Identifying Distinct Trajectories of Negative Symptoms Following First-Episode Psychosis: A Two-Year Study of Patients Admitted to an Early Intervention Service

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Abstract

The course of negative symptoms following first-episode psychosis (FEP) is markedly heterogeneous, with negative symptom remission a key predictor of functional outcomes. Based on theoretical considerations, many have proposed that negative symptoms could resolve into putatively more homogeneous clusters, yet few studies have applied a data-driven approach to characterize symptom trajectories without a priori definitions of grouping variables. Hence, we aimed to identify distinct trajectories of negative symptoms within an FEP cohort admitted to an early intervention service. Using data collected from 326 patients admitted to PEPP-Montréal, we conducted Latent Class Growth Analysis to identify distinct groups of patients with similar patterns of change in Scale for the Assessment of Negative Symptoms (SANS) global scores over two years. After identifying the most parsimonious model, we explored potential predictors of latent class membership using multinomial logistic regression. Our findings support the existence of three distinct negative symptom trajectories: low and remitting (n = 118, 36.2%), moderate and improving (n = 141, 43.3%), and high and stable (n = 67, 20.6%). Compared to both the high and stable and moderate and improving trajectories, membership in the low and remitting trajectory (the reference group) was associated with older age at entry, affective diagnoses, higher IQ, greater years of completed education, and fewer positive symptoms at program entry. Our results provide converging evidence from a data-driven approach for the existence of subpopulations of FEP patients. Furthermore, our findings provide a theoretical foundation for future research exploring the prevention, pathophysiology, and treatment of negative symptoms within subgroups of FEP patients as part of an early intervention service.

Identifying Distinct Trajectories of Negative Symptoms Following First-Episode Psychosis: A Two-Year Study of Patients Admitted to an Early Intervention Service

Psychosis is a highly complex condition, typically first emerging in young adulthood, consisting of a constellation of symptoms spanning far beyond its defining feature of impaired reality testing (Arciniegas, 2015). Impairments associated with psychosis can be broadly classified into four categories: positive symptoms (e.g., hallucinations, delusions, and disorganized thinking); negative symptoms (e.g., reduced motivation and expression); cognitive symptoms (e.g., impairments in memory, attention, and executive function); and affective dysregulation (e.g., depression and mania) (van Os & Kapur, 2009). While often equated with schizophrenia, psychosis is associated with myriad psychiatric disorders, comprising both affective psychoses (e.g., bipolar disorder) and non-affective psychoses (e.g., schizophrenia spectrum disorders) (American Psychiatric Association, 2013; van Os & Kapur, 2009)

Long understood to be a core feature of psychosis (Kraepelin, 1919), negative symptoms have historically been neglected in the clinical literature due to their relative lack of salience and diagnostic specificity compared to positive symptoms (Dollfus & Lyne, 2017; Galderisi, Farden, & Kaiser, 2017). Indeed, the manifestation of negative symptoms varies widely between patients, with impairments being divided into five key constructs: blunted affect, alogia, avolition, asociality, and anhedonia (Kirkpatrick, Fenton, Carpenter, & Marder, 2006). Negative symptoms can be characterized as being either primary – that is, intrinsic to the underlying disease process - or secondary, being indirectly caused by other factors such as positive symptoms or another underlying psychopathology (Correll & Schooler, 2020; Kirkpatrick et al., 2006). For example, patients may be suffering from persecutory delusions, and therefore experience social withdrawal (Correll & Schooler, 2020).

Although secondary negative symptoms may improve following remission of their underlying cause, current treatment options for primary negative symptoms are extremely limited (Bitter, 2020; Correll & Schooler, 2020). Recently, much work has focused on early intervention in first-episode psychosis (FEP), during which biological, psychological and psychosocial influences are hypothesized to be most malleable (Birchwood, Todd, & Jackson, 1998). Identifying subgroups of FEP patients sharing a similar underlying etiology or pathophysiology, suggested by the markedly heterogeneous nature of negative symptoms, could potentially allow for better targeting of such interventions. Indeed, many have posited the existence of such subgroups. Notably, deficit syndrome is a proposed disease distinct from schizophrenia involving enduring, primary negative symptoms lasting at least one year (Kirkpatrick, Buchanan, McKenney, Alphs, & Carpenter, 1989) and may have a distinct etiology. Since being proposed, numerous neuroimaging studies have identified key structural and functional abnormalities in patients meeting diagnostic criteria for deficit syndrome (Kirkpatrick, Mucci, & Galderisi, 2017). For example, several studies have found white matter abnormalities specific to patients with deficit syndrome, leading Kirkpatrick et al. (2017) to suggest that such widespread deficits may relate to problems in early brain migration. However, there is recent evidence suggesting that the current conceptualization of deficit syndrome may not be specific to schizophrenia; several studies have observed features characteristic of deficit syndrome in patients diagnosed with affective psychoses (Hovington, Bodnar, Joober, Malla, & Lepage, 2012; Peralta & Cuesta, 2004). Alternatively, the construct of persistent negative symptoms (PNS) is a more recent and significantly broader concept than that of deficit syndrome. Developed to encapsulate all patients with negative symptoms unaddressed by current treatments, PNS is defined as either primary or secondary negative symptoms evident for six consecutive months after the stabilization of FEP

(Buchanan, 2007). Neuroimaging studies lend some support for the distinctiveness of PNS, with structural abnormalities reported in several frontal, temporal, limbic and subcortical regions (Ince & Ucok, 2018). Moreover, distinct cognitive impairments have been observed in patients with PNS (Hovington & Lepage, 2012; Ince & Ucok, 2018), with emerging evidence that there are also considerable neurocognitive differences between patients suffering from primary and secondary PNS (Lepage et al., 2021).

Within the literature, many have attempted to assess how such hypothesized subgroups and their associated covariates relate to symptom trajectories. For example, a three-year follow-up study of FEP patients identified a multitude of predictors of developing PNS (Chang et al., 2011). While studies such as that of Chang et al. (2011) have contributed to the development of PNS, such an approach relies on a priori definitions of group membership, rendering it vulnerable to potentially invalid researcher assumptions. More recently, several studies have taken a bottom-up, or data-driven, approach to assessing negative symptom trajectories. Namely, rather than group membership being informed by theoretical constructs, groups of patients are derived based on similar patterns of change in symptomatology. Such data-driven studies are useful in that they can be used to test convergence with top-down approaches, thereby allowing us to assess the validity of theoretical constructs (Jung & Wickrama, 2008; Nagin, 2009).

There have thus far been relatively few data-driven studies assessing negative symptom trajectories. From the studies we identified that have used such an approach, two identified three trajectories (Chan et al., 2020; Chang et al., 2019), five identified four trajectories (Abdin et al., 2017; Austin et al., 2015; Chen et al., 2013; Gee et al., 2016; Stiekema et al., 2018), and one identified five trajectories (Pelayo-Teran et al., 2014). In general, trajectory memberships were found to be predicted by numerous baseline characteristics, although vast methodological

differences between studies may obscure convergent findings (Appendix I contains a brief overview of previous reports; see Habtewold et al., 2020 for a systematic review on the topic). Indeed, within the literature, differences in duration of follow-up (ranging from 6 weeks to 10 years), population being studied (e.g., chronic schizophrenia versus FEP), and treatments employed (e.g., antipsychotic trials verses treatment as usual) limit the generalizability of findings. Moreover, several previous studies suffered from small sample sizes, limited assessments, and poorly documented statistical analyses.

The present study applied a data-driven approach to characterize symptom trajectories within a large FEP cohort assessed at nine timepoints over two years. Using current best-practice guidelines for statistical analysis, we aimed to identify latent classes (i.e., clusters) of patients sharing similar longitudinal trajectories of negative symptoms. Additionally, we aimed to determine which baseline patient characteristics were associated with latent class membership.

Methods

Participants and Treatment Setting

Patients were treated at the Prevention and Early Intervention Program for Psychosis (PEPP-Montréal), a specialized early intervention (SEI) program located at the Douglas Mental Health University Institute and affiliated with McGill University. In addition to providing rapid and accessible treatment, PEPP-Montréal provides patients with an array of enhanced services during the two-year period following admission; patients are followed by a case manager as well as a psychiatrist and are supported with a variety of specialized, phase-specific interventions such as medication management, family support, cognitive-behavioral therapy, and work preparation programs (for a comprehensive overview of program details, see Iyer, Jordan, MacDonald, Joober, & Malla, 2015). Systematic reviews have shown that such enriched

interventions lead to significant improvements in functioning and symptomatology when compared to standard care (Harvey, Lepage, & Malla, 2007).

The initial dataset included 762 patients admitted to PEPP-Montréal from 2003 through 2018. Our sample consisted of 326 such patients meeting the following inclusion criteria: 1) aged 14-35 and experiencing a first episode of affective or non-affective psychosis; 2) received less than one month of antipsychotic treatment prior to baseline assessment; and 3) had been assessed at a minimum of five out of nine timepoints. All patients consented to having their data used for research purposes and procedures were approved by the Douglas Research Ethics Board. Patients with an IQ equal to or lower than 70 or who were unable to communicate in either English or French were deemed unable to provide informed consent and were therefore excluded.

Data Collection

Upon admission to PEPP-Montréal, duration of untreated psychosis (DUP) was estimated using the Circumstances of Onset and Relapse Schedule (Iyer et al., 2015). Additional patient characteristics including age, co-morbid diagnoses, years of completed education, IQ, sex, and visible minority status were also recorded at baseline. One year after admission, patients were retrospectively diagnosed by trained psychiatrists according to DSM-IV criteria (American Psychiatric Association, 1994). During the study period, patients were assessed via semi-structured interview at nine time points: baseline, month 1, month 2, month 3, month 6, month 9, month 12, month 18, and month 24. Negative symptom severity was assessed using the Scale for the Assessment of Negative Symptoms (SANS). The SANS consists of items measuring deficits in five domains: blunted affect, alogia, avolition, asociality, and attention. For each domain, clinicians assess the severity of specific symptoms within that domain, as well as provide a global rating of domain-specific symptom severity (Andreasen, 1982). For the present study, we

calculated SANS global scores as the sum of global ratings of blunted affect, alogia, avolition, and asociality. Consistent with previous reports (Pelayo-Teran et al., 2014), we excluded global rating of attention, which is widely considered to be an unreliable construct of negative symptoms (Bitter, 2020; Blanchard & Cohen, 2006; Buchanan & Carpenter, 1994; Correll & Schooler, 2020; Hovington et al., 2012).

Statistical Analysis

Latent Class Growth Analysis (LCGA) is a statistical technique used to identify subgroups in longitudinal data without any a priori assumptions regarding the nature or existence of such groups themselves (Van Der Nest, Passos, Candel, & Van Breukelen, 2020). For a given model with *k* latent classes, the method of maximum likelihood is used to define the best fitting set of *k* polynomial functions, each with unique growth factor estimates (e.g., intercept, slope, quadratic factor) (Andruff, Carraro, Thompson, Gaudreau, & Louvet, 2009; Muthén & Muthén, 2017; Nagin, 2009). Conceptually, subgroups are defined such that constituent individuals are maximally similar to each other and maximally dissimilar to those in other groups with respect to the development of a given variable (Jung & Wickrama, 2008)

Using Mplus version 8.4 via the MplusAutomation package (Hallquist & Wiley, 2018) in R version 4.04, we created a script to systematically determine the most parsimonious set of model parameters with respect to residual variance restrictions, class structure, and polynomial order. In general, we followed model selection procedures outlined in a recent paper (Van Der Nest et al., 2020), For all models calculated, factor loadings were coded such that they represented the true time intervals between data points (i.e., model convergence was determined based on the actual length of time between assessments). Missing data were handled using the maximum likelihood estimation under MCAR (missing completely at random). We followed the

reporting standards specified in the Guidelines for Reporting on Latent Trajectory Studies Checklist to the extent possible (Van De Schoot, Sijbrandij, Winter, Depaoli, & Vermunt, 2017).

In accordance with best practice (Frankfurt, Frazier, Syed, & Jung, 2016; Van Der Nest et al., 2020), we fit a Growth Curve Model (GCM) prior to beginning model selection. Using GCM, a linear equation is defined for each individual with the aggregate individual growth factors used to model the mean population trajectory (Duncan & Duncan, 2009). Thus, a GCM provides unique estimates of variance for growth factors which may be used to evaluate the overall heterogeneity in the population prior to conducting LCGA (Frankfurt et al., 2016). By contrast, in LCGA the variance and covariance for the model growth factors within a given class are assumed to be zero (Jung & Wickrama, 2008). Rather, individual variation from that trajectory is treated as residual variance, which may be permitted to vary between timepoints and across classes (for a mathematical overview, see Nagin, 2009; Van Der Nest et al., 2020). While evidently precluding any analysis of within-class variance, this allows for faster model computation and can facilitate the identification of latent subpopulations (Frankfurt et al., 2016; Van Der Nest et al., 2020).

Initially, we used Group-Based Trajectory Modeling (GBTM), a subtype of LCGA assuming equal residual variances across time and classes, to narrow down the maximum class structure of our model. This initial step is recommended because using more constrained parameters allows for easier class identification, thus further reducing computing time (Van Der Nest et al., 2020). Consistent with recommendations (Van Der Nest et al., 2020), we performed GBTM using the highest sensible polynomial order which, given computational limitations, was assumed to be three. Based on the fact that the highest class structure previously identified was five (Pelayo-Teran et al., 2014), we conducted GBTM up to a maximum anticipated class

structure of six. After calculating GBTM models for $k = 1{:}6$, the optimal class structure was initially selected based on the Bayesian Information Criterion (BIC). However, because the BIC may overestimate the increase in fit provided by additional classes in the model (Van Der Nest et al., 2020), we attempted to further reduce k using the Approximate Likelihood-Ratio Test (aLRT). Essentially, the aLRT is used to evaluate whether the null hypothesis of $k - 1$ classes should be rejected in favor of k classes (Van Der Nest et al., 2020). We used the aLRT to attempt to reduce k until the null hypothesis could be rejected, at which point we arrived at the most parsimonious class structure for GBTM.

Subsequently, we evaluated whether relaxing model constraints on residual variance would improve model fit. Hence, three LCGA models were calculated at the optimal class structure previously identified: 1) allowing for unconstrained residual variance across classes; 2) allowing for unconstrained residual variance across time; 3) allowing for unconstrained residual variance across both classes and time. Based on the BIC, the optimal set of model restrictions was selected from among the GBTM and these three LCGA models.

Next, using the previously identified class structure and residual variance restrictions, we attempted to reduce the model polynomial order by comparing the following models: 1) providing for linear functions describing class trajectories; 2) providing for quadratic functions describing class trajectories; and 3) providing for cubic functions describing class trajectories. The model with the optimal polynomial order was selected based on the BIC. Finally, the aLRT was used to attempt to reduce the class structure of this model in the manner previously described for GBTM.

Following the identification of the final model, we used mixed modeling and chi-square tests to conduct exploratory analysis regarding potential predictors of latent class membership.

Based on previous findings in the literature, we evaluated class differences for the following variables: age at entry, co-morbid substance use disorder diagnosis, duration of untreated psychosis, IQ, retrospective diagnosis (affective or non-affective psychosis), Scale for the Assessment for Positive Symptoms (SAPS) global score at baseline, sex, visible minority status, and years of completed education. Subsequently, for all variables that differed significantly between one or more classes ($p < 0.05$), univariate multinomial logistic regression was performed using the least pernicious trajectory as the reference group. We operationalized the least pernicious trajectory as that with the lowest SANS global score at baseline

Results

Overall Sample Characteristics

Baseline demographic and clinical characteristics for the overall sample (n = 326) are presented in Table 1. Our sample was disproportionately male (66%) with a mean age of 23.7 (SD = 4.8). Overall, educational attainment was relatively low (M = 11.9 years, SD = 2.7), although IQ appeared to be normal (M = 98.5, SD = 14.8). Average estimated duration of untreated psychosis (DUP) was 43.2 weeks (SD = 88.3), with the high variance observed reflective of the extremely long DUP suffered by a small minority of patients. As to be expected during an acute psychotic episode, Scale for the Assessment for Positive Symptoms (SAPS) global score is high at baseline (M = 11.81, SD = 3.08), with vast decreases in positive symptoms observed by month 3 (M = 3.55, SD = 3.65). Notably, although most patients (65.6%) received a retrospective diagnosis of non-affective psychosis, a substantial minority received an affective diagnosis. Figure 1 shows the number of missing assessments at each timepoint. Given the disproportionately large amount of data missing at month 1 (37.4%), we ensured that the overall latent class structure of the model was replicated with and without month 1 included.

Table 1: Overall Sample Characteristics at Baseline

	Overall Sample (n = 326)
Age at Entry (M, SD)	23.71 (4.78)
Male (n, %)	215 (65.95%)
Years of Education (M, SD)	11.93 (2.66)
Non-Affective Psychosis (n, %)	214 (65.64%)
IQ at Baseline (M, SD)	98.45 (14.80)
Estimated Weeks DUP (M, SD)	43.18 (88.28)
SAPS Global Score at Baseline (M, SD)	11.81 (3.08)
SAPS Global Score at Month 3 (M, SD)	3.55 (3.65)

Note: DUP, Duration of Untreated Psychosis; SAPS, Scale for the Assessment of Positive Symptoms

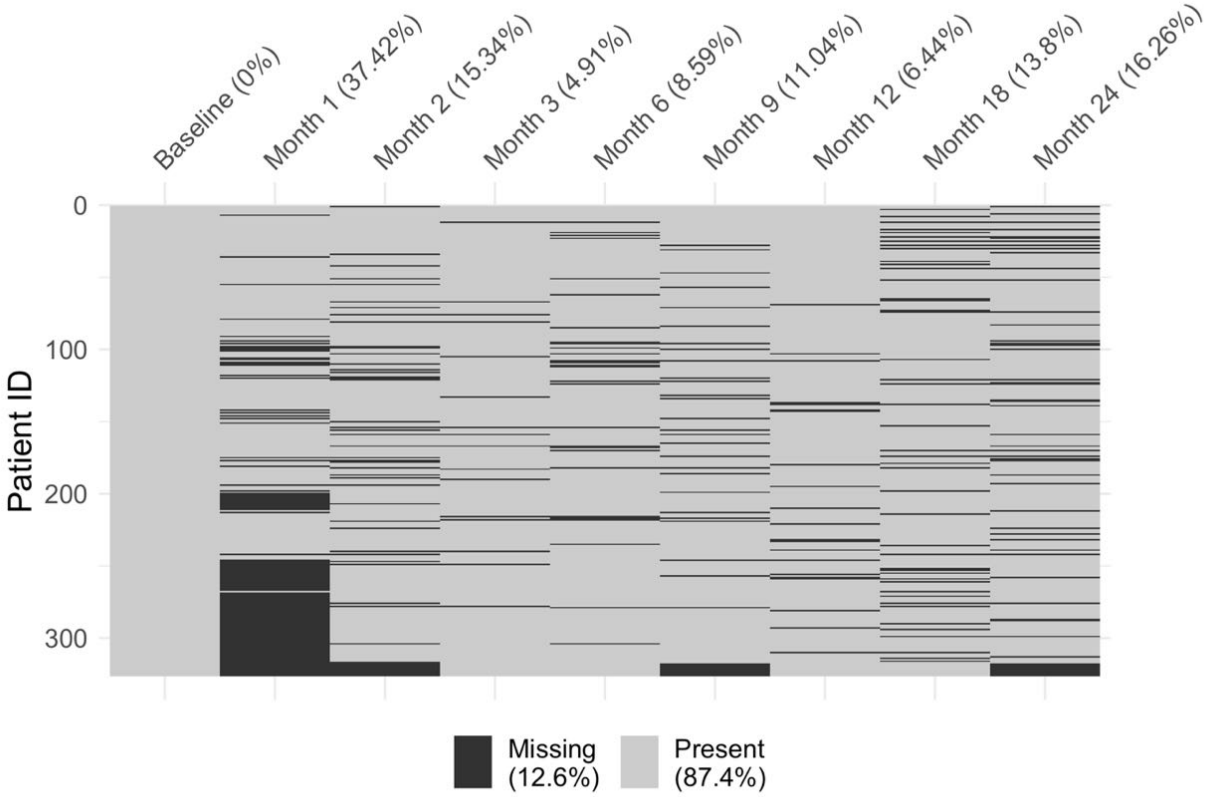

Figure 1: Percentage of SANS Scores Missing at Each Assessment

Initial Growth Curve Model

Figure 2 shows the estimated Growth Curve Model (GCM), representing a linear equation defining the overall sample trajectory with respect to SANS global scores (for

reference, observed mean scores are superimposed on the graph). The overall sample trajectory appears to be non-linear. In general, patients appear to experience a significant decline in negative symptoms during the two months following admission. Further reductions are more limited, although generally negative symptoms continue to decline throughout the study period.

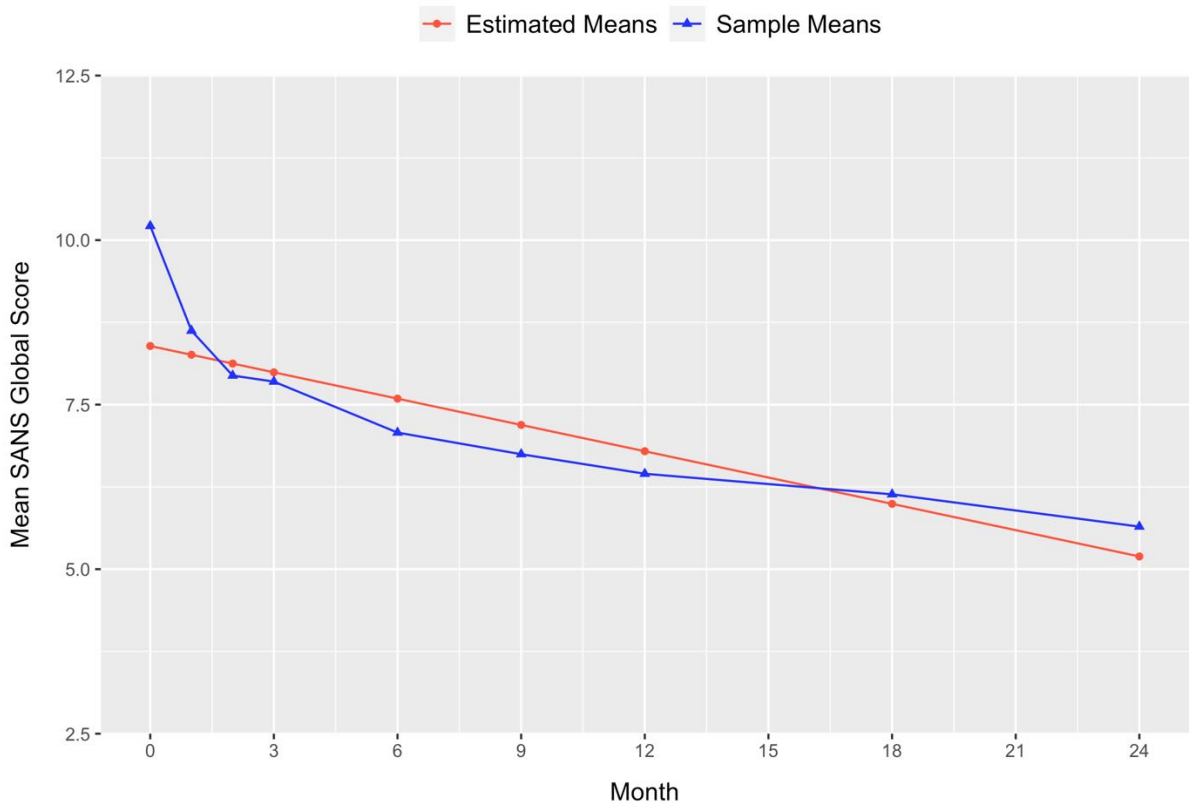

Figure 2: Simple Growth Curve Model

Model Selection

Table 2 displays the BIC and the aLRT p-values testing model *k* against model *k – 1* for all models calculated. Initial model fitting indicated that for all GBTM models, increasing the class structure of the model resulted in improvements (decreases) in the BIC. Thus, based on the BIC, the six-class GBTM provided the best fit for the data. However, as previously stated, the BIC tends to overestimate the optimal number of classes for the data. Hence, we refined the class structure using the aLRT (i.e., identified the best model with respect to the BIC which also had a

significant aLRT p-value, finding that the optimal GBTM class structure was three (BIC = 13,305.28; aLRT: p = .004). Subsequently, relaxing model restrictions indicated that permitting residual variance across classes, but not time, provided the most parsimonious solution (BIC value: LCGA unrestricted residual variance across classes < GBTM < LCGA unrestricted residual variance across timepoints < LCGA unrestricted residual variance across both classes and timepoints). Attempting to reduce the polynomial order of the model proved unsuccessful, with the overall addition of cubic growth factors significantly improving model fit (BIC value: cubic model < quadratic model < linear model). Similarly, the aLRT indicated that a three-class structure should not be further reduced. Therefore, we rejected the null hypothesis and concluded that a three-class model with cubic growth factors and unrestricted residual variance across classes provided the most parsimonious solution (BIC = 13,304.93; aLRT: p = .004).

Table 2: Model Fit Statistics

Model	BIC	aLRT P-Value
GBTM		
6-Class Cubic GBTM	13,161.62	.169
5-Class Cubic GBTM	13,194.39	.175
4-Class Cubic GBTM	13,233.61	.125
3-Class Cubic GBTM	13,305.28	.004
2-Class Cubic GBTM	13,552.37	.000
1-Class Cubic GBTM	14,465.95	NA
LCGA		
3-Class Cubic LCGA (RVAC)	13,304.93	.004
3-Class Cubic LCGA (RVAT)	13,320.84	.006
3-Class Quadratic LCGA (RVAC)	13,332.58	.003
3-Class Cubic LCGA (URRV)	13,375.40	.313
3-Class Linear LCGA (RVAC)	13,422.92	.010
2-Class Cubic LCGA (RVAC)	13,549.94	.003
1-Class Cubic LCGA (RVAC)	14,465.95	NA

Note: GBTM, group-based trajectory modeling; LCGA, latent class growth analysis; RVAC, unrestricted residual variance across classes; RVAT, unrestricted residual variance across timepoints; URRV, unrestricted residual variance across both classes and timepoints

Negative Symptom Trajectories

The final model was characterized by three distinct trajectories: i) a high and stable trajectory (HS) (n = 67, 20.6%) characterized by high negative symptoms which remained relatively stable over the course of treatment; ii) a moderate and improving trajectory (MI) (n = 141, 43.3%) showing a significant improvement following treatment, with symptoms plateauing at a moderate level; and iii) a low and remitting trajectory (LR) (n = 118, 36.2%) characterized by a substantial initial decline in negative symptom severity, improving close to the point of remission, which was generally maintained over the course of treatment. Estimated class trajectories are displayed in Figure 3.

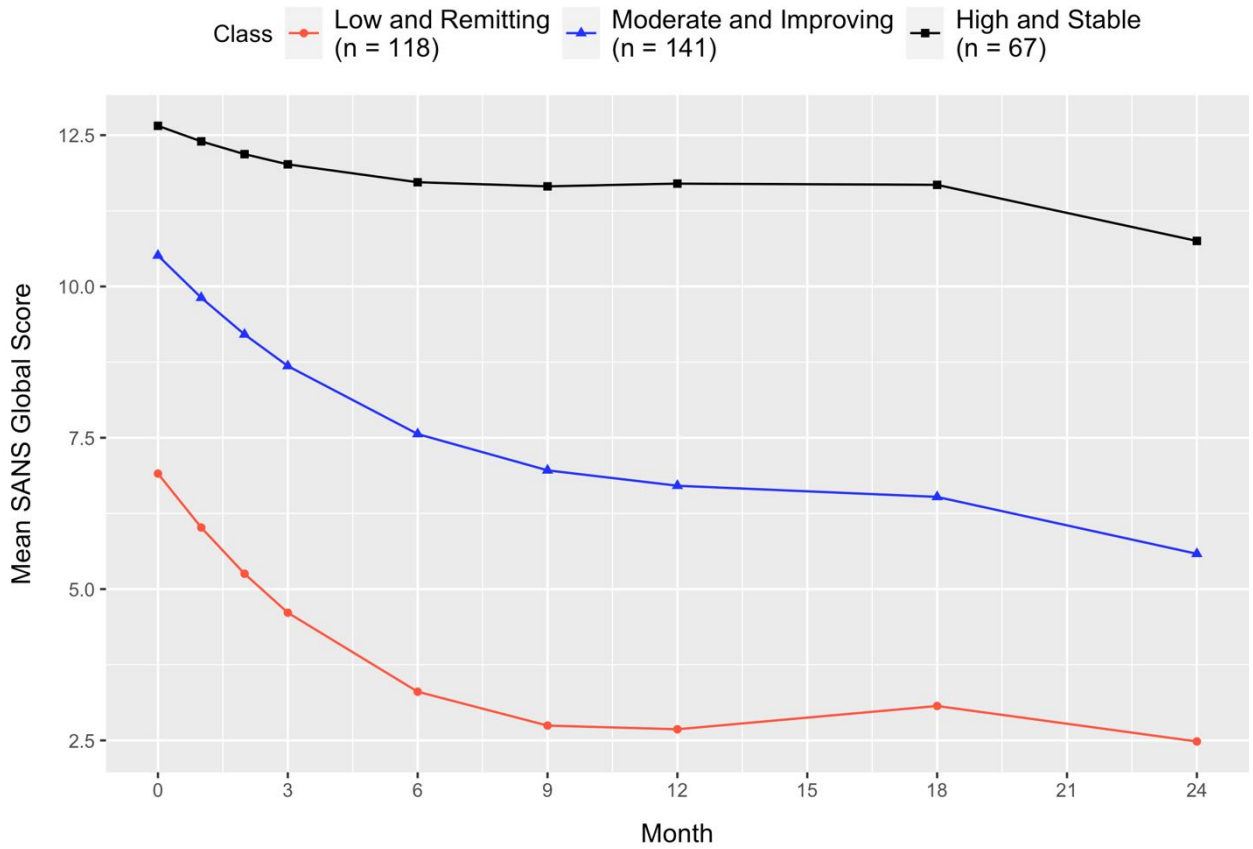

Figure 3: Estimated SANS Global Scores by Class

Appendix II shows all individual patient trajectories, color-coded by class, providing a visual representation of variability within classes. Exclusively for the purpose of Appendix II, missing data (representing 12.6% of all scores) were imputed in R as the median of a patient's class trajectory at a given timepoint. Additionally, baseline patient characteristics by class are provided in Appendix III.

Variables Associated with Latent Class Membership

Results from univariate multinomial logistic regressions are shown in Table 3. Compared to both the high and stable and moderate and improving trajectories, membership in the low and remitting trajectory was associated with older age at entry (HS: OR = .875; MI: OR = 0.918), affective diagnosis (HS: OR = 3.660; MI: OR = 2.441), higher IQ (HS: OR = 0.960; MI: OR = 0.977), lower SAPS global score at baseline (HS: OR = 1.138; MI: OR = 1.100) as well as greater years of completed education (HS: OR = 0.781; MI: OR = 0.830). Neither male sex nor estimated duration of untreated psychosis significantly predicted class membership.

Table 3: Odds Ratios for Multinomial Logistic Regressions

	High and Stable		Moderate and Improving	
Variable	OR (95% CI)	P-Value	OR (95% CI)	P-Value
Age at Entry	0.875 (0.830-0.923)	<.001	0.918 (0.878-0.960)	0.001
Estimated DUP	1.005 (0.999-1.012)	0.140	1.005 (0.999-1.011)	0.198
Non-Affective	3.660 (2.049-6.534)	0.039	2.441 (1.585-3.758)	0.024
IQ	0.960 (0.941-0.980)	0.001	0.977 (0.962-0.993)	0.016
Male Sex	2.689 (1.535-4.712)	0.065	2.058 (1.338-3.166)	0.050
SAPS at Baseline	1.138 (1.041-1.244)	0.025	1.100 (1.028-1.176)	0.028
Years of Education	0.781 (0.700-0.871)	<.001	0.830 (0.765-0.901)	<.001

Note: OR, odds ratio; CI, confidence interval; DUP, duration of untreated psychosis; SAPS, Scale for the Assessment of Positive Symptoms

Discussion

Summary of Findings

The present study used Latent Class Growth Analysis to assess whether negative symptom trajectories following first-episode psychosis (FEP) could resolve into relatively more homogeneous clusters. Our findings indicate that a three-class structure best describes observed longitudinal trends. Additionally, we observed that numerous baseline characteristics predict membership in the least pernicious trajectory. These results are in line with previous findings demonstrating that it is possible to identify subgroups of FEP patients without a priori knowledge of grouping variables.

Negative Symptom Trajectories

Overall, the majority of patients in our sample demonstrate substantial improvement over the study period. Indeed, both the low and remitting and moderate and improving trajectories experience a substantial initial decline in symptomatology following admission. By contrast, the high and stable trajectory experiences minimal initial decline in symptoms, with no significant improvement observed over the course of treatment. This finding of a latent class following a high and stable trajectory is consistent with many previous reports (Abdin et al., 2017; Austin et al., 2015; Chen et al., 2013; Gee et al., 2016), potentially suggesting that a common subpopulation is being recognized across studies. Indeed, supposing that the high and stable group was derived from the same population as the other two groups, representing patients with generally more severe disease resulting from the same underlying physiological processes, we would expect to see a similar relative decline in symptomatology over time. Thus, the distinctiveness of symptom severity within the high and stable group provides evidence that divergent mechanisms potentially underlie these group differences.

Despite these key similarities, our findings diverge from previous studies in several respects. First, the identification of a three-class structure is inconsistent with several previous reports, which generally support the existence of a four-class structure (Abdin et al., 2017; Austin et al., 2015; Chen et al., 2013; Gee et al., 2016; Stiekema et al., 2018). Second, whereas most previous work identified a class experiencing a substantial worsening of negative symptoms over time (Abdin et al., 2017; Austin et al., 2015; Chan et al., 2020; Chang et al., 2019; Gee et al., 2016; Stiekema et al., 2018), we did not identify such a class in our analysis. Given that patients with affective diagnoses generally experience lower levels of negative symptoms than do non-affective patients (van Os & Kapur, 2009), these discrepancies may be due to the relatively high proportion of patients suffering from affective psychosis within our sample. Indeed, most previous studies excluded those with affective psychosis from analysis (Austin et al., 2015; Chan et al., 2020; Chang et al., 2019; Chen et al., 2013; Pelayo-Teran et al., 2014; Stiekema et al., 2018). Additionally, while Abdin et al. (2017) did not exclude patients with affective psychosis from their study, they reported that affective patients constituted just 8.8% of their sample. Similarly, Gee et al. (2016) conducted analysis using data from The UK National EDEN Study, which reported prevalence of affective disorders at 14% (Birchwood et al., 2014). By comparison, 34% of patients in our sample received a diagnosis of affective psychosis. Given that non-affective patients were overrepresented in both the high and stable and moderate and improving classes, reducing or eliminating the proportion of patients with affective psychoses would almost certainly alter our findings. Furthermore, the diverse methodologies employed by different studies potentially obfuscate other similarities between our findings and the extant literature. For example, only two other studies (Austin et al., 2015; Pelayo-Teran et al., 2014) also used the Scale for the Assessment of Negative Symptoms (SANS) to assess

symptomatology. Moreover, Pelayo-Teran et al. (2014) conducted analysis using six-weeks of data from an antipsychotic trial, while Austin et al. (2015) assessed trajectories over ten years and did not exclude the attention component of the SANS from calculations.

Thus, while not surprising that our overall class trajectories do not wholly overlap with any other study, our findings nevertheless represent a novel contribution to the literature; our study was able to identify a latent class with consistently high levels of negative symptoms in a sample including a significant proportion of patients with affective psychosis. This supports the contention that impairments akin to those observed in deficit syndrome (Kirkpatrick et al., 2006; Kirkpatrick et al., 2017) can be observed within a representative sample of FEP patients. Considering that current antipsychotic drugs are generally effective at treating positive symptoms (Bitter, 2020; Correll & Schooler, 2020), it is likely that patients in the high and stable group are generally experiencing primary negative symptoms, whereas those in the other two groups are experiencing mostly secondary negative symptoms. Hence, following the substantial improvement in positive symptoms observed in all groups (see Appendix III), those in the low and remitting and moderate and improving groups experienced reductions in negative symptoms. Recently, our lab has reported that patients from the same sample suffering from persistent negative symptoms (PNS) can be subdivided into two groups: those suffering from idiopathic PNS (i.e., PNS resulting from primary negative symptoms) and those suffering from secondary PNS (Lepage et al., 2021). Our results tentatively support the validity of this distinction, although more work is needed to quantitatively assess overlap between findings.

Baseline Predictors of Trajectories

Concerning predictors of symptom trajectories, our findings also show substantial convergence with the literature. Previous reports have found that more pernicious symptom

course is associated with younger age (Abdin et al., 2017; Stiekema et al., 2018), non-affective and schizophrenia diagnoses (Abdin et al., 2017; Austin et al., 2015; Pelayo-Teran et al., 2014; Stiekema et al., 2018), poor educational attainment (Abdin et al., 2017; Chan et al., 2020; Chang et al., 2019; Stiekema et al., 2018), and higher levels of positive symptoms (Chan et al., 2020; Chang et al., 2019; Chen et al., 2013; Stiekema et al., 2018). Contrary to most previous studies (Abdin et al., 2017; Austin et al., 2015; Chan et al., 2020; Chang et al., 2019; Gee et al., 2016; Stiekema et al., 2018), we did not find that male sex was associated with membership in more pernicious trajectories (compared to the low and remitting trajectory), although findings approached significance (high and stable: $p = 0.065$; moderate and improving: $p = 0.050$). Interestingly, although several previous studies have found that poor cognitive performance predicts more pernicious trajectories (Chang et al., 2019; Stiekema et al., 2018), our finding that IQ predicts symptom trajectories appears to be a unique contribution. This is consistent with findings from Lepage et al. (2021) who demonstrated that those suffering from idiopathic PNS exhibited greater impairments in verbal and working memory, as well as significantly lower IQ ($M = 93.17$) than patients with secondary PNS (Lepage et al., 2021). Although we did not assess the relationship between specific neurocognitive measures and symptom trajectories, we did observe that those in the high and stable group tend to have a significantly lower IQ ($M = 93.95$) than average.

Clinical Significance

Given the ever-growing adoption of big data techniques within the scientific community, our findings provide a theoretical foundation for future research exploring more targeted interventions within subgroups of FEP patients. Currently, although numerous pharmacological agents and psychological interventions have been shown to significantly reduce negative

symptoms, effect sizes are generally not clinically significant (for a review of randomized control trials, see Fusar-Poli et al., 2015). Supposing that impairments within different subgroups were supported by distinct mechanisms, different subgroups of patients may respond preferably to a given treatment. For example, supposing that negative symptomatology in the high and stable group was driven largely by cognitive deficits, specific therapies could be used to target such impairments. While such treatments may not significantly benefit the overall sample, improvements for patients within the high and stable group may be substantial. Using predictive analytic techniques, baseline variables could be used to assess the probability that patients will follow a given trajectory. Hence, if a patient was assessed to have a high probability of following the high and stable trajectory, this could be used to inform treatment choices. Considering the importance of FEP in determining long-term patient outcomes (Birchwood et al., 1998), this approach could yield significant benefits in re-establishing patient functioning following an initial psychotic episode.

Limitations

First, while we included patients with affective diagnoses to reflect the true heterogeneity seen in first-episode psychosis, it is important to acknowledge that most work on theoretical subtypes of FEP patients has focused on those with non-affective diagnoses. Thus, the inclusion of those with affective psychosis makes difficult any theoretical inferences specific to schizophrenia-spectrum disorders. However, at the same time, it makes this work more generalizable as this represents the reality of FEP clinics. Second, although we ensured that the large amount of data missing at month 1 did not impact the overall class-structure, the present study did not include a robust sensitivity analysis. Therefore, the number of missing data points may have influenced the final class-structure. Finally, it is important to bear in mind the

significant heterogeneity observed within classes (see Appendix II). This marked heterogeneity is representative of psychosis more broadly. Indeed, considering the substantial overlap between even long-established diagnoses, some have questioned the utility of a categorical system for categorizing psychosis (for a critique of the concept of schizophrenia, see Guloksuz & van Os, 2018). However, there remains considerable clinical utility in using a categorical approach (Ahmed, Strauss, Buchanan, Kirkpatrick, & Carpenter, 2018), a fact acknowledged by even critics of a categorical approach (Guloksuz & van Os, 2018). Indeed, the decision as to whether a treatment should be used is an inherently binary one (Ahmed et al., 2018; Guloksuz & van Os, 2018).

Future Directions

Currently, results from data-driven studies remain relatively equivocal. Considering the vast methodological differences observed across studies, a comprehensive analysis evaluating how differences in length of assessment, symptom scale used, and statistical methodologies influence findings within the same dataset is sorely needed. Such a study could potentially allow for the convergence of data-driven findings, thus providing a tangible benchmark from which a systematic assessment of convergence with theoretical constructs could be undertaken. Given the emerging evidence of overlap between data-driven approaches and theoretical concepts, this could prove instrumental in determining the optimal categorization scheme. Indeed, just as the delineation of such subgroups should not be based purely on theoretical considerations, it should also not be wholly informed by clustering of symptom trajectories. Rather, both approaches should be used to inform the optimal categorization system based on clinical utility. For example, in our study, aggregating the low and remitting and moderate and improving trajectories could potentially facilitate the identification of risk factors for following the high and

stable trajectory. Nevertheless, further work is needed to identify more specific neurocognitive predictors of trajectory membership, which could be used in combination with basic demographic predictors identified in our study. This work could pave the way for future research exploring the use of predictive analytics in FEP to better tailor interventions to individual patient needs.

Conclusion

The present study provides converging evidence for the existence of latent subpopulations in first-episode psychosis. In particular, our results indicate that a distinct subgroup of first-episode psychosis patients do not experience any significant improvement in negative symptoms with current treatment methods. This supports the idea that a subpopulation of patients akin to deficit syndrome can be identified in a representative sample of first-episode psychosis patients. Nevertheless, future research should quantitatively evaluate how our findings converge with theoretical concepts including idiopathic and secondary PNS. Such work has important clinical implications in developing more targeted interventions to improve patient outcomes.

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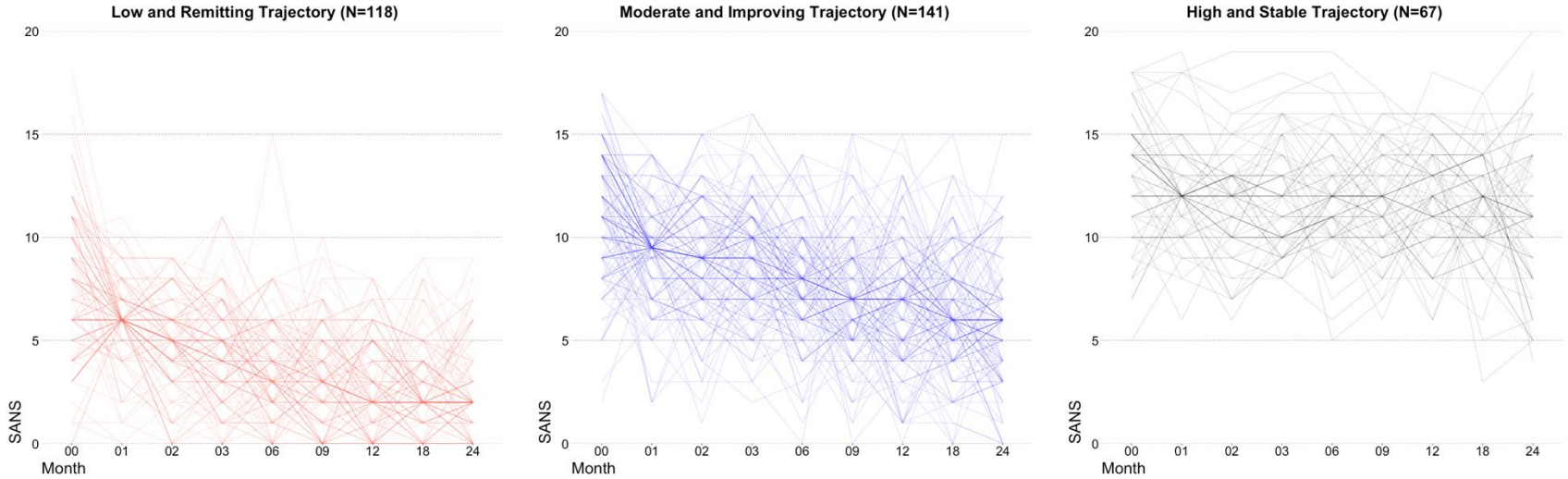
Appendix 1: Main Characteristics (Methods and Results) of Previous Data-Driven Studies on Negative Symptoms

	Sample Size	Non-Affective Excluded?	Statistical Method	Study Period (Assessments)	Symptom Scale Used	Identified Trajectories and Associated Predictors
Pelayo-Terán et al., 2014	118	Yes	GBTM	6 Weeks (6)	SANS Global Scores	Five: Responders* (19%), Mild Non-Responders[1] (37%), Moderate Non-Responders (18%), Partial Responders[1] (11%), Poor Responders[1] (15%)
Chen et al. 2013	400	Yes	GMM	1 Year (7)	PANNS (Total Score)	Four: Class 1 (11%), Class 2 (71%), Class 3 (2%), Class 4 (16%)
Austin et al. 2015	496	Yes	LCA	10 Years (5)	SANS (Global Score)	Four: Response* (28%), Delayed Response (19%), Relapse[1] (26%), No Response[1,2] (27%)
Gee et al. 2016	1006	No	LCGA	1 Year (3)	PANNS (Other)	Four: Minimal Decreasing* (64%), Mild Stable (14%), High Decreasing (17%), High Stable[2] (5.4%)
Abdin et al. 2017	1724	No	LCGA	2 Years (5)	PANNS (Unspecified)	Four: Early Response and Stable* (84%), Early Response and Relapse[3] (6%), Slower/No Response[1,3,4] (9%), Delayed Response[1,2,5] (1%)
Stiekema et al. 2017	1067	Yes	GBTM	6 Years (3)	PANNS (SA/ED)	Four: Decreased-High (6%), Decreased-Low (21%) Increased (15%), Decreased-Low (58%); High (6%), Decreased (17%), Increased (14%), Low (64%)
Chang et al. 2018	138	Yes	LCGA	3 Years (4)	HEN (Total Scores)	Three: Minimal-Stable* (60%), Mild-Stable (29%), High-Increasing[6] (11%)
Chan et al. 2020	209	Yes	Ward's Method	10 Years (64)	CGI-NEG (Mean Scores)	Three: Low* (56%), Improving (29%), Relapsed[2] (15%)

*Statistical Method: GMM, Growth Mixture Modeling. Symptom Scales: SANS, Scale for the Assessment of Negative Symptoms; PANNS, Positive and Negative Syndrome Scale; CGI-NEG, Clinical Global Impressions Schizophrenia (Negative Symptom Component); HEN, High Royds Evaluation of Negativity. Predictors Identified (note that only predictors that are similar to those tested in our study and were assessed specific to each class are reported, for a more comprehensive review see Habtewold et al. (2020); the reference group is indicated by *): 1, schizophrenia diagnosis; 2, male sex; 3, lower education; 4, longer DUP; 5, younger age; 6, cognitive impairment.*

Appendix II: Individual Patient Trajectories For Each Identified Latent Class



Appendix III: Characteristics of Identified Latent Classes at Baseline

	High & Stable (N = 67)	Moderate & Improving (N = 141)	Low & Remitting (N = 118)
Basic Demographics			
Age at Entry (Mean, SD)	22.26 ± 3.97	23.20 ± 4.69	25.14 ± 4.98
Male (n, %)	51 (76.12%)	100 (70.92%)	64 (54.24%)
Years of Education (Mean, SD)	11.17 ± 2.56	11.54 ± 2.56	12.82 ± 2.61
Clinical Characteristics			
Non-Affective Psychosis (n, %)	53 (79.10%)	101 (71.63%)	60 (50.85%)
IQ at Baseline (Mean, SD)	93.95 ± 15.09	97.56 ± 14.84	102.44 ± 13.67
Estimated DUP (Mean, SD)	58.56 ± 104.31	48.96 ± 87.89	26.64 ± 75.58
SAPS Global Score at Baseline (Mean, SD)	12.37 ± 3.12	12.06 ± 2.96	11.18 ± 3.11
SAPS Global Score at Month 3 (Mean, SD)	5.31 ± 4.23	3.99 ± 3.62	2.04 ± 2.62