Concordance and factor structure of subthreshold positive symptoms in youth at clinical high risk for psychosis

Monica E. Calkins [a,*], Scott W. Woods [b], Carrie E. Bearden [c], Lu Liu [d], Tyler M. Moore [a], Kristin S. Cadenhead [e], Tyrone D. Cannon [f], Barbara A. Cornblatt [g], Thomas H. McGlashan [b], Diana O. Perkins [h], Larry J. Seidman [i], Ming T. Tsuang [e], Elaine F. Walker [j], Daniel H. Mathalon [k], Matcheri Keshavan [i], William S. Stone [i], Jean Addington [d]

[a] Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, United States of America
[b] Department of Psychiatry, Yale University, New Haven, CT, United States of America
[c] Departments of Psychology and Psychiatry and Biobehavioral Sciences, UCLA, Los Angeles, CA, United States of America
[d] Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada
[e] Department of Psychiatry, UCSD, La Jolla, CA, United States of America
[f] Department of Psychology, Yale University, New Haven, CT, United States of America
[g] Department of Psychiatry, Zucker Hillside Hospital, Long Island, NY, United States of America
[h] Department of Psychiatry, University of North Carolina, Chapel Hill, NC, United States of America
[i] Department of Psychiatry, Harvard Medical School at Beth Israel Deaconess Medical Center and Massachusetts Mental Health Center, Boston, MA, United States of America
[j] Departments of Psychology and Psychiatry, Emory University, Atlanta, GA, United States of America
[k] Department of Psychiatry, University of California, San Francisco, San Francisco, CA, United States of America

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ABSTRACT

Prevailing models of psychosis risk incorporate positive subthreshold symptoms as defining features of risk or transition to psychotic disorders. Despite this, relatively few studies have focused on characterizing longitudinal symptom features, such as prevalence, concordance and structure, which may aid in refining methods and enhancing classification and prediction efforts. The present study aimed to fill these gaps using longitudinal 24-month follow-up data from the well-characterized NAPLS-2 multi-site investigation of youth at clinical high risk (CHR) who had (n = 86) and had not (n = 268) transitioned to a threshold psychotic disorder since baseline. At baseline, among sub-delusional ideas, unusual thought content and suspicious/persecutory thinking were very common in CHR youth, and were highly concordant. Perceptual abnormalities (P4) were also common across youth regardless of symptom course and eventual transition to psychosis. Grandiose ideas were rare. Exploratory factor analysis extracted two constituent factors at multiple follow-up intervals, but there was marked instability in the structure over 24 months, and clear indicators for a single positive symptom factor. Together these findings support suggestions to combine sub-delusional symptoms into a single symptom category for classification purposes, in efforts to reduce clinical heterogeneity and ease measurement burden.

1. Introduction

Recent years have seen increased research attention and interest in characterizing unique symptom, function, and biobehavioral features that are associated with varying trajectories and outcomes among youth at clinical high risk for psychosis (Addington et al., 2019a). While predictive models including several salient symptom domains have been investigated (e.g., Ruhrmann et al., 2010), in many risk models, positive subthreshold symptoms are considered to be defining features of psychosis risk and transition to psychosis (Fusar-Poli et al., 2013; Miller et al., 2003; Woods et al., 2009; Yung and Nelson, 2011). Positive symptom categories include several types of sub-delusional ideations or preoccupations (unusual thought content, suspiciousness or persecutory thinking, and grandiose ideas), as well as unusual perceptual experiences and disorganized communication. Such symptom subtypes have been included with other risk features in developing and validating individualized risk calculators (Cannon et al., 2016; Fusar-Poli et al., 2017; Fusar-Poli et al., 2019; Osborne and Mittal, 2019; Zhang et al., 2018; Zhang et al., 2019) aiming to enhance capacity to predict individuals most at risk of transitioning to psychotic

* Corresponding author at: Department of Psychiatry, University of Pennsylvania, 10 Gates Pavilion, 3400 Spruce Street, Philadelphia, PA 19104, United States of America.
E-mail address: mcalkins@pennmedicine.upenn.edu (M.E. Calkins).

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disorders, as well as to inform group selection for investigations of pathophysiological processes underlying the development of psychotic disorders (Addington et al., 2019a).

At the same time, there has been growing interest in minimizing heterogeneity of methods to assess various risk factors (Fusar-Poli et al., 2015) while still reflecting heterogeneous outcomes. Despite the prominence of positive symptoms as defining features of risk and transition to psychotic disorders, relatively few studies have focused on characterizing longitudinal symptom features, such as prevalence, concordance and structure, that may aid in refining methods and enhancing classification and prediction efforts. Prior evidence from the North American Prodrome Longitudinal Study (NAPLS-2) of clinical high risk (CHR) youth suggested that unusual thought content, suspiciousness and perceptual abnormalities were more common at baseline than grandiosity and disorganized communication (Addington et al., 2015). A similar pattern was also observed in the NAPLS-1 sample (Woods et al., 2009). While there is some meta-analytic evidence that differing criteria for determining clinical or ultra-high risk states do not impact transition rate estimates (Schultze-Lutter et al., 2015), it is unknown whether differences in base rates of individual positive symptoms are relevant to longitudinal symptom course or clinical outcome. Recent efforts (National Institute of Mental Health, 2020) have focused on harmonizing common diagnostic instruments for CHR, noting that while positive symptom content was very similar, the instruments sometimes differed in how content was organized into the items. For example, nihilism was rated on P1 on one instrument and on P2 on the other, and grandiosity was rated on P3 on one instrument and on P2 on the other. These observations led to the suggestion of combining subthreshold positive symptom items such as the sub-delusional rating scales (unusual thought content, suspiciousness, and grandiosity) (National Institute of Mental Health, 2020). Such approaches could potentially reduce perceived positive symptom heterogeneity and ease measurement burden, greatly facilitating simplified and efficient large-scale international collaboratives.

To address such questions, we need improved understanding of the temporal stability of inter-relationships among subthreshold positive symptoms. Several factor analytic evaluations conducted on the Scale of Psychosis-risk Symptoms have included positive, negative, disorganized and/or general symptom scales (Comparelli et al., 2011; Fluckiger et al., 2019; Hawkins et al., 2004; Klaassen et al., 2011; Lemos et al., 2006; Tang et al., 2014; Tso et al., 2017). While these investigations varied in overall findings and methods (e.g., sample sizes), all reported an identifiable positive symptom factor including unusual thought content and suspiciousness/persecutory thinking, with less consistent loadings for perceptual abnormalities, grandiosity and disorganized communication. Michel et al. (2019) reported low one-year temporal stability of SIPS assessed aggregated positive symptoms in a small sample of CHR youth. No study to our knowledge has focused solely on the factor structure of positive symptoms and its stability over time.

The present study aimed to fill these gaps using longitudinal 24-month follow-up data from the large and well-characterized NAPLS-2 multi-site investigation to evaluate positive symptom prevalence, concordance, and structure.

2. Material and methods

2.1. Participants

All participants are part of the second North American Prodrome Longitudinal Study (NAPLS-2). Participants are help-seeking and were recruited through various sources: family physicians, mental health clinics, social services, and school and college counsellors. Many were self-referred in response to community educational efforts. Recruitment efforts have been described in detail elsewhere (Addington et al., 2012). The NAPLS-2 sample consisted of 764 youth at CHR (436 males, 328 females) recruited across the eight NAPLS-2 sites. All participants were assessed with the Structured Interview for Psychosis-risk Syndromes (SIPS) (McGlashan et al., 2010) to determine if they met Criteria for Psychosis-risk Syndromes (COPS) [i.e., one or more of the following high risk syndromes: attenuated psychotic symptoms syndrome (APSS); brief intermittent psychotic symptoms syndrome (BIPS); or genetic risk and deterioration syndrome (GRD)]. Of the total 764 NAPLS-2 participants, 86 made the transition to psychosis, 390 did not complete the 2-year study (Stowkowy et al., 2018), 21 were retained for 2 years but were excluded because they had significant missing data at 24 months ($n = 10$) or they met GRD criteria only ($n = 11$). Thus, the sample described in this paper includes 268 participants who had not made the transition to psychosis and had completed 2 years of follow-up and 86 participants who transitioned to psychosis. Participants were between 12 and 35 years of age. Exclusion criteria included meeting criteria for any current or past axis I psychotic disorder, IQ less than 70, or past or current history of a clinically significant central nervous system disorder.

2.2. Measures

The Structured Interview for Psychosis-risk Syndromes (SIPS) (McGlashan et al., 2010; Woods et al., 2019) was used to determine whether an individual met COPS criteria. The Scale of Psychosis-risk Symptoms (SOPS) was used to rate the severity of attenuated psychotic symptoms. The SOPS consists of 19 items in 4 symptom domains (i.e., positive, negative, general, and disorganized symptoms).

The Structured Clinical interview for DSM-IV (SCID) (First et al., 1995) was used to determine the presence of current and past psychiatric disorders, including transition to a psychotic disorder. Transition to psychosis was determined by meeting the Presence of Psychotic Symptoms (POPS) criteria (McGlashan et al., 2010). POPS requires that at least one of the five SOPS attenuated psychotic symptoms had reached a psychotic level of intensity (rated 6) for a frequency of less than or equal to 1 h per day for 4 days per week, or that psychotic symptoms were seriously impacting functioning (e.g., disorganizing or dangerous to self or others).

For those who had not made the transition to psychosis, three different clinical outcomes were determined at the 2-year follow-up assessments. These were: (1) remission defined as remission from all CHR syndromes, (i.e. participants had ratings <2 on all five SOPS positive symptoms scales); (2) symptomatic but not currently meeting criteria for a prodromal risk syndrome, i.e., rating 3–5 on any one of the five positive symptoms on the SOPS which had neither worsened nor begun in the previous 12 months; and (3) progression, i.e., participant currently met criteria for an attenuated psychotic symptom syndrome (APSS; at least one of the five positive symptoms began or had increased in the previous 12 months (McGlashan et al., 2010; Woods et al., 2014)). As previously reported, these groups did not differ in medication use (Addington et al., 2019b).

2.3. Procedures

This study was approved by the Institutional Review Boards of all eight NAPLS-2 sites. Written informed consent, including parental consent, was obtained from all adult participants and parents/guardians of minors. After the initial screening assessment with SCID and SIPS, vignettes were developed for each CHR participant to obtain a consensus determination of COPS criteria. SOPS attenuated psychotic symptoms were described at length and included both recent and longstanding symptoms. The vignettes were written so raters from all eight sites could review the information under each symptom category and provide a reliable rating. Once approved at the site level, the vignette was presented on a conference call for a consensus decision on both symptom ratings and diagnosis. The NAPLS-2 consensus call, chaired by JA, was held once a week and attended by clinical raters from each of the

eight sites. Submitted vignettes were individually reviewed and a consensus was reached on each symptom rating, diagnosis, and ultimate admission into the study. Clinical raters were experienced research clinicians. Gold standard post-training agreement on determining the prodromal diagnoses was excellent (kappa = 0.90) (Addington et al., 2012). Diagnostic interviews at all sites were conducted by trained raters. SOPS data were collected at five time points: baseline, 6-, 12-, 18- and 24-month follow-up.

2.4. Statistical analyses

In order to calculate symptom frequency and concordance, SOPS symptom ratings were each dichotomized to "present and clinically significant" (rating ≥ 3) or "absent/not significant" (rating 0–2). While dichotomization entails loss of information regarding symptom severity, we elected this approach to parallel the use of the symptoms in the SIPS classification approach (McGlashan et al., 2010; Woods et al., 2019). Comparisons of symptom occurrence at baseline in those who transitioned v. those who did not were analyzed using chi-square. Omnibus Cochrane's Q tests were used for the full sample, individuals who transitioned, and individuals who did not transition (remission, symptomatic, progression), respectively, to examine overall differences in the proportions of the 5 symptoms, followed by pairwise McNemar statistic with Bonferroni correction (0.05/50 = 0.001) conducted for each symptom pair.

We performed exploratory factor analyses on the five positive SOPS items (scored 0–6, not dichotomized) using least-squares extraction and oblique (oblimin) rotation. These analyses were performed across five time points (Baseline, 6-, 12-, 18- and 24- month), as well as collapsed across timepoints, to assess temporal stability of the factor structure. Based on prior evidence for a unitary positive symptom factor, we anticipated these analyses would result in over-extractions, but performed them nonetheless to investigate whether >1 factor would produce meaningful results that were stable over time.

We also wished to compare the predictive accuracy of a collapsed P1-P3 score (i.e., using the maximum rating obtained on any of P1, P2 or P3) with that of the alternative approach preserving the information across the items (i.e., P1, P2, and P3). To do this, we compared the area under the receiver operating characteristic (ROC) curve (AUC) of the collapsed P1-P3 with the AUC's of the individual continuous items P1-P3 (possible values = 0, 0.33, 0.67, 1) in predicting later transition to psychosis. To test whether the above AUCs were significantly different from each other, we performed bootstrapped difference testing. Specifically, we randomly selected N participants with replacement, performed the above analyses to get AUCs for the two score types, recorded the difference between those two AUCs, and repeated this 10,000 times. This resulted in a distribution of 10,000 differences, and if zero lies within two standard deviations of the mean of this distribution, the difference is not significant.

3. Results

Demographic characteristics of the total sample, individuals who transitioned to psychosis, and individuals who did not transition are presented in Table 1. Among those who did not transition by 24 months, 38.4% (n = 103) were in remission, 34.3% (n = 92) were symptomatic and 27.2% (n = 72) were prodromal progression (Addington et al., 2011).

Symptom frequencies at baseline (for all participants) and at transition (for those who transitioned) are presented in Table 2. The most common symptom reported at baseline was PI (unusual thought content), followed by P4 (perceptual abnormalities), P2 (suspiciousness), P5 (disorganized communication), and finally P3 (grandiosity). Dichotomized symptom frequencies for those who transitioned were similar (χ^2 P1 = 0.52, P2 = 2.94, P3 = 0.80, P4 = 0.20; df = 1, 352; all p's n. s.), except for P5 (χ^2 = 8.86; df = 1, 353; $p < 0.01$) which was disproportionately more frequent in those who transitioned. The symptoms that reached a psychotic level for individuals who experienced a transition showed a similar pattern with P1 being the most frequent, and P3 and P5 being the least common.

At baseline, for 11.0% (n = 39) of participants, a single symptom determined CHR criteria (P1, n = 12; P2 n = 9; P3 n = 0; P4 n = 15; and P5, n = 3). Among the remaining participants with multiple significant symptoms, 26.6% (n = 94) had 2 symptoms, 41.0% (n = 145) had 3 symptoms, 16.1% (n = 57) had 4 symptoms, and 5.4% (n = 19) rated on all 5 symptoms. The most common combination for two symptoms was P1 and P4, three symptoms was P1, P2 and P4, and for four symptoms, it was P1, P2, P4 and P5. At baseline, 94.1% of participants had at least one type of subthreshold delusional symptom (PI, P2 or P3), and 86% had at least one of these symptoms plus P4.

Omnibus Cochran's Q tests of dichotomous P1-P5 symptom ratings for the total sample (Cochran's Q = 465.47, df = 4, 353), for those who transitioned (Cochran's Q = 111.04, df = 4, 85), and for those who did not transition (progression Cochran's Q = 115.86, df = 4, 72; symptomatic Cochran's Q = 135.17, df = 4, 92; remission Cochran's Q = 135.18, df = 4, 92) were highly significant ($p < 0.001$), indicating

Table 1
Demographic characteristics.

Variable	Total sample n = 354	Non-transition n = 268	Transition n = 86	Test statistic
		Mean (SD)		t
Age (years)	18.5 (4.19)	18.7 (4.36)	17.9 (3.57)	−1.51
Education (years)	11.2 (2.69)	11.3 (2.73)	10.9 (2.53)	−1.1
		Number (%)		χ^2
Sex				
Female	200 (56.5)	146 (54.48)	54 (62.79)	1.83
Male	154 (43.5)	122 (45.52)	32 (37.21)	
Race				
First Nations/Indigenous American	6 (1.69)	5 (1.87)	1 (1.16)	2.65
Asian	26 (7.34)	18 (6.72)	8 (9.30)	
Black	63 (17.8)	52 (19.4)	11 (12.79)	
Caucasian	207 (58.47)	155 (57.84)	52 (60.47)	
Mixed race	52 (14.69)	38 (14.18)	14 (16.28)	
Marital status				
Single, never married	341 (96.33)	258 (96.27)	83 (96.51)	0.01
Other	13 (3.67)	10 (3.73)	3 (3.49)	
Current working				
Yes	86 (24.29)	71 (26.49)	15 (17.44)	2.89
No	268 (75.71)	197 (73.51)	71 (82.56)	
Current enrolled as a student				
Yes	293 (82.77)	223 (83.21)	70 (81.40)	0.15
No	61 (17.23)	45 (16.79)	16 (18.60)	

Table 2
Symptom occurrence at admission and at transition among those who experienced a transition to psychosis.

Group	Timepoint	P1	P2	P3	P4	P5
Total sample	Baseline	82.2	66.9	17.5	79.4	32.2
Individuals who did not transition	Baseline	81.3	64.4	17.6	79.8	28.1
Individuals who transitioned	Baseline	84.7	74.4	16.3	79.1	45.3
	Transition - symptom reaching psychotic intensity	77.9	43.0	11.6	44.2	16.3
	Transition - symptom present at baseline	70.9	40.7	2.3	43.0	12.8
	Transition - symptom new at transition	11.6	30.2	10.5	27.9	30.2

Values are %. Total sample n = 354. Individuals who did not transition to psychosis, n = 267. Individuals who transitioned, n = 86. Symptoms are dichotomized based on ≥ 3 rating. P1 = unusual thought content; P2 = suspiciousness/persecutory ideas; P3 = grandiosity; P4 = unusual perceptual abnormalities; P5 = disorganized communication.

that within group proportions of at least two of the positive symptom types were different from each other. Post-hoc McNemar results, showing pairwise comparisons of symptom types, are presented in Table 3. In all groups except the total sample, the within-subject proportions of P1 and P2 were not significantly different, reflecting a high concordance of these two items at baseline. Similarly, P1 and P4 were both present in approximately two-thirds of each group. P3 had low concordance with all other symptoms across groups, likely due to its overall lower prevalence.

Results of the factor analyses revealed marked instability across timepoints, as shown by the clearly different factor configurations in Fig. 1. However, parallel analysis with Glorfeld correction (Glorfeld, 1995; Horn, 1965) suggested only one (positive symptom) factor in all six data sub-sets shown in Fig. 1, and over-extraction of factors such as we do here, where the factors in Fig. 1 have only one major indicator, can result in unusual and unstable solutions (Fava and Velicer, 1992). Thus, instability of EFA factor patterns here should be interpreted with caution, because of the expected over-extraction. Repeating the analyses using list-wise deletion to omit individuals missing data at any timepoint did not alter this pattern of results.

Results of the bootstrapped significance tests revealed that there was no difference between the predictive power for transition (as measured by AUC) of the collapsed P1-P3 score (AUC = 0.640) and P1 (AUC = 0.638). P2 (AUC = 0.593) and P3 (AUC = 0.484) were lower.

Finally, we examined whether individuals who did not transition to psychosis reported comparable significant symptoms at baseline and 24 months. Among the symptomatic group, 71.7% reported fewer symptom types, 22.8% reported the same number, and 5.4% reported more symptom types than at baseline. Among those classified as prodromal progressive, 45.2% had fewer symptom types, 45.2% remained the same, and 9.6% reported more symptom types. Repeating this analysis in those who had any of P1/P2/P3 significant items, in the symptomatic group, 60.9% reported fewer symptoms, 37% reported the same symptoms, and only 2.2% reported more symptom types. For those classified as prodromal progressive, 27.4% reported fewer symptoms, 57.5% reported the same number, and 5.4% reported more symptoms.

Table 3
Concordance between baseline symptom pairs in the total sample, individuals who transitioned, and individuals who did not transition (progression, symptomatic, remission).

	P1	P2	P3	P4
Total sample (n = 354)				
P2	55.6* (197)	–	–	–
P3	16.4* (58)	11.0* (39)	–	–
P4	66.4 (235)	52.8* (187)	14.1* (50)	–
P5	26.6* (94)	24.0* (85)	7.6* (27)	55.6* (87)
Transition (n = 86)				
P2	64.0 (55)	–	–	–
P3	16.3* (14)	12.8* (11)	–	–
P4	66.3 (57)	59.3 (51)	14.0* (12)	–
P5	38.4* (33)	33.7* (29)	9.3* (8)	33.7* (29)
Progression (n = 72)				
P2	59.7 (43)	–	–	–
P3	18.1* (13)	9.7* (7)	–	–
P4	72.2 (52)	52.8 (38)	13.9* (10)	–
P5	20.8* (15)	20.8* (15)	2.8 (2)	16.7* (12)
Symptomatic (n = 92)				
P2	62.0 (57)	–	–	–
P3	15.2* (14)	12.0* (11)	–	–
P4	67.4 (62)	62.0 (57)	14.1* (13)	–
P5	26.1* (24)	23.9* (22)	6.5 (6)	23.9* (22)
Remission (n = 103)				
P2	39.8 (41)	–	–	–
P3	15.5* (16)	8.7* (9)	–	–
P4	62.1 (64)	39.8* (41)	14.6* (15)	–
P5	21.4* (22)	18.4* (19)	10.7 (11)	23.3* (24)

Note: Values are % (n) present on both symptoms in the pair. Symptoms are dichotomized based on ≥ 3 rating. P1 = unusual thought content; P2 = suspiciousness/persecutory ideas; P3 = grandiosity; P4 = unusual perceptual abnormalities; P5 = disorganized communication.
* $p < 0.001$.

4. Discussion

We examined several features of prospective positive symptoms in youth at clinical high risk for psychosis. Among sub-delusional ideas, unusual thought content (P1) and suspicious/persecutory thinking (P2) were very common in clinical high-risk youth, while grandiose ideas (P3) were rare. Perceptual abnormalities (P4) were also common across youth regardless of symptom course and eventual transition to psychosis. While less frequent overall, disorganized communication was disproportionately more frequent in youth who subsequently transitioned to psychosis. Youth who subsequently transitioned to psychosis also most frequently experienced an intensification of specific symptoms already present at baseline, although nearly a third experienced emergence of either suspiciousness (P2) or perceptual abnormalities (P4).

At baseline, the vast majority of youth experienced more than one type of positive symptom, and in particular, baseline unusual thought content (P1) and suspiciousness (P2) were highly concordant across all groups. Nearly all at-risk youth reported at least one type of sub-delusional symptom at baseline. Although exploratory factor analysis extracted two constituent factors at each time point, there was marked instability in the structure over 24 months, and clear indicators for a single positive symptom factor. Future studies with larger samples will benefit from formal testing of longitudinal structural changes through traditional measurement invariance testing (Meredith, 1993). Moreover, prediction of transition to psychosis was not affected by collapsing sub-delusional symptom categories compared to individual item predictions. Together these findings support the suggestion to combine sub-delusional symptoms into a single symptom category (National Institute of Mental Health, 2020) for classification purposes. These findings may motivate simplification of current rating scales and inform development and interpretation of future risk calculators. To solidify these findings, future research should: 1) compare our current factor configuration findings to other unsupervised machine learning (clustering) algorithms, such as non-parametric Mokken scale analysis (Molenaar, 1991) or numerous available k-means approaches (Milligan and Cooper, 1987), and; 2) compare predictive utility of the factors proposed here to alternative non-clustering methods of prediction, such as regularized regression (Zou and Hastie, 2005) and ensembling (Dietterich, 2000).

The focus of our investigation was limited to subthreshold positive symptoms as operationally defined by the SOPS positive symptom scales, each of which broadly covers a wide range of phenomenologically heterogeneous positive symptoms. Thus, findings could differ from those obtained with instruments possessing a higher resolution to ascertain specific subcomponents of positive symptoms. In addition, more granular rating scales, including with continuous ratings reflecting positive symptom severity (e.g., Carrion et al., 2016), may be useful for particular research contexts which seek to investigate associations of particular variables and specific symptom categories. Furthermore, given some evidence that subthreshold positive psychosis symptoms may reflect clinical state factors, while schizotypal symptom domains reflect potentially independent trait vulnerability factors (Michel et al., 2019), psychosis prediction may ultimately be enhanced by considering both symptom domains (Fluckiger et al., 2019). Along these lines, there is ample evidence that non-positive symptom domains, including negative and basic symptoms, are conceptually and practically meaningful for determination and/or prediction of at-risk states (e.g., Ruhrmann et al., 2010). Availability of alternative strategies for positive symptom measurement, as suggested here, can facilitate large scale, multi-site

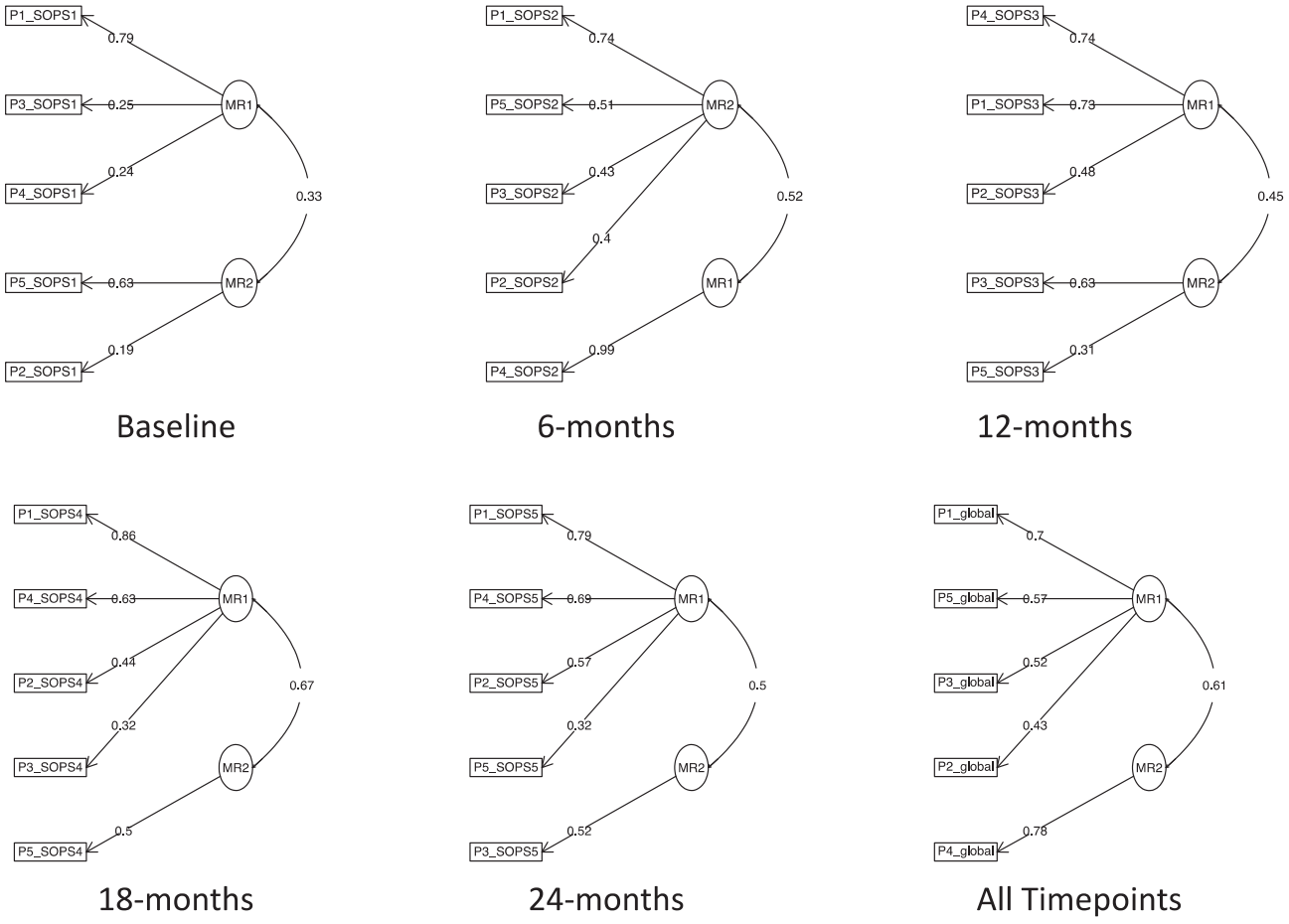

Fig. 1. Factor analyses of SOPS ratings across all timepoints, and at baseline, 6-, 12-, 18-, 24-month follow-up assessments. P1 = unusual thought content; P2 = suspiciousness/persecutory ideas; P3 = grandiosity; P4 = unusual perceptual abnormalities; P5 = disorganized communication.

prospective investigations incorporating other psychosis spectrum symptom domains and biobehavioral risk factors.

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The NIMH had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

CRediT authorship contribution statement

Drs. Addington, Cannon, Cadenhead, Cornblatt, McGlashan, Perkins, Seidman, Tsuang, Woods, Walker, Mathalon, and Bearden were responsible for the design of the study and for the supervision of all aspects of data collection. Dr. Calkins wrote the initial manuscript with help from Dr. Addington. Ms. Liu, Dr. Moore and Dr. Calkins were responsible for statistical analyses. All authors listed have contributed to and approved the final manuscript.

Declaration of competing interest

The authors have declared that there are no conflicts of interest with respect to this paper.

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