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Abstract

The validity of the classification of non-affective and affective psychoses as distinct entities has been disputed, but despite calls for alternative approaches to defining psychosis syndromes, there is a dearth of empirical efforts to identify transdiagnostic phenotypes of psychosis. We aimed to investigate the validity and utility of general and specific symptom dimensions of psychosis cutting across schizophrenia, schizoaffective disorder and bipolar disorder with psychosis. Multidimensional item-response modeling was conducted on symptom ratings of the Positive and Negative Syndrome Scale, Young Mania Rating Scale, and Montgomery-Åsberg Depression Rating Scale in the multi-centre Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) consortium, which included 933 patients with a diagnosis of schizophrenia (n=397), schizoaffective disorder (n=224), and bipolar disorder with psychosis (n=312). A bifactor model with 1 general symptom dimension, 2 distinct dimensions of non-affective and affective psychosis, and 5 specific symptom dimensions of positive, negative, disorganized, manic and depressive symptoms provided the best model fit. There was further evidence on the utility of symptom dimensions for predicting B-SNIP psychosis Biotypes with greater accuracy than categorical DSM diagnoses. General, positive, negative and disorganized symptom dimension scores were higher in African American vs. Caucasian patients. Symptom dimensions accurately classified patients into categorical DSM diagnoses. This study provides evidence on the validity and utility of transdiagnostic symptom dimensions of psychosis that transcend traditional diagnostic boundaries of psychotic disorders. Findings further show promising avenues for research at the interface of dimensional psychopathological phenotypes and basic neurobiological dimensions of psychopathology.

Introduction

The validity of categorical classification in psychiatry is disputed because the clinical and neurobiological boundaries between disorders are dubious[1-17]. Therefore, there have been calls for alternative approaches to psychiatric classification that are empirically- and psychometrically-informed through the investigation of neural and psychological mechanisms that transcend current syndromes[18-20]. Some projects address the shortcomings of classic psychiatric classification, such as the Research Domain Criteria (RDoC) framework that integrates many levels of information (from genes to self-report) to further our understanding of basic cross-disorder dimensions of functioning[6, 7, 21, 22]. The Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP)[23, 24] addresses overlap across psychosis syndromes by examining a broad array of endophenotypes. Recently, the Hierarchical Taxonomy of Psychopathology (HiTOP) consortium has emerged as a research effort that quantifies disorders according to several levels of psychopathology, including spectra, syndromes and symptom components, and characterizes them dimensionally[25]. However, to date, evidence on the link between transdiagnostic dimensions of clinical phenotypes and basic brain-based biomarkers is limited.

In psychosis, the overlap of symptoms across diagnostic categories is especially prevalent, which leads to high comorbidity as seen with schizophrenia, schizoaffective disorder, and bipolar disorder[26, 27]. While the Kraepelinian dichotomy regarded dementia praecox/schizophrenia and manic depression as distinct diagnostic entities, recent research has challenged this dichotomy[4, 5] and places schizophrenia and bipolar disorder on a transdiagnostic psychosis spectrum[4] with schizoaffective disorder as an intermediate diagnostic category[23]. This overlap may be a result of shared genetic and environmental etiological factors[4, 28-30]. Findings also show, however, non-shared genetic and environmental risks[4, 28, 30], which supports the heterogeneity of psychotic disorders.

There remains a dearth of empirical efforts to identify a transdiagnostic phenotype of psychosis. The pentagonal model with five dimensions of positive symptoms, negative symptoms, cognitive disorganization, mania, and depression has received support in previous factor-analytic work[31]. However, recent research has demonstrated evidence for a bifactor model with a general psychosis factor encompassing non-affective and affective symptoms in patients with schizophrenia, schizoaffective and bipolar disorder, as well as five specific psychosis dimensions of positive, negative, disorganized, manic and depressive symptoms[4, 5]. This model was found to better fit empirical symptom data than a pentagonal model[4, 5] and a model allowing for distinct non-affective and affective psychosis factors[32]. It provides support for a psychosis spectrum ranging from bipolar disorder to schizoaffective disorder to schizophrenia. Further, in this bifactor model, shared etiological factors may be associated with the general psychosis factor, whereas non-shared etiological factors could contribute to more specific psychosis dimensions[4, 5]. This approach could also hone the diagnostic process by placing patients broadly on the psychosis spectrum and using the specific symptom dimensions to classify patients into specific diagnoses[4, 5]. While initial support for the diagnostic utility of these dimensions has been found using the operational criteria system[4], such transdiagnostic models and their diagnostic utility need to be further tested with more detailed measures of psychosis, mania, and depression and cross-validated across a large multisite consortium such as B-SNIP. This would allow for improved understanding of the utility of these dimensions not only for diagnosis in research and clinical care in the United States, but also in relation to basic neurobiological constructs such as the three recently identified B-SNIP psychosis Biotypes[33] in an attempt to connect dimensional psychopathological phenotypes with neurobiological mechanisms[12, 14, 25].

Therefore, this study aimed to investigate transdiagnostic dimensions of psychosis spectrum disorders cutting across non-affective and affective psychotic symptoms in patients with schizophrenia, schizoaffective disorder, and psychotic bipolar I disorder using widely established measures for assessing psychosis, mania, and depression (i.e., PANSS, YMRS, MADRS) in the B-SNIP consortium. We aimed to investigate: 1) whether

there is a general dimension of psychosis spectrum disorders underlying all affective and non-affective psychotic symptoms; 2) whether formation of a) specific symptom dimensions (positive, negative, disorganized, depressive and manic symptoms) and b) distinct dimensions of affective and non-affective psychosis is justified in addition to a general psychosis dimension; 3) associations of socio-demographic and clinical variables with general, affective, non-affective and specific symptom dimensions; and 4) the utility of these dimensions for classifying patients into a) categorical DSM diagnoses of psychotic disorders and b) the B-SNIP Biotypes.

Method

Sample

This study used data collected as part of the multisite B-SNIP consortium the same diagnostic assessment methodology across psychotic disorders[23]. Specifically, patients with a diagnosis of schizophrenia, schizoaffective disorder, and psychotic bipolar disorder were recruited from five sites in the United States through regional advertising and from inpatient and outpatient clinics in 2008-2012[23]. Patients were in a non-acute symptom state, clinically stable and provided informed consent.

Measures

Participants were assessed extensively for their socio-demographic and clinical characterization (including age, gender, ethnicity and DSM diagnosis) with a variety of instruments[23, 24]. In this study, the responses of three well-established diagnostic instruments were investigated: the Positive and Negative Syndrome Scale (PANSS), which is a 30-item clinical interview that measures the severity of psychotic symptoms on a scale of 1-7; the Young Mania Rating Scale (YMRS)[34], a 11-item measure to assess manic symptoms; and

the Montgomery-Åsberg Depression Rating Scale (MADRS)[35], a 10-item measure to assess depressive symptoms. Social functioning was measured using the Birchwood Social Functioning Scale (SFS)[36].

Statistical analysis

Multidimensional item response modeling was conducted with the mirt package of the R environment (i.e., the Metropolis-Hastings Robbins-Monro algorithm[37]) for model estimation. Model fit was examined using the Log-Likelihood (LL), the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and the Sample size-Adjusted BIC (SABIC)[38]. Better model fit is indicated with lower values than for the comparison model.

Given there is no definite evidence on the factorial structure of the PANSS, we first analyzed symptom ratings on the PANSS only and compared 18 previously published factor solutions[5]. Based on the modeling strategy in our earlier study[5], we estimated three alternative item response models based on previously reported factor solutions reported for the PANSS[5] (see Figure S1 in the online data supplement): **1)** a unitary (unidimensional) model with 1 general factor explaining all symptom ratings to reflect a general dimension of the psychosis spectrum (**model A**); **2)** a pentagonal (multidimensional) model with correlated specific factors to reflect specific positive, negative, disorganized, depressive and manic symptom dimensions (**model B**, corresponding to the pentagonal model of psychosis[31]); and **3)** a bifactor model with 1 general factor independent from 5 uncorrelated (orthogonal) specific factors (**model C**; corresponding to the bifactor model in our earlier study[5, 39]). Given the latter is a full likelihood method, data was assumed to be missing at random.

Using the best-fitting model for the PANSS identified in this initial step, we next conducted the primary analysis to investigate general and specific symptom dimensions based on all measures for assessing psychosis, mania, and depression (i.e., PANSS, YMRS, MADRS) by comparing model A-C, additionally allowing for factor loadings

for YMRS and MADRS items on the general factor as well as on specific manic and depressive symptom factors, respectively (Figure S2). To investigate whether formation of distinct dimensions for affective and non-affective psychosis was justified in addition to 1 general dimension and 5 specific symptom dimensions, model comparison of the primary analysis further included: **4)** a bifactor model with 1 general psychosis dimension, 5 uncorrelated specific factors (positive, negative, disorganized, depressive and manic symptom dimensions), and 2 uncorrelated factors to reflect distinct dimensions of affective and non-affective psychosis (**model D**); and **5)** a model with 5 uncorrelated specific factors (positive, negative, disorganized, depressive and manic symptom dimensions) and 2 uncorrelated factors (distinct affective and non-affective psychosis dimensions) but without a general factor (**model E**;[32]). To ensure stable model estimation, the prevalence of responses per category per item was set to be at least 10% of the sample. Due to low coverage in the more severe categories, responses were collapsed into three categories for the PANSS, YMRS and MADRS.

The association of socio-demographic characteristics (i.e., age, gender, ethnicity), DSM diagnosis, and social functioning (as independent variables) with factor scores of general and specific psychosis dimensions (as outcome variables) were analyzed using linear regression. Last, multinomial Receiver Operating Characteristic (ROC) analysis[40] were conducted in Stata version 14[41] to investigate the extent to which factor scores of general, affective, non-affective and specific dimensions allow for accurate classification of patients into a) categorical DSM diagnoses of psychotic disorders and b) the B-SNIP Biotypes.

Results

Basic sample characteristics

Basic characteristics of the total B-SNIP sample (n=933 patients) and the B-SNIP sample used for estimating item response models (n=860) were almost identical (see Table S1 in the online data supplement): the mean age at interview was 36 years and approximately half were male; the sample primarily consisted of patients

with Caucasian or African American ethnicity; and the most common diagnosis was schizophrenia, followed by psychotic bipolar disorder and schizoaffective disorder.

Dimensionality of psychotic disorders

Initial analysis of symptom ratings on the PANSS indicated that a bifactor model with 1 general and 5 specific factors based on the PANSS 5-factor solution by Emsley et al.[42] best matched the B-SNIP sample data (AIC=53209.8, BIC=53920.0, SABIC=53443.7) (Table S2 and S3), thereby, replicating our bifactor model in schizophrenia spectrum disorder[5]. Building on this initial step, we next compared item response models for symptom ratings on all measures for assessing psychosis, mania, and depression (i.e., PANSS, YMRS, MADRS; Figure S2). This showed that the bifactor model with general, non-affective, affective and 5 specific factors (i.e., model D) to reflect a general dimension of the psychosis spectrum (general factor), distinct dimension of non-affective and affective psychosis (non-affective and affective psychosis factors), and specific positive, negative, disorganized, depressive and manic symptom dimensions (5 specific factors) provided the best model fit as indicated by the lowest AIC, BIC and SABIC (AIC=65988.4, BIC=67201.4, SABIC=66391.6) compared with alternative models (Table 1).

[Insert Table 1]

Findings on the best-fitting model showed that the largest amount of item variance was explained by the general psychosis dimension (ω_H =0.67) followed by negative (ω_S=0.45), depressive (ω_S=0.38) and positive (ω_S=0.30) symptom dimensions (Table 2). Overall, factor loadings were heterogenous in magnitude across symptom dimensions. Factor loadings for the general psychosis dimension were moderate to strong for most positive, negative, disorganized, manic and depressive symptom ratings of PANSS and YMRS items, but weaker for MADRS items (Table 2). The non-affective psychosis dimensions showed the strongest factor loadings for

negative and disorganized symptom ratings on the PANSS. Factor loadings for the affective psychosis dimension were strongest for MADRS depressive symptom ratings and, to a lesser extent, YMRS manic symptom ratings. Specific positive and negative symptom dimensions demonstrated moderate to strong factor loadings for most items of the PANSS, whereas factor loadings for the specific disorganized symptom dimension were only weak to moderate at most. Factor loadings for specific manic and depressive symptom factors were strongest for YMRS and MADRS, respectively.

[Insert Table 2]

Symptom dimensions by socio-demographic characteristics, social functioning, and DSM diagnosis

Symptom profiles showed that, compared with psychotic bipolar disorder, factor scores on the general, non-affective, affective, positive, negative, disorganized and depressive symptom dimensions were higher for schizoaffective disorder (all $p<0.05$) (Figure S3 and Table 3). By contrast, factor scores on the specific manic symptom dimension were lower for schizoaffective than psychotic bipolar disorder ($p<0.001$). Further, factor scores on the non-affective, positive, negative and disorganized symptom dimensions were higher, and factor scores on the affective and manic symptom dimensions lower, for schizophrenia than for psychotic bipolar disorder (all $p<0.001$).

Table 3 further shows that factor scores for the general psychosis dimension were significantly higher for patients with African American than Caucasian ethnicity ($p=0.001$) and with lower social functioning ($p<0.001$). Further, factor scores for the non-affective psychosis dimension were lower in women ($p<0.001$) but higher in younger patients ($p=0.001$) and patients with lower social functioning ($p=0.023$). Factor scores for the affective psychosis dimension increased with increasing age ($p=0.017$) and were higher in female patients ($p<0.001$) and those with lower social functioning ($p=0.020$). Older patients had higher factor scores on specific positive

and disorganized symptom dimensions. Female patients scored lower on the specific positive symptom dimension and higher on the specific depressive symptom dimension (all $p<0.05$). Compared with Caucasian patients, patients with African American ethnicity had higher factor scores on the positive, negative and disorganized symptom dimensions and lower scores on the depressive symptom dimension (all $p<0.05$). Social functioning decreased as scores on positive, negative, disorganized and depressive symptom dimensions increased, whereas social functioning increased with increasing scores on the manic symptom dimension (all $p<0.05$).

[Insert Table 3]

Utility of general, non-affective, affective and specific symptom dimensions

When we examined the utility of symptom dimensions for classifying patients correctly into categorical DSM diagnoses of psychotic disorders using multinomial ROC analysis (Figure S4), this showed that the proportion of patients correctly classified into diagnostic categories based on factor scores of general, non-affective, affective and specific symptom dimensions (M=0.57, 95% CI 0.53-0.62) was higher compared with classifying patients by chance (M=0.39, 95% CI 0.33-0.44).

We next examined the utility of symptom dimensions for accurately predicting the B-SNIP psychosis Biotypes. Figure 1 (and Table 3) shows high non-affective, positive, negative and disorganized symptom factor scores for Biotype 1, high affective, manic and depressive symptom factor scores for Biotype 3, and high general symptom dimension (and moderate other symptom dimension) factor scores for Biotype 2. There was evidence that the proportion of patients correctly classified into B-SNIP Biotypes based on factor scores of general, non-affective, affective and specific symptom dimensions (Figure S5a, M=0.41, 95% CI 0.35-0.47) was higher than what would be expected by chance (M=0.35, 95% CI 0.29-0.41); however, this did not hold for

categorical DSM diagnoses (Figure S5b; DSM diagnoses, M=0.41, 95% CI 0.36-0.46; random accuracy, M=0.38, 95% CI 0.31-0.44). As can be seen in Figure 2, findings on ROC curves further indicated that patients were classified into B-SNIP Biotypes with greater accuracy based on symptom dimensions (Figure 2a, AUC=0.87) than DSM diagnoses (Figure 2b, AUC=0.68).

[Insert Figure 1 and 2]

Discussion

Main findings

This study provides evidence on a transdiagnostic dimension underlying affective and non-affective psychotic symptoms in patients with psychotic disorder in the B-SNIP consortium. There was further evidence to suggest that formation of distinct dimensions of non-affective and affective psychosis as well as specific psychosis dimensions of positive symptoms, negative symptoms, disorganization, mania, and depression is justified. Transdiagnostic, non-affective, affective and specific symptom dimensions were differentially associated with age, gender, ethnicity, and social functioning and classified patients correctly into categorical DSM diagnoses. Finally, there was evidence on the utility of symptom dimensions for predicting the B-SNIP Biotypes with greater accuracy than DSM diagnoses.

Methodological considerations

In the current study, we examined the dimensionality of psychotic disorders in a large sample of patients with schizophrenia, schizoaffective and bipolar disorder with psychosis. This sample allowed for multidimensional item response modeling to identify variance driven by a transdiagnostic psychosis dimension independent from variance due to non-affective, affective and specific symptom dimensions based on symptom ratings using widely used and extensively studied measures of psychosis, mania, and

depression (i.e., the PANSS, YMRS, and MADRS). While further sub-dimensions of mania, depression and other specific symptom dimensions (positive, negative and disorganized symptoms) may have been considered, the focus of the current study was on transdiagnostic, affective/non-affective psychosis and specific symptom dimensions, but not subcomponents of these (e.g. avolition as a subcomponent of the negative symptom dimension; euphoria as a subcomponent of mania or anhedonia as a subcomponent of depression). Models to account for these subcomponents would have been difficult to estimate even with the sample size obtained in this study given the high number of items required and free parameters to be estimated in such models. Further, a more stringent measurement design (e.g. a multitrait-multimethod design) would have been required to disentangle measurement from substantive conceptual variance. The use of YMRS and MADRS as more detailed measures of mania and depression, however, did allow us to capture a broader spectrum of variance than would have been the case when using the PANSS alone and hence provided a better reflection of these specific symptom dimensions. They now need to be investigated further to disentangle method and substantive conceptual variance using comprehensive measures of psychopathology in large samples of psychotic disorders including psychotic depression.

Comparison with previous research

Evidence on a transdiagnostic dimension underlying affective and non-affective psychotic symptoms in the current sample of clinically stable patients is consistent with our earlier findings on such a dimension in patients with early and enduring psychosis[4, 5]. Reverberating the results of numerous previous studies[31], including our own[4, 5], we identified five specific symptom dimensions of positive symptoms, negative symptoms, disorganization, mania and depression. Our findings move beyond those from previous research in providing evidence of distinct non-affective and affective psychosis dimensions in addition to transdiagnostic and specific symptom dimensions. These were primarily characterized by negative and

disorganized symptom ratings (for the non-affective dimension) and depressive and manic symptom ratings (for the affective dimension). According to the recently proposed hierarchical taxonomy of psychopathology[25], the broad transdiagnostic psychosis dimension may best be interpreted at the level of psychopathological super-spectra or higher-order dimensions, whereas specific symptom dimensions may be may be classified at lower levels as symptom components, and non-affective and affective psychosis dimensions as psychopathological spectra or syndromes[25]. While the latter may resemble the previously reported thought disorder and internalizing dimensions[2], the extent to which the transdiagnostic psychosis dimension overlaps with, or is independent from, a general psychopathology factor[43] remains to be established. As the evidence base on the dimensionality of psychotic disorders continues to emerge and strengthen, the need for transdiagnostic investigations of psychotic and non-psychotic disorders becomes more pressing to examine important spectra or syndromes across disorders.

Notably, our finding of higher factor scores on the positive, negative and disorganized symptom dimensions and lower scores on the depressive symptom dimension in patients with African American ethnicity compared with Caucasian patients is in line with earlier studies reporting higher positive[44, 45], negative[45] and disorganized[44] symptom scores as well as lower depressive symptom scores [44] in patients with Black African compared with White Dutch and White British ethnicity in the Netherlands[45] and the UK[44], respectively. Our findings additionally showed that factor scores on the transdiagnostic psychosis dimension were higher for African American than Caucasian patients. Overall, the associations between transdiagnostic, non-affective, affective and specific symptom dimensions on the one hand, and age, gender, ethnicity and social functioning on the other, were broadly consistent with the clinical and social epidemiology of psychosis and, therefore, in support of their concurrent validity[17, 46-49].

These, however, need not only be valid but also useful.[14] In order to elucidate the utility of the symptom dimensions we identified here, we investigated their accuracy for classifying patients into categorical DSM diagnoses and the B-SNIP psychosis Biotypes. Consistent with findings from our previous study[4], overall, strong diagnostic utility of the transdiagnostic, non-affective, affective and specific symptom dimensions for allocating patients to DSM diagnoses was demonstrated with the PANSS, YMRS, and MADRS, which are all established clinical symptom measures that can be used in both research and routine care. Given our findings on symptom profiles by DSM diagnoses (Figure S3) were consistent with operational definitions of current classification systems, these may provide a basis for a psychometrically-informed approach for more accurate classification of patients into these diagnoses. When we examined the utility of symptom dimensions in relation to the recently identified B-SNIP Biotypes[33], this showed patients were classified into these Biotypes with greater accuracy based on symptom dimensions than categorical DSM diagnoses. Findings further showed more pronounced non-affective (Biotype 1), affective (Biotype 3) and transdiagnostic (Biotype 2) dimensional symptom profiles for individual B-SNIP Biotypes (Figure 1). More generally, these findings show how dimensional psychopathological phenotypes can be characterized by connecting them to basic neurobiological constructs and, vice versa, offer valid dimensional psychopathological phenotypes to research into basic neurobiological dimensions of psychopathology such as RDoC[12, 21, 22, 25]. In other words, joining hands rather than viewing phenomenological and neurobiological approaches as separate or competing endeavors may be the way forward.

Conclusions

Our findings provide new evidence on the dimensionality of psychosis spectrum disorders and, specifically, suggest a transdiagnostic psychosis dimension, distinct non-affective and affective psychosis dimensions and 5 specific symptom dimensions best account for symptom data collected using widely established measures in patients with schizophrenia, schizoaffective and bipolar disorder with psychosis. There was also strong

evidence on the utility of these dimensions in relation to categorical DSM diagnoses and B-SNIP psychosis Biotypes. This should inform use of dimensional approaches in current diagnostic classification systems. Findings further show promising avenues for research at the interface of dimensional psychopathological phenotypes and other transdiagnostic approaches such as RDoC focusing on basic neurobiological dimensions of psychopathology[1-17, 21, 22]. This needs to be extended to transdiagnostic investigations of shared and non-shared genetic and socio-environmental factors of symptom dimensions of psychotic and non-psychotic disorders to examine overlap (and independence) of important spectra or syndromes and more fully map and model the dimensionality of mental disorders as a basis for (more) valid diagnostic classification systems.

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References

1. Carpenter WT, Bustillo JR, Thaker GK, van Os J, Krueger RF, Green MJ. The psychoses: cluster 3 of the proposed meta-structure for DSM-V and ICD-11. *Psychol Med.* 2009;39(12):2025-2042.
2. Krueger RF, Eaton NR. Transdiagnostic factors of mental disorders. *World Psychiatry.* 2015;14(1):27-29.
3. Krueger RF, Piasecki TM. Toward a dimensional and psychometrically-informed approach to conceptualizing psychopathology. *Behav Res Ther.* 2002;40(5):485-499.
4. Reininghaus U, Bohnke JR, Hosang G, Farmer A, Burns T, McGuffin P, Bentall RP. Evaluation of the validity and utility of a transdiagnostic psychosis dimension encompassing schizophrenia and bipolar disorder. *Br J Psychiatry.* 2016;209(2):107-113.
5. Reininghaus U, Priebe S, Bentall RP. Testing the psychopathology of psychosis: evidence for a general psychosis dimension. *Schizophr Bull.* 2013;39(4):884-895.
6. Cuthbert BN. The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. *World Psychiatry.* 2014;13(1):28-35.
7. Cuthbert BN, Workgroup NR. The RDoC framework: continuing commentary. *World Psychiatry.* 2014;13(2):196-197.
8. First MB, Rebello TJ, Keeley JW, Bhargava R, Dai Y, Kulygina M, Matsumoto C, Robles R, Stona AC, Reed GM. Do mental health professionals use diagnostic classifications the way we think they do? A global survey. *World Psychiatry.* 2018;17(2):187-195.
9. Jablensky A. Psychiatric classifications: validity and utility. *World Psychiatry.* 2016;15(1):26-31.
10. Kotov R, Krueger RF, Watson D. A paradigm shift in psychiatric classification: the Hierarchical Taxonomy Of Psychopathology (HiTOP). *World Psychiatry.* 2018;17(1):24-25.
11. Maj M. The DSM-5 approach to psychotic disorders: is it possible to overcome the 'inherent conservative bias'? *Schizophr Res.* 2013;150(1):38-39.
12. Maj M. Narrowing the gap between ICD/DSM and RDoC constructs: possible steps and caveats. *World Psychiatry.* 2016;15(3):193-194.
13. Maj M. The need for a conceptual framework in psychiatry acknowledging complexity while avoiding defeatism. *World Psychiatry.* 2016;15(1):1-2.
14. Maj M. Why the clinical utility of diagnostic categories in psychiatry is intrinsically limited and how we can use new approaches to complement them. *World Psychiatry.* 2018;17(2):121-122.
15. McGorry PD, Hartmann JA, Spooner R, Nelson B. Beyond the "at risk mental state" concept: transitioning to transdiagnostic psychiatry. *World Psychiatry.* 2018;17(2):133-142.
16. Owen MJ, O'Donovan MC. Schizophrenia and the neurodevelopmental continuum:evidence from genomics. *World Psychiatry.* 2017;16(3):227-235.
17. van Os J, Reininghaus U. Psychosis as a transdiagnostic and extended phenotype in the general population. *World Psychiatry.* 2016;15(2):118-124.
18. Krueger RF, Piasecki TM. Toward a dimensional and psychometrically-informed approach to conceptualizing psychopathology. *Behaviour research and therapy.* 2002;40(5):485-499.
19. Widiger TA. A dimensional model of psychopathology. *Psychopathology.* 2005;38(4):211-214.
20. Barch DM. The Neural Correlates of Transdiagnostic Dimensions of Psychopathology: Am Psychiatric Assoc; 2017.
21. Cuthbert BN, Insel TR. Toward new approaches to psychotic disorders: the NIMH Research Domain Criteria project. *Schizophr Bull.* 2010;36(6):1061-1062.

22. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Med.* 2013;11:126.

23. Tamminga CA, Ivleva EI, Keshavan MS, Pearlson GD, Clementz BA, Witte B, Morris DW, Bishop J, Thaker GK, Sweeney JA. Clinical phenotypes of psychosis in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). *American Journal of psychiatry.* 2013;170(11):1263-1274.

24. Tamminga CA, Pearlson G, Keshavan M, Sweeney J, Clementz B, Thaker G. Bipolar and schizophrenia network for intermediate phenotypes: outcomes across the psychosis continuum. *Schizophrenia bulletin.* 2014;40(Suppl_2):S131-S137.

25. Kotov R, Krueger RF, Watson D, Achenbach TM, Althoff RR, Bagby RM, Brown TA, Carpenter WT, Caspi A, Clark LA, Eaton NR, Forbes MK, Forbush KT, Goldberg D, Hasin D, Hyman SE, Ivanova MY, Lynam DR, Markon K, Miller JD, Moffitt TE, Morey LC, Mullins-Sweatt SN, Ormel J, Patrick CJ, Regier DA, Rescorla L, Ruggero CJ, Samuel DB, Sellbom M, Simms LJ, Skodol AE, Slade T, South SC, Tackett JL, Waldman ID, Waszczuk MA, Widiger TA, Wright AGC, Zimmerman M. The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *J Abnorm Psychol.* 2017;126(4):454-477.

26. Laursen TM, Agerbo E, Pedersen CB. Bipolar disorder, schizoaffective disorder, and schizophrenia overlap: a new comorbidity index. *J Clin Psychiatry.* 2009;70(10):1432-1438.

27. Rosen C, Marvin R, Reilly JL, Deleon O, Harris MS, Keedy SK, Solari H, Weiden P, Sweeney JA. Phenomenology of first-episode psychosis in schizophrenia, bipolar disorder, and unipolar depression: a comparative analysis. *Clin Schizophr Relat Psychoses.* 2012;6(3):145-151.

28. Cardno AG, Owen MJ. Genetic relationships between schizophrenia, bipolar disorder, and schizoaffective disorder. *Schizophrenia bulletin.* 2014;40(3):504-515.

29. Lichtenstein P, Yip BH, Björk C, Pawitan Y, Cannon TD, Sullivan PF, Hultman CM. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *The Lancet.* 2009;373(9659):234-239.

30. Laursen TM, Munk-Olsen T, Nordentoft M, Bo MP. A comparison of selected risk factors for unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia from a danish population-based cohort. *The Journal of clinical psychiatry.* 2007;68(11):1673-1681.

31. van Os J, Kapur S. Schizophrenia. *The Lancet.* 2009;374(9690):635-645.

32. Russo M, Levine SZ, Demjaha A, Di Forti M, Bonaccorso S, Fearon P, Dazzan P, Pariante CM, David AS, Morgan C, Murray RM, Reichenberg A. Association between symptom dimensions and categorical diagnoses of psychosis: a cross-sectional and longitudinal investigation. *Schizophr Bull.* 2014;40(1):111-119.

33. Clementz BA, Sweeney JA, Hamm JP, Ivleva EI, Ethridge LE, Pearlson GD, Keshavan MS, Tamminga CA. Identification of Distinct Psychosis Biotypes Using Brain-Based Biomarkers. *Am J Psychiatry.* 2016;173(4):373-384.

34. Young R, Biggs J, Ziegler V, Meyer D. A rating scale for mania: reliability, validity and sensitivity. *The British Journal of Psychiatry.* 1978;133(5):429-435.

35. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *The British journal of psychiatry.* 1979;134(4):382-389.

36. Birchwood M, Smith J, Cochrane R, Wetton S, Copestake S. The Social Functioning Scale. The development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. *Br J Psychiatry.* 1990;157:853-859.

37. Chalmers RP, Flora, D. B. . Maximum-Likelihood Estimation of Noncompensatory IRT Models With the MH-RM Algorithm. *Applied Psychological Measurement.* 2014;38(5):339–358.

38. Kass RE, Wasserman L. A reference Bayesian test for nested hypotheses and its relationship to the Schwarz criterion. *Journal of the american statistical association.* 1995;90(431):928-934.
39. Gibbons RD, Hedeker DR. Full-information bi-factor analysis. *Psychomatrika.* 1992;57(3):423-436.
40. Peterson LE, Coleman MA. Machine learning-based receiver operating characteristic (ROC) curves for crisp and fuzzy classification of DNA microarrays in cancer research. *International Journal of Approximate Reasoning.* 2008;47(1):17-36.
41. StataCorp. Stata Statistical Software: release 14. *StataCorp, LP.* 2015.
42. Emsley R, Rabinowitz J, Torreman M, Group R-I-EPGW. The factor structure for the Positive and Negative Syndrome Scale (PANSS) in recent-onset psychosis. *Schizophr Res.* 2003;61(1):47-57.
43. Lahey BB, Applegate B, Hakes JK, Zald DH, Hariri AR, Rathouz PJ. Is there a general factor of prevalent psychopathology during adulthood? *J Abnorm Psychol.* 2012;121(4):971-977.
44. Kirkbride JB, Hindocha C, Hameed Y, Perez J, Jones PB. Do symptom dimensions vary between ethnic groups at first presentation to early intervention in psychosis services?: evidence from the SEPEA study. *Early Intervention in Psychiatry.* 2016;10(Suppl. 1):15-16.
45. Veling W, Selten JP, Mackenbach JP, Hoek HW. Symptoms at first contact for psychotic disorder: comparison between native Dutch and ethnic minorities. *Schizophr Res.* 2007;95(1-3):30-38.
46. Cantor-Graae E, Selten JP. Schizophrenia and migration: a meta-analysis and review. *Am J Psychiatry.* 2005;162(1):12-24.
47. Reininghaus U, Craig TK, Fisher HL, Hutchinson G, Fearon P, Morgan K, Dazzan P, Doody GA, Jones PB, Murray RM, Morgan C. Ethnic identity, perceptions of disadvantage, and psychosis: findings from the AESOP study. *Schizophr Res.* 2010;124(1-3):43-48.
48. Reininghaus U, Morgan C, Simpson J, Dazzan P, Morgan K, Doody GA, Bhugra D, Leff J, Jones P, Murray R, Fearon P, Craig TK. Unemployment, social isolation, achievement-expectation mismatch and psychosis: findings from the AESOP Study. *Soc Psychiatry Psychiatr Epidemiol.* 2008;43(9):743-751.
49. van Os J, Reininghaus U. Comprehensive Textbook of Psychiatry (Kaplan & Sadock's). In: Sadock B, Sadock, V., Ruiz, P., ed. Baltimore, USA: Lippincott Williams & Wilkins; 2017.

Tables

Table 1. Model fit statistics for unitary (unidimensional), pentagonal (multidimensional), and bifactor models of psychosis based on PANSS, YMRS, and MADRS symptom ratings

	LL	FP	AIC	BIC	SABIC
Unidimensional (unitary) model (model A)	-35660.2	153	71626.4	72354.2	71868.3
Multidimensional (pentagonal) model with 5 correlated specific factors (model B)	-33615.3	163	67556.5	68331.9	67814.3
Bifactor model with 1 general factor and 5 specific symptom factors (model C)	-33253.0	204	66914.1	67884.5	67236.6
Bifactor model with 1 general factor, 2 factors for non-affective and affective psychosis, and 5 specific symptom factors (model D)	**-32739.2**	**255**	**65988.4**	**67201.4**	**66391.6**
Bifactor model with 2 factors for non-affective and affective psychosis and 5 specific symptom factors (model E)	-33372.9	204	67153.7	68124.2	67476.3

Note: PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; LL= Log-likelihood; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; SABIC, Sample size-Adjusted Bayesian Information Criterion. All response vectors with at least one response were analyzed (n=860). Responses to all three instruments recoded into three categories. Model D provides the best model fit as indicated by lower BIC, AIC and SABIC compared to other models

Table 2. Factor loadings in bifactor model with general, non-affective, affective, and 5 specific symptom factors based on PANSS, YMRS, and MADRS symptom ratings

Items		General	Non-affective	Affective	Positive symptoms	Negative symptoms	Disorganisation	Mania	Depression
PANSS									
Delusions	P1	**0.55**	**0.22**		0.75				
Hallucinatory behaviour	P3	**0.45**	**0.20**		0.48				
Grandiosity	P5	**0.54**	**-0.00**		0.20				
Suspiciousness	P6	**0.63**	**0.04**		0.32				
Unusual thought content	G9	**0.55**	**0.34**		0.53				
Lack of judgement and insight	G12	**0.48**	**0.32**		0.15				
Blunted affect	N1	**0.09**	**0.69**			0.44			
Emotional withdrawal	N2	**0.42**	**0.28**			0.73			
Poor rapport	N3	**0.38**	**0.59**			0.40			
Passive social withdrawal	N4	**0.30**	**0.16**			0.80			
Lack of spontaneity	N6	**0.28**	**0.69**			0.39			
Motor retardation	G7	**0.27**	**0.66**			0.38			
Disturbance of volition	G13	**0.55**	**0.30**			0.35			
Active social avoidance	G16	**0.50**	**0.02**			0.71			
Conceptual disorganization	P2	**0.58**	**0.27**				0.44		
Difficulty in abstract thinking	N5	**0.24**	**0.32**				0.06		
Stereotyped thinking	N7	**0.61**	**0.40**				0.46		
Mannerisms and posturing	G5	**0.55**	**0.50**				0.20		
Disorientation	G10	**0.57**	**0.22**				-0.11		
Poor attention	G11	**0.67**	**0.27**				0.15		
Preoccupation	G15	**0.68**	**0.23**				0.34		
Excitement	P4	**0.70**		**0.14**				0.32	
Hostility	P7	**0.74**		**0.16**				0.09	
Uncooperativeness	G8	**0.72**		**-0.07**				0.07	
Poor impulse control	G14	**0.76**		**0.10**				0.05	
Somatic concern	G1	**0.46**		**0.16**					0.14
Anxiety	G2	**0.52**		**0.38**					0.39
Guilt feelings	G3	**0.33**		**0.21**					0.26

Tension	G4	**0.64**		**0.22**					0.17
Depression	G6	**0.40**		**0.30**					0.68
YMRS									
Elevated mood	1	**0.31**		**0.11**				0.81	
Increased motor activity-energy	2	**0.28**		**0.17**				0.79	
Sexual interest	3	**0.24**		**0.15**				0.52	
Sleep	4	**0.16**		**0.88**				0.22	
Irritability	5	**0.48**		**0.44**				0.16	
Speech (rate and amount)	6	**0.38**		**0.22**				0.73	
Language - thought disorder	7	**0.51**		**0.19**				0.47	
Content	8	**0.55**		**0.10**				0.35	
Disruptive - aggressive behavior	9	**0.63**		**0.22**				0.27	
Appearance	10	**0.26**		**0.07**				0.16	
Insight	11	**0.38**		**-0.11**				0.12	
MADRS									
Apparent sadness	1	**0.29**		**0.29**					0.74
Reported sadness	2	**0.27**		**0.36**					0.81
Inner tension	3	**0.39**		**0.52**					0.38
Reduced sleep	4	**0.12**		**0.96**					-0.03
Reduced appetite	5	**0.23**		**0.57**					0.26
Concentration difficulties	6	**0.31**		**0.43**					0.37
Lassitude	7	**0.24**		**0.36**					0.56
Inability to feel	8	**0.30**		**0.39**					0.55
Pessimistic thoughts	9	**0.27**		**0.41**					0.60
Suicidal thoughts	10	**0.30**		**0.39**					0.63
ω_H / ω_S		**0.67**	**0.23**	**0.25**	**0.30**	**0.45**	**0.09**	**0.20**	**0.38**

Note: PANSS, Positive and Negative Syndrome Scale, YMRS, Young Mania Rating Scale, MADRS, Montgomery-Åsberg Depression Rating Scale, in n=860 patients, ω_H / ω_S, proportion of item variance explained by general, non-affective and affective factors (ω_H) as well as specific factors (ω_S)

Table 3. Factors scores of general, non-affective, affective and specific symptom dimensions by socio-demographic and clinical variables

	Latent factor scores							
	General	**Non-affective**	**Affective**	**Positive symptoms**	**Negative symptoms**	**Disorganisation**	**Mania**	**Depression**
	B (95% CI, p)	B (95% CI, p)	B (95% CI, p)	B (95% CI, p)	B (95% CI, p)	B (95% CI, p)	B (95% CI, p)	B (95% CI, p)
Age	-0.00 (-0.01 – 0.00, 0.167)	-0.01 (-0.01 – -0.00, 0.001)	0.01 (0.00 – 0.01, 0.017)	0.01 (0.00 – 0.01, 0.010)	0.00 (-0.00 – 0.01, 0.282)	0.01 (0.01 – 0.01, <0.001)	0.00 (-0.00 – 0.01, 0.401)	-0.00 (-0.01 – 0.00, 0.356)
Gender								
Women vs. men	0.09 (-0.04 – 0.22, 0.156)	-0.33 (-0.44 – -0.22, <0.001)	0.26 (0.15 – 0.38, <0.001)	-0.16 (-0.27 – -0.05, 0.006)	-0.02 (-0.14 – 0.09, 0.683)	-0.07 (-0.17 – 0.03, 0.179)	-0.02 (-0.13 – 0.09, 0.684)	0.22 (0.10 – 0.34, 0.001)
Ethnicity								
African American vs. Caucasian	0.22 (0.09 – 0.35, 0.001)	0.05 (-0.08 – 0.17, 0.456)	-0.04 (-0.17 – 0.08, 0.487)	0.23 (0.11 – 0.35, <0.001)	0.16 (0.03 – 0.29, 0.013)	0.20 (0.09 – 0.30, <0.001)	0.00 (-0.11 – 0.12, 0.977)	-0.16 (-0.30 – -0.03, 0.017)
Other vs. Caucasian	0.02 (-0.24 – 0.28, 0.855)	0.00 (-0.24 – 0.24, 0.976)	0.02 (-0.22 – 0.26, 0.858)	0.22 (-0.02 – 0.45, 0.071)	0.12 (-0.12 – 0.37, 0.325)	0.06 (-0.14 – 0.27, 0.554)	-0.10 (-0.33 – 0.13, 0.377)	0.09 (-0.17 – 0.35, 0.489)
Social functioning	-0.01 (-0.01 – -0.00, <0.001)	-0.00 (-0.01 – -0.00, 0.023)	-0.00 (-0.01 – -0.00, 0.020)	-0.01 (-0.01 – -0.01, <0.001)	-0.01 (-0.02 – -0.01, <0.001)	-0.01 (-0.01 – -0.00, <0.001)	0.01 (0.01 – 0.01, <0.001)	-0.01 (-0.01 – -0.00, <0.001)
DSM psychosis diagnosis								
Schizoaffective vs bipolar disorder	0.34 (0.17 – 0.50, <0.001)	0.27 (0.13 – 0.41, <0.001)	0.15 (0.01 – 0.30, 0.042)	0.87 (0.74 – 1.00, <0.001)	0.58 (0.43 – 0.73, <0.001)	0.46 (0.33 – 0.58, <0.001)	-0.30 (-0.48 – -0.15, <0.001)	0.29 (0.13 – 0.45, <0.001)
Schizophrenia vs bipolar disorder	0.06 (-0.09 – 0.21, 0.417)	0.70 (0.58 – 0.83, <0.001)	-0.40 (-0.54 – -0.28, <0.001)	0.75 (0.63 – 0.87, <0.001)	0.55 (0.42 – 0.68, <0.001)	0.53 (0.42 – 0.64, <0.001)	-0.24 (-0.37 – -0.12, <0.001)	-0.08 (-0.22 – 0.06, 0.286)
B-SNIP biotypes								
Biotype 2 vs biotype 1	0.16 (-0.01 – 0.34, 0.070)	-0.13 (-0.29 – 0.04, <0.132)	0.19 (0.03 – 0.35, 0.022)	-0.09 (-0.25 – 0.07, 0.283)	-0.05 (-0.22 – 0.12, 0.574)	-0.16 (-0.30 –	-0.01 (-0.16 – 0.15, <0.924)	0.11 (-0.06 – 0.29, <0.001)

						-0.01, 0.033)		
Biotype 3 vs biotype 1	0.03 (-0.14 – 0.20, 0.712)	-0.37 (-0.53 – -0.22, <0.001)	0.12 (-0.03 – -0.28, 0.117)	-0.26 (-0.42 – -0.11, 0.001)	-0.21 (-0.37 – -0.05, 0.010)	-0.30 (-0.44 – -0.16, <0.001)	0.02 (-0.12 – 0.17, 0.751)	0.13 (-0.04 – 0.29, 0.129)

Figures

Figure 1. Symptom profiles by the B-SNIP biotypes

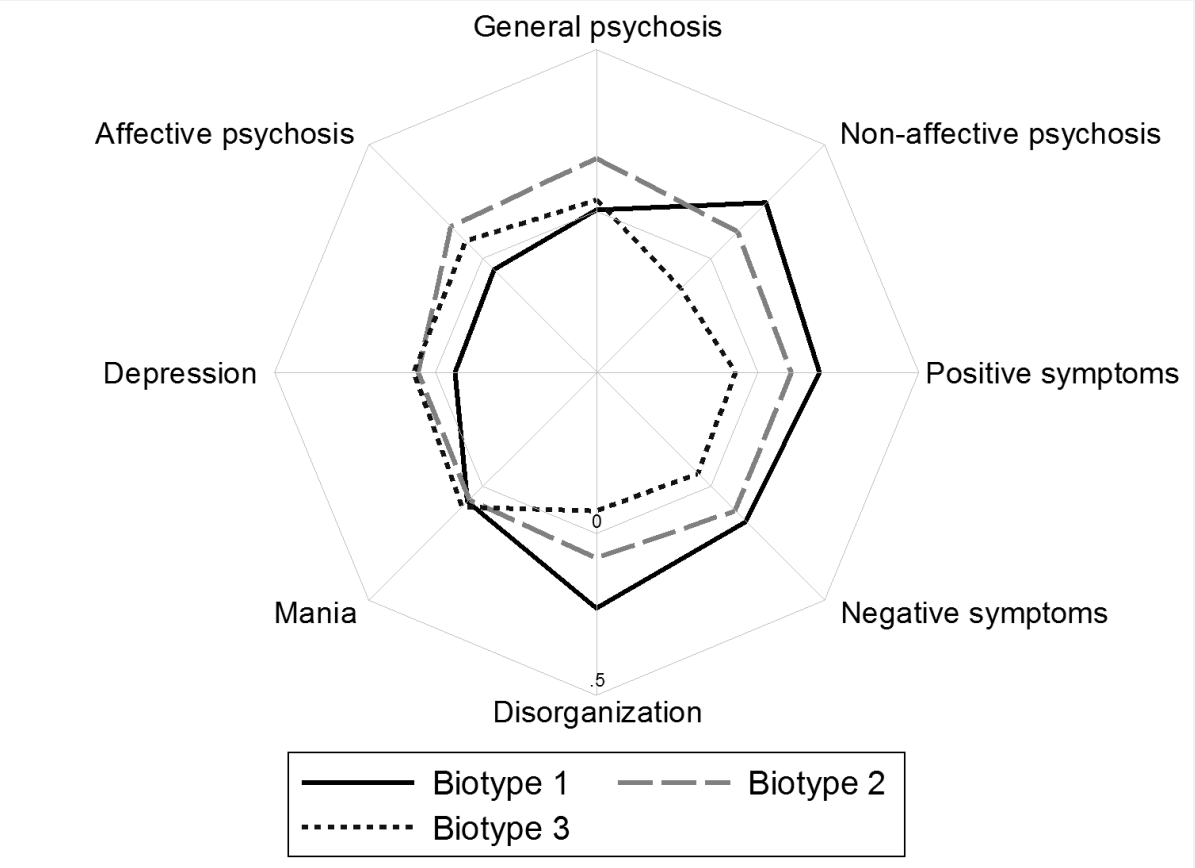

Figure 2. ROC curves of transdiagnostic, non-affective, affective and specific symptom dimensions used in the prediction of B-SNIP biotypes and categorical DSM diagnoses.

Figure 2a. ROC curves of symptom dimensions used in the prediction of B-SNIP biotypes

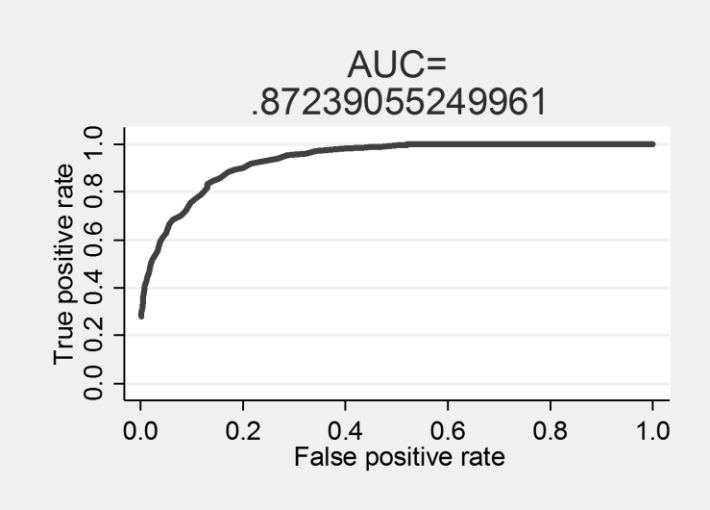

Figure 2b. ROC curves of categorical DSM diagnoses used in the prediction of B-SNIP biotypes