSCs; n = 100; PREDICT study). Indicators in the LPA model included baseline Scale of Prodromal Symptoms (SOPS), Calgary Depression Scale for Schizophrenia (CDSS), and neurocognitive performance as measured by multiple instruments, including category instances (CAT). Subgroups were further characterized using covariates measuring demographic and clinical features. Results: Three classes emerged: class 1 (mild, transition rate 5.6%), lowest SOPS and depression scores, intact neurocognitive performance; class 2 (paranoid-affective, transition rate 14.2%), highest suspiciousness, mild negative symptoms, moderate depression; and class 3 (negative-neurocognitive, transition rate 29.3%), highest negative symptoms, neurocognitive impairment, social cognitive impairment. Classes 2 and 3 evidenced poor social functioning. Conclusions: Results support a subgroup approach to research, assessment, and treatment of help-seeking individuals. Class 3 may be an early risk stage of developing schizophrenia.

Key words: clinical high risk/ultra high risk/neurocognition/psychosis/functioning/early intervention/negative symptoms

Introduction

Individuals at clinical high risk (CHR) often present with a mixture of difficulties in addition to subthreshold psychotic symptoms, such as neurocognitive decline, premorbid dysfunction, and anxious/mood disorders.1–4 Heterogeneity impedes research by obscuring potentially discrete subtypes, which hinders clinical research, evaluation, and treatment.

Latent subgroup models are a novel approach in explicating risk in CHR and are within a group of statistical methods known as latent variable mixture modeling (LVMM). LVMM, such as latent profile analysis (LPA), aims to identify homogenous subgroups within heterogeneous cohorts, each with independent symptom constellations and differential associations with conversion and functional ability.5,6 LVMM may improve accuracy in identifying who among the CHR group will subsequently convert to psychosis. Imaging studies have provided support for latent CHR subgroups, finding significant neurobiological heterogeneity in gray matter volume.7

LVMM has been applied in 2 CHR studies with mixed results.8,9 Velthorst et al8 used a modified latent class factor analysis to investigate symptom profiles of 288 CHR and unaffected control (UC) individuals. “At risk” and “healthy” classes emerged, but classification did not enhance prediction of conversion. Possible reasons for this include incorporation of UCs with limited variability and lack of diversity in predictive indices.

Valmaggia et al9 applied a LVMM approach to a sample of 318 CHR individuals’ ratings on the Comprehensive Assessment of the At-Risk Mental States.10 A 4-class model emerged, each associated with different rates of transition to psychosis. The subgroup with the highest transition rate (class 4, 41.2%) was characterized by the highest symptom ratings, lowest overall functioning, and highest unemployment rate. Classes were best separated by differences in negative symptoms and social/role functioning, indicating that these variables...
are useful in determining risk. Thus, LVMM identified individuals with a specific constellation of negative symptoms and role impairments that were associated with a higher conversion rate.9

The present paper seeks to extend previous LVMM findings through application of LPA in a large group of prospectively identified CHR and help-seeking control (HSC) individuals and build upon Valmaggia et al’s model by incorporating measures of pre-morbid, social and role functioning, neurocognition, and social cognition. The aim is to enhance model validity by adding diagnostically relevant clinical and neurocognitive indicators and to further characterize latent subgroups with covariates. Supplementary table 1 defines all acronyms included in the present article.

Methods

Sample

The sample consisted of 171 CHR participants (98 males, 73 females) with a mean age of 19.8 (SD = 4.5) and 100 HSC participants (56 males, 44 females) with a mean age of 19.4 (SD = 3.9) years. Data were collected as a part of National Institute of Mental Health (NIMH) funded, multisite study “Enhancing the Prospective Prediction of Psychosis” (PREDICT). Procedures are described in greater detail in prior publications (eg,11–14). PREDICT was conducted at the Universities of North Carolina at Chapel Hill (62 CHR, 24 HSC), Toronto (69 CHR, 45 HSC), and Yale (40 CHR, 31 HSC). All CHR participants met Criteria of Prodromal Syndromes (COPS) derived from the Structured Interview for Prodromal Syndromes (SIPS15). Twenty-nine CHR individuals converted to psychosis (17.0% within CHR; 10.7% within total sample).

The HSC group was comprised of individuals who responded to CHR recruitment, appeared to have prodromal symptoms at phone screen but upon administration of the SIPS did not meet COPS criteria. The HSC group contains the following subgroups: (1) family high risk, no deterioration in Global Assessment of Functioning (n = 16), (2) attenuated symptoms present for more than 1 year (n = 39), (3) current attenuated symptoms but due to another disorder (n = 2), (4) only negative symptoms (n = 4), and (5) attenuated symptoms not meeting severity or frequency criterion (n = 24). HSC individuals were included as a clinically relevant control group, as CHR and HSC individuals are more symptomatically similar to one another than non-psychiatric controls. Inclusion of such self-presenting, help-seeking individuals typically seen at CHR clinics provides greater better representation of clinical realism and diversity. Further, five HSC individuals converted to psychosis (5.0% within HSC; 1.8% within total sample).

Exclusion criteria included presence of an axis I psychotic disorder, age-scaled intelligence quotient (IQ) < 70, history of a clinically significant central nervous system disorder that may confound/contribute to CHR symptoms, or past/current use of antipsychotics.

Measures

SIPS and Scale for Assessment of Prodromal Symptoms (SOPS15) were used to assess criteria for prodromal syndrome, conversion, and severity of attenuated psychotic symptoms. Structured clinical interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV16) was used to assess current/lifetime substance abuse/dependence.

Conversion to psychotic disorder is defined as at least 1 of 5 attenuated SOPS positive symptoms reaching a psychotic level of intensity (rated 6) for a frequency of ≥1 h/d for 4 d/wk in the past month. If the symptom meets intensity but not frequency criteria, it must seriously impact functioning (ie, severely disorganized or dangerous to self/others) to be considered conversion.15

Calgary Depression Scale for Schizophrenia (CDSS17) was used to measure depression and has been validated in CHR individuals.18

Neurocognitive Measures. Neurocognitive measures were selected based on demonstrated reliability, validity, absence of ceiling/floor effects in CHR population, ability to discriminate individuals with schizophrenia from UCs, and appropriateness for administration in individuals as young as 14. Verbal fluency was measured with category instances (CAT19), executive functioning with Wisconsin Card Sorting Test, 64-card computerized version (WCST20) and Trail Making Test B (TMT B21), speed of processing with TMT A,21 verbal explicit memory with Rey Auditory Verbal Learning Test (RA VLT22), and attention with Continuous Performance Test-Identical Pairs (CPT-IP23). Neurocognitive tests, indices, ranges, and normative UC data are provided in supplementary table 2.

IQ was measured using the Wechsler Adult Intelligence Test or the Wechsler Intelligence Scale for Children-III, depending on the participants’ age.24,25

Social Cognition. Theory of mind (ToM) was assessed with the “Reading the Mind in the Eyes” Task (Eyes Task26), emotion perception (EP) in faces with the Face Emotion Identification Task (FEIT27) and the Face Emotion Discrimination Task (FEDT27), and EP in voices with the Affective Prosody Task (AP28). All social cognitive tests, ranges, and normative data from UC groups are provided in supplementary table 2.

Functioning Measures. Premorbid functioning was assessed using the Premorbid Adjustment Scale (PAS29) using administration and scoring procedures outlined by van Mastrigt and Addington.30 Adult PAS ratings were not included in the present analyses due to young age of the
sample (44.6% <19 y). Social functioning was measured using Social Functioning Scale (SFS) with the employment item removed (range: 0–213). Role functioning was measured using the employment subscale of the Heinrichs-Carpenter Quality of Life Scales (QLS) (range: 0–18).

**Procedures**

PREDICT was a longitudinal study of predictors of conversion to psychosis. Study protocols and informed consent documents were reviewed and approved by institutional review boards of the 3 study sites. Formal consent procedures were conducted with participants. Clinical raters were experienced research clinicians who underwent a training program developed at Yale to identify prodromal syndromes with adequate reliability and demonstrated reliability throughout PREDICT. Gold standard post-training agreements were excellent ($\kappa = 0.90$).

JA chaired weekly conference calls with all clinical raters to review inclusion criteria for all participants. Research assistants were trained in neurocognitive assessments by R.S.E.K. and social cognitive assessments by D.L.P.

**Statistical Analyses.** Data analyses were performed using Mplus version 7 with Mixture Add-On and SPSS version 23.

**Model Selection**

Number of classes were not estimated a priori, but were ascertained from a combination of model fit statistics and interpretability. Model of best fit was determined from examinations of: (1) Akaike's Information Criteria (AIC), Bayesian Information Criteria (BIC), sample-size adjusted BIC (ssa BIC) (lower values indicate the model of best fit), (2) Bootstrapped Likelihood Ratio Tests (BLRT), (3) Mean estimated average posterior probabilities, and (4) Entropy indices.

An alternative interpretation of information criteria (eg, AIC, BIC, ssa BIC) and log likelihood values is to plot indices against the number of latent classes and examine for the “leveling off” point of the curve (eg, scree plot). The model associated with a subsequent decrease in absolute value of slope may provide a model that balances model fit statistic improvement and parsimony. Substantive interpretability and parsimony of models were considered in model selection.

**Data Analytic Plan**

Transition rates were computed as the percentage of converters within each class and were compared using $\chi^2$ tests of significance. Separation of LPA model indicators was assessed using univariate ANOVAs and effect sizes as measured by $r^2$. Indicator profiles were generated depicting estimated sample means. ANOVAs, independent samples $t$ tests, and chi-square tests of significance were conducted to compare classes on covariates. When appropriate, pairwise comparisons were conducted using Bonferroni correction for multiple comparisons. Z-square cell comparison tests with Bonferroni correction were used to probe significant omnibus chi-square tests and determine which groups significantly differed.

**Results**

**Latent Profile Analysis.**

The AIC, BIC, and ssa BIC values decreased with each class addition and did not readily discriminate a model of best fit. BLRT value remained significant ($P < .0001$) with each class addition. Entropy values remained high for each class model ($k = 2–5$), ranging from 0.80 (no predictive power) to 1 (perfect prediction).

<table>
<thead>
<tr>
<th>Number of Classes</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loglikelihood</td>
<td>-14339.751</td>
<td>-14026.772</td>
<td>-13839.33</td>
<td>-13729.856</td>
<td>-13644.023</td>
</tr>
<tr>
<td>No. of parameters</td>
<td>52</td>
<td>79</td>
<td>106</td>
<td>133</td>
<td>160</td>
</tr>
<tr>
<td>AIC</td>
<td>28783.501</td>
<td>28211.544</td>
<td>27890.66</td>
<td>27725.713</td>
<td>27608.047</td>
</tr>
<tr>
<td>BIC</td>
<td>28970.812</td>
<td>28496.111</td>
<td>28272.484</td>
<td>28204.795</td>
<td>28184.386</td>
</tr>
<tr>
<td>ssa BIC</td>
<td>28805.935</td>
<td>28245.626</td>
<td>27936.39</td>
<td>27783.091</td>
<td>27677.074</td>
</tr>
<tr>
<td>Entropy</td>
<td>n/a</td>
<td>0.909</td>
<td>0.884</td>
<td>0.907</td>
<td>0.925</td>
</tr>
<tr>
<td>Bootstrap LRT</td>
<td>P &lt; .0001</td>
<td>P &lt; .0001</td>
<td>P &lt; .0001</td>
<td>P &lt; .0001</td>
<td>P &lt; .0001</td>
</tr>
</tbody>
</table>

Table 1. Fit Indices and Class Sizes for the Latent Profile Analysis of SOPS Symptom Scores, CDSS Total Score, and Neurocognitive Scores

Note: SOPS, Scale of Prodromal Symptoms; AIC, Akaike's Information Criteria (smaller number suggests a better model); BIC, Bayesian Information Criteria (smaller number suggests a better model); ssa BIC, sample size-adjusted Bayesian Information Criteria (smaller number suggests a better model); Entropy, an overall measure of how well a model predicts class membership, ranging from 0 (no predictive power) to 1 (perfect prediction) (above 0.80 indicates adequate predictive power); LRT, parametric bootstrapped likelihood ratio test to compare $n$ with $n – 1$ classes (significant LRT indicates the $n$-class solution is better than an ($n – 1$)-class solution; Class size, estimated class size based on most likely class membership.
from 0.88 to 0.93. Fit indices and BLRT alone indicated the 5-class model. However, accepting the model associated with the lowest values does not prioritize model interpretability and parsimony.44

Supplementary figure 1 provides scree plots of AIC, BIC, ssa BIC, and log likelihood value. Leveling off point of the curves occurred at 3 classes in each plot, indicating that significant improvements in model fit are not gained through further class additions. Of note, the BIC is considered to be the best of the presently available information criteria,41 which showed clearest leveling off at 3 classes. The 3-class solution indicated high classification quality, adequate entropy score of 0.88, and mean posterior probabilities ranging from 93.9% to 95.6%. Supplementary table 3 summarizes latent class membership based on estimated posterior probabilities. Indicators evidenced meaningful separation. The 4- and 5-class models were examined and evidenced poor separation across a majority of indicators and thus did not result in substantively meaningful or interpretable class structures.

Individuals were assigned to classes as indicated by highest posterior probability value as such: class 1 (mild cluster; n = 124), class 2 (paranoid-affective cluster; n = 106), and class 3 (negative-neurocognitive cluster, n = 41).

**Classes and Risk Probability.** The overall transition rate in the full combined sample of CHRs and HSCs at 2 years was 12.5%. Transition rate significantly differed across groups in the overall model (χ²(2, N = 271) = 16.08, P < .001). Pairwise comparisons indicated that transition to psychosis was more likely in individuals in class 3 (negative-neurocognitive; transition rate 29.3%, n = 12 converters) than class 1 (mild; transition rate 5.6%, n = 7 converters) at the P < .05 level. There were no significant differences in pairwise comparisons between class 2 (paranoid-affective; transition rate 14.2%, n = 15 converters) and classes 1 or 3. Diagnoses at transition are provided in Supplementary table 4.

**Characteristics of the 3-Class Solution.** Table 2 shows results from the LPA and ANOVAs. Figures 1 and 2 show latent profile plots of estimated means. ANOVA results indicated that all indicators were influential in the clustering process, with the exception of SOPS grandiose ideas (P3) and bizarre thinking (D2).

Examinations of the SOPS latent profile plot and pairwise comparisons indicated that class 1 (mild) evidenced the lowest scores across SOPS and CDSS total. Class 1 largely evidenced SOPS estimated means of 1–2, which indicates mild/questionable presence and depression comparable to UC sample norms (normative mean: 2.6, SD: 2.7).45

Class 2 (paranoid-affective) estimated means were significantly more severe for suspiciousness/persecutory ideas than classes 1 and 3. Class 2 evidenced significantly more severe ratings than class 1 on unusual thought content and perceptual abnormalities. Class 2 had significantly higher depression ratings (on SOPS dysphoric mood and CDSS total scores) and significant sleep disturbance compared to other classes. Class 2 had mild negative symptom ratings (≤2), with the exception of occupational functioning, which was near moderate (3).

Class 3 (negative-neurocognitive) membership was associated with the highest ratings (between 2–4) in a majority of negative symptoms, and to a lesser degree, disorganized symptoms. This was confirmed through pairwise comparisons. Class 3 evidenced comparable ratings to class 2 on avolition and decreased experience of emotions.

Regarding neurocognitive performance, classes 1 (mild) and 2 (paranoid-affective) performed comparably across indices. Class 3 (negative-neurocognitive) evidenced significant impairment compared to classes 1 and 2 across neurocognitive indices (P < .05). As neurocognitive test scores were not age corrected in the LPA model, comparisons among classes on neurocognitive indices were also run as ANCOVAs with age as a covariate. All overall models remained significant (P < .001) and pairwise comparisons using Bonferroni correction for multiple comparisons remained significant (P < .05), indicating that classes significantly differed on neurocognitive performance when accounting for age-related variance.

**Characterizing the 3-Class Solution With Covariates.** Table 3 provides results from ANOVAs and pairwise comparisons between classes regarding demographics and covariates.

**Demographic Characteristics.** There were significant differences in age and clinic location between classes. Individuals in class 3 (negative-neurocognitive) were significantly younger than class 2 (paranoid-affective). Individuals from Yale were more likely to be classified in class 3 and less likely to be classified in class 2. Conversely, individuals from UNC were more likely to be classified in class 2 and less likely to be classified in class 3.

Given site effects, comparisons among classes on indicators (SOPS, CDSS total score, neurocognitive indices) were conducted as ANCOVAs with site as a covariate. All results were unchanged, indicating that classes significantly differed on indicators when accounting for site-related variance. Classes showed no significant differences in sex or racial/ethnic composition.

**Risk Group.** CHR individuals were significantly more likely to be categorized in class 2 (paranoid-affective) than class 1 (mild). Conversely, HSC individuals were more likely to be categorized in class 1 than 2. Supplementary table 5 provides symptom and functional descriptives of risk subgroups within each class.

**Premorbid Functioning.** Classes had significant overall group differences across PAS subscales. From childhood through early adolescence (age ≤ 15), individuals in class
<table>
<thead>
<tr>
<th>Domain</th>
<th>Indicator</th>
<th>Class 1 Mild</th>
<th>Class 2 Paranoid-Affective</th>
<th>Class 3 Negative-Neurocognitive</th>
<th>ANOVA P</th>
<th>Pairwise</th>
<th>Effect Size ($r^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Class 2 Paranoid-Affective ($n = 106$)</td>
<td>Class 3 Negative-Neurocognitive ($n = 41$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 124)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>P. 1 Unusual Thought Content/Delusional Ideas</td>
<td>2.4 (0.18)</td>
<td>3.1 (0.15)</td>
<td>2.6 (0.40)</td>
<td>.002</td>
<td>2&gt;1</td>
<td>.05</td>
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<td></td>
<td>P. 2 Suspiciousness/Persecutory Ideas</td>
<td>1.8 (0.17)</td>
<td>2.7 (0.15)</td>
<td>1.9 (0.37)</td>
<td>P &lt; .001</td>
<td>2&gt;1,3</td>
<td>.08</td>
</tr>
<tr>
<td></td>
<td>P. 3 Grandiose Ideas</td>
<td>1.0 (0.13)</td>
<td>1.0 (0.13)</td>
<td>0.9 (0.23)</td>
<td>.629</td>
<td></td>
<td>.00</td>
</tr>
<tr>
<td></td>
<td>P. 4 Perceptual Abnormalities/Hallucinations</td>
<td>1.7 (0.17)</td>
<td>2.6 (0.15)</td>
<td>2.2 (0.37)</td>
<td>P &lt; .001</td>
<td>2&gt;1</td>
<td>.07</td>
</tr>
<tr>
<td></td>
<td>P. 5 Disorganized Communication</td>
<td>1.1 (0.14)</td>
<td>1.6 (0.13)</td>
<td>1.7 (0.25)</td>
<td>.001</td>
<td>2&gt;3,1</td>
<td>.06</td>
</tr>
<tr>
<td></td>
<td>N. 1 Social Anhedonia</td>
<td>0.9 (0.18)</td>
<td>1.8 (0.17)</td>
<td>2.8 (0.68)</td>
<td>P &lt; .001</td>
<td>3&gt;1,2, 2&gt;1</td>
<td>.16</td>
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<td></td>
<td>N. 2 Avolition</td>
<td>0.8 (0.19)</td>
<td>2.3 (0.19)</td>
<td>2.8 (0.45)</td>
<td>P &lt; .001</td>
<td>3&gt;2,1</td>
<td>.35</td>
</tr>
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<td></td>
<td>N. 3 Decreased Expression of Emotion</td>
<td>0.5 (0.16)</td>
<td>1.1 (0.16)</td>
<td>1.9 (0.46)</td>
<td>P &lt; .001</td>
<td>3&gt;1,2, 2&gt;1</td>
<td>.16</td>
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<td>N. 4 Decreased Experience of Emotions and Self</td>
<td>0.7 (0.12)</td>
<td>1.8 (0.16)</td>
<td>1.5 (0.45)</td>
<td>P &lt; .001</td>
<td>2&gt;3,1</td>
<td>.15</td>
</tr>
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<td>N. 5 Decreased Ideational Richness</td>
<td>0.4 (0.11)</td>
<td>0.8 (0.11)</td>
<td>2.2 (0.58)</td>
<td>P &lt; .001</td>
<td>3&gt;1,2, 2&gt;1</td>
<td>.29</td>
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<tr>
<td></td>
<td>N. 6 Occupational Functioning</td>
<td>1.2 (0.42)</td>
<td>2.9 (0.26)</td>
<td>3.8 (0.36)</td>
<td>P &lt; .001</td>
<td>3&gt;1,2, 2&gt;1</td>
<td>.25</td>
</tr>
<tr>
<td></td>
<td>D. 1 Odd Behavior or Appearance</td>
<td>0.5 (0.12)</td>
<td>0.6 (0.11)</td>
<td>2.0 (0.64)</td>
<td>P &lt; .001</td>
<td>3&gt;1,2</td>
<td>.20</td>
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<tr>
<td></td>
<td>D. 2 Bizarre Thinking</td>
<td>0.7 (0.14)</td>
<td>0.8 (0.11)</td>
<td>1.2 (0.27)</td>
<td>.081</td>
<td></td>
<td>.02</td>
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<td>D. 3 Trouble with Focus and Attention</td>
<td>1.2 (0.21)</td>
<td>2.3 (0.14)</td>
<td>2.5 (0.24)</td>
<td>P &lt; .001</td>
<td>2&gt;3,1</td>
<td>.23</td>
</tr>
<tr>
<td></td>
<td>D. 4 Impairment in Personal Hygiene</td>
<td>0.3 (0.13)</td>
<td>0.7 (0.14)</td>
<td>1.3 (0.47)</td>
<td>P &lt; .001</td>
<td>3&gt;1,2, 2&gt;1</td>
<td>.09</td>
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<td></td>
<td>G. 1 Sleep Disturbance</td>
<td>0.9 (0.13)</td>
<td>2.5 (0.15)</td>
<td>1.7 (0.47)</td>
<td>P &lt; .001</td>
<td>2&gt;3,1, 3&gt;1</td>
<td>.29</td>
</tr>
<tr>
<td></td>
<td>G. 2 Dysphoric Mood</td>
<td>1.3 (0.20)</td>
<td>3.5 (0.15)</td>
<td>3.0 (0.51)</td>
<td>P &lt; .001</td>
<td>2&gt;3,1, 3&gt;1</td>
<td>.44</td>
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<tr>
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<td>G. 3 Motor Disturbances</td>
<td>0.3 (0.06)</td>
<td>0.8 (0.10)</td>
<td>0.8 (0.40)</td>
<td>P &lt; .001</td>
<td>2&gt;3,1</td>
<td>.08</td>
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<td>G. 4 Impaired Tolerance to Normal Stress</td>
<td>0.8 (0.14)</td>
<td>2.6 (0.18)</td>
<td>2.4 (0.52)</td>
<td>P &lt; .001</td>
<td>2&gt;3,1</td>
<td>.30</td>
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<td></td>
<td>DEP CDSS Total Score</td>
<td>2.0 (0.28)</td>
<td>5.8 (0.45)</td>
<td>3.8 (1.15)</td>
<td>P &lt; .001</td>
<td>2&gt;3,1, 3&gt;1</td>
<td>.24</td>
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<td>NC CAT Total Score</td>
<td>47.2 (1.62)</td>
<td>49.9 (1.41)</td>
<td>32.5 (2.41)</td>
<td>P &lt; .001</td>
<td>1&gt;2&gt;3</td>
<td>.22</td>
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<td>NC WCST Perseverative Errors</td>
<td>6.4 (0.36)</td>
<td>6.8 (0.43)</td>
<td>12.9 (2.68)</td>
<td>P &lt; .001</td>
<td>3&gt;1,2</td>
<td>.20</td>
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<td></td>
<td>NC TMT A</td>
<td>26.6 (1.22)</td>
<td>24.2 (0.82)</td>
<td>43.2 (4.91)</td>
<td>P &lt; .001</td>
<td>3&gt;1,2</td>
<td>.36</td>
</tr>
<tr>
<td></td>
<td>NC TMT B</td>
<td>62.0 (5.51)</td>
<td>53.8 (1.86)</td>
<td>107.3 (9.90)</td>
<td>P &lt; .001</td>
<td>3&gt;1,2</td>
<td>.35</td>
</tr>
<tr>
<td></td>
<td>NC CPT D’3</td>
<td>2.7 (0.09)</td>
<td>2.9 (0.09)</td>
<td>1.8 (0.27)</td>
<td>P &lt; .001</td>
<td>1&gt;2&gt;3</td>
<td>.18</td>
</tr>
<tr>
<td></td>
<td>NC RAVLT Total Score</td>
<td>53.52 (2.74)</td>
<td>55.46 (1.05)</td>
<td>43.10 (5.17)</td>
<td>P &lt; .001</td>
<td>1&gt;2&gt;3</td>
<td>.21</td>
</tr>
</tbody>
</table>

Note: SOPS, Scale for Assessment of Prodromal Symptoms; CDSS, Calgary Depression Scale for Schizophrenia; P, positive symptom subscale; N, negative symptom subscale; D, disorganized symptom subscale; G, general symptom subscale; DEP, depression symptoms; NC, neurocognition; CAT: category instances; WCST, Wisconsin Card Sorting Test; TMT, Trail Making Test; CPT, Continuous Performance Test; RAVLT, Rey Auditory Verbal Learning Test. Mean parameter estimates and associated standard errors for each latent class are provided; mean parameter estimate (standard error). Pairwise comparisons are significant at the $P < .05$ level.
Latent Profile Analysis Predicting Psychosis

3 (negative-neurocognitive) showed significant social and academic maladjustment scores compared to classes 1 and 2, whereas classes 1 and 2 had comparable impairment during this time. Regarding late adolescence (age 16–18) social maladjustment ratings, class 3 continued to perform at the most impaired level compared to classes 1 and 2. However, class 2 evidenced significant social maladjustment compared to class 1, suggesting that for class 2, poor functioning begins in late adolescence.

Social Functioning. Classes 2 and 3 had significant impairment on the SFS compared to class 1.

Role Functioning. Class 3 had significant impairment in QLS total score compared to classes 1 and 2. Class 2 evidenced significant impairment in QLS total score compared to class 1.

Social Cognition. Classes had significant overall models measuring group differences on the Eyes Task, FEIT, and AP. The overall model for FEDT approached significance ($P = .053$). Pairwise comparisons indicated that class 3 (negative-neurocognitive) had significant social cognitive deficits compared to classes 1 (mild) and 2 (paranoid-affective) across measures, indicating class 3 was impaired in ToM and EP.

As social cognitive performance tends to be associated with age and IQ, comparisons among classes on social cognition were repeated as ANCOVAs with age as a covariate. Overall models and pairwise comparisons remained significant, indicating that classes evidenced significant differences in social cognitive performance when accounting for age-related variance.

Age-scaled IQ was added as a covariate and overall models for Eyes Task and AP Task remained significant ($P < .05$); however, FEDT was no longer significant. Pairwise comparisons for AP remained significant ($P < .05$). Eyes Task contrast between classes 2 and 3 was no longer significant. Thus, significant group differences in facial EP performance and ToM may be partially accounted for by neurocognitive ability, but not for AP.

Intelligence. Classes were compared across age-scaled IQ. Classes were significantly different, with impairment in class 3 (negative-neurocognitive) compared to classes 1 (mild) and 2 (paranoid-affective).

Discussion

Consistent with prior work, the present study found that classes were best distinguished by separation in negative/
general symptoms and classes that exhibited the greatest baseline negative symptoms and behavioral change ratings had the highest risk of transition to psychosis (ie, class 3). This is consistent with the growing literature establishing an association between high baseline negative symptoms and subsequent conversion to psychosis. Class 3 (negative-neurocognitive) was further characterized by significantly impaired neurocognition. Inclusion of neurocognition in the model may have elicited the emergence of class 3, a novel putative subgroup.

The CHR paradigm was recently conceptually revised into a clinical staging model comprised of subgroups associated with increasing clinical severity and risk of transition. The first stage (CHR−) is characterized by moderate negative symptoms, neurocognitive symptoms, and minimal positive symptoms (none ≥ 3). It is possible that class 3’s (negative-neurocognitive) symptomatology is consistent with the CHR− stage and thus they represent a discrete subgroup on the prodromal illness trajectory.

Conversely, class 2 (paranoid-affective) was characterized by significantly higher suspiciousness and CDSS total near the cutoff associated with major depression. Class 2 largely evidenced nonspecific distress, with an emphasis in affective symptoms and sleep disturbance compared to other classes. Class 2 was not clearly consistent with any subgroup in Carrión et al’s clinical staging model and instead may be at risk for a broad range of psychopathology (eg, affective disorders). Given that the inclusion criteria of this study was 1 follow-up visit (ie, 6 mo), it may be that CHR criteria are sensitive to emergent psychosis for some, but that timing was insufficient to capture emergence of nonpsychotic disorders, which take years to manifest past adolescence/early adulthood (eg, average age was 15.7–19.6 across classes). This is consistent with clinical staging model theory, which posits that nonspecific distress crystallizes over time into discrete categorical syndromes. Identifying subgroups at this time may be difficult due to the ephemeral nature of distress and symptomatology through adulthood.

**Rate of Transition to Psychosis**

Class 3 (negative-neurocognitive) had the highest conversion rate (29%) and was not characterized by significantly greater positive symptoms as would be expected based on the clinical staging model. The rate of transition is higher in the present sample (29.3% in class 3) than the comparable class in the clinical staging model (5.9% in CHR−).

Class 2 (paranoid-affective) was associated with the highest suspiciousness, greatest depressive symptoms, intact neurocognition, and lower conversion rate (14.9%). Given that clinical depression is both associated with and predictive of persistent paranoia, it is possible that effective treatment of depression in class 2 may reduce severity of positive symptomatology and prevent subsequent transition to psychosis.

**Further Characterizing Subgroups With Covariates**

Class 3 (negative-neurocognitive) had significantly lower social cognitive performance consistent with the proposed conceptualization of class 3 as an early risk stage of developing schizophrenia. In contrast, classes 1 and 2 performed comparably to UCs on measures of ToM and facial EP according to norms from age-matched UCs. Results from a meta-analysis of social cognitive performance in CHR individuals found medium effect sizes for ToM (d = 0.47) and EP (d = 0.44). Thus, one would expect class 2 (paranoid-affective) to have EP and ToM deficits, given that CHR individuals comprised 74.5% of this class. Further, results comparing CHR and HSC individuals from this sample found no significant differences in EP or ToM performance. Thus, it is possible that specific constellations of symptoms (ie, those associated with class 3) account for social cognitive deficits in heterogeneous CHR samples.

Regarding demographics, class 2 (paranoid-affective) was significantly older than class 3 (negative-neurocognitive). Longitudinal findings indicated negative symptom onset predates positive symptom onset and that
negative/disorganized symptoms predicted positive symptoms over time.\textsuperscript{47} Further, CHR− individuals were the youngest subgroup in the clinical staging model.\textsuperscript{58} Thus, it follows that the youngest group may be characterized by predominant negative symptoms.

Classes also had significant differences in clinic of origin. Each of the 3 clinics used standardized inclusion criteria, screening/assessment measures, and recruitment methods, and raters evidenced significant agreement in routine assessment reliability checks. Although such processes were standardized, site differences may be due to selective recruitment processes.

Class 3 (negative-neurocognitive) exhibited the greatest premorbid academic/social and baseline social/role dysfunction, with scores comparable to individuals with established schizophrenia.\textsuperscript{29} Class 2 (paranoid-affective) evidenced functional deterioration over time, and was statistically comparable to class 3's dysfunction in late adolescent academic maladjustment score. Class 2 (paranoid-affective) had significant social/role impairment, but to a lesser degree and with later onset than class
3. Taken together, such findings are consistent with the view of class 3 as an early risk stage of developing schizophrenia subgroup.

Limitations and Strengths

As LVMM are influenced by subtle sample differences, the present model must be replicated to ensure validity of the present class structure. Sample size prohibited cross-validation, which would enhance confidence regarding taxon validity. However, the present model is complex with several indicator variables and parameters; thus, use of cross-validation procedures would likely generate results with increased error. Further, the present model does not include other predictive indicators such as basic symptoms (ie, subtle, subjective disturbances in one's mental processes) and biological markers (eg, electrophysiological, imaging, metabolic, genetic markers).

The present class structure evidenced significant site differences. We elected not to include site as a covariate in the LPA model, because in the case of employing a single covariate, the log-linear model is identical whether site is treated as an active covariate or an additional indicator variable. Given that there were no significant site differences in transition rate, we instead used site as an inactive descriptive covariate. Significant differences between indicators remained when controlling for site, indicating true variance in symptomatology drove the LPA.

Strengths of the present study include ecological validity in application of LPA to the combined sample. Our use of neurocognitive scores as indicators is novel and the first study to utilize such. The current study is further strengthened by inclusion of a range of covariates (functioning, social cognition) to characterize subgroups.

Conclusions

Overall, the results support a subgroup approach to research, assessment, and treatment of help-seeking individuals. Three classes emerged with adequate separation on a majority of indicator variables (SOPS, CDSS, neurocognition). Despite the well-established association between poor outcome, negative symptoms, and neurocognitive deficits, such symptom clusters are insufficiently targeted in CHR individuals. We join other researchers who have advocated for a transdiagnostic, heuristic approach to CHR individuals that has been emphasized in understanding the progression to psychotic and other mental illnesses.

Supplementary Material

Supplementary data are available at Schizophrenia Bulletin online.

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